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World Journal of Orthopedics (*World J Orthop*, *WJO*, online ISSN 2218-5836, DOI: 10.5312) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJO covers topics concerning arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthropathy, bone tumors and osteoporosis, minimally invasive therapy, diagnostic imaging. Priority publication will be given to articles concerning diagnosis and treatment of orthopedic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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EDITORIAL

Orthopaedic education in the era of surgical simulation: Still at the crawling stage

Kivanc Atesok, Peter MacDonald, Jeff Leiter, James Dubberley, Richard Satava, Ann VanHeest, Shepard Hurwitz, J Lawrence Marsh

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Abstract

Surgical skills education is in the process of a crucial transformation from a master-apprenticeship model to simulation-based training. Orthopaedic surgery is one of the surgical specialties where simulation-based skills training needs to be integrated into the curriculum efficiently and urgently. The reason for this strong and pressing need is that orthopaedic surgery covers broad human anatomy and pathologies and requires learning enormously diverse surgical procedures including basic and advanced skills. Although the need for a simulation-based curriculum in orthopaedic surgery is clear, several obstacles need to be overcome for a smooth transformation. The main issues to be addressed can be summarized as defining the skills and procedures so that simulation-based training will be most effective; choosing the right time period during the course of orthopaedic training for exposure to simulators; the right amount of such exposure; using objective, valid and reliable metrics to measure the impact of simulation-based training on the development and progress of surgical skills; and standardization of the simulation-based curriculum nationwide and internationally. In the new era of surgical education, successful integration of simulation-based surgical skills training into the orthopaedic curriculum will depend on efficacious solutions to these obstacles in moving forward.

Key words: Surgical simulation; Orthopaedic surgery; Education; Skills training

Core tip: Simulation-based surgical skills training outside the operating room has become essential for modern trainees due to restricted work-hours, cost pressures, emphasis on patient safety, and the increasing number of minimally invasive and technically challenging procedures. Orthopaedic surgery has fallen behind some other surgical specialties in integrating surgical simulation into its curriculum due to several obstacles. The authors aim to clarify these obstacles and suggest solutions for a smooth transformation to simulation-based curriculum in orthopaedic surgery.

Atesok K, MacDonald P, Leiter J, Dubberley J, Satava R, VanHeest A, Hurwitz S, Marsh JL. Orthopaedic education in the era of surgical simulation: Still at the crawling stage. *World J Orthop* 2017; 8(4): 290-294 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i4/290.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i4.290

INTRODUCTION

The traditional method of teaching surgical skills in the operating rooms (OR) has been based on the master-apprenticeship (*i.e.*, learning on the patient) model for over one hundred years[1]. Although this model has been successful throughout many generations, simulation-based surgical skills training outside the OR has become essential for modern trainees due to restricted work-hours, cost pressures, emphasis on patient safety, and the increasing number of minimally invasive and technically challenging procedures[2]. In general surgery, once the need for surgical skills training outside the OR was recognized, surgical simulation was formally acknowledged as evidence-based and integrated into residency curriculum and board certification[3,4].

Orthopaedic surgery arguably covers the broadest human anatomy and related pathologies among the surgical specialties. Hence, the learning of countless basic and advanced surgical procedures during orthopaedic surgery training is required. In addition, as a specialty with a focus on both bone tissue pathologies and soft tissue disorders, trainees are expected to be familiar with a diverse range of both surgical and non-surgical equipment throughout the course of their training, which indicates a strong need for simulation-based skills training. However, orthopaedic surgery has fallen behind some other surgical specialties in integrating surgical simulation into its curriculum.

Although efforts are underway to make this training a part of orthopaedic education, issues that must be addressed include the definition of skills fundamental to orthopaedic surgery that are amenable to simulation. The optimal time period and amount of exposure to the chosen simulations during orthopaedic training must be determined. There must be objective, valid and reliable metrics to measure the effects of simulation training on both the development and progress of surgical skills. Finally, simulation-based curriculum for training in orthopaedic surgery needs to be standardized at national and international levels.

CURRENT OBSTACLES TO SIMULATION-BASED EDUCATION IN ORTHOPAEDICS

Defining areas in need of simulation-based skills training

Simulation-based training should aim to hasten the process of learning surgical skills in a safe environment that is away from the stress of the OR and also allows the opportunity to both make and learn from mistakes without causing harm to patients. Because orthopaedic surgery encompasses the broadest human anatomy, simulated orthopaedic procedures need to be defined carefully so that both basic and advanced orthopaedic surgical skills can be improved outside the OR effectively.

Currently, the majority of the educational programs in United States have already integrated simulated training of basic surgical skills in to their first postgraduate year (PGY1) either as a one-time intensive course (*i.e.*, boot camp) or as longitudinal training sessions throughout the year since this training is required by the American Board of Orthopaedic Surgery (ABOS) and Residency Review Committee (RRC) in orthopaedic surgery. However, the content of these courses is not well-defined. In addition, there is no consensus among orthopaedic training programs as to what type of advanced procedures need simulator training. Almost all advanced orthopaedic surgical skills' courses that are presently available are limited in terms of both procedure types and practiced surgical tools due to their commercial nature. As one of the first steps forward, priority will need to be given to the definition of both basic and advanced surgical skills to be trained on simulators in orthopaedic education.

Another important issue is the use of simulators for training and certification or recertification of orthopaedic surgeons already in practice. Simulation-based training might offer a valuable opportunity for practicing orthopaedic surgeons who have completed residency or fellowship training to learn new procedures and/or update their existing skills. Further, simulations may have a future role to assess surgical skills as benchmarks for certification or recertification of practicing orthopaedic surgeons. Likewise, simulators can be beneficial in selecting students for specialty training in orthopaedic surgery based on their aptitude in simulated performance of basic surgical skills. Nevertheless, all these potential areas in which simulators could have benefits need to be further identified and studied rigorously before simulators can be used in certification/recertification and trainee selection processes.

Arthroscopic surgery is an area where orthopaedic simulation is more advanced and that simulation-based

training can be very effective in improving skills of orthopaedic trainees[5-7]. During the past few decades, there have been dramatic improvements in arthroscopic surgery of the knee, shoulder, hip, elbow, wrist and ankle joints. However, the amount of time that the trainees could spend for practicing arthroscopic surgery skills is limited because the duration of residency training is still the same as it was decades ago. Further, there are different arthroscopic procedure types for each joint, which makes it nearly impossible for trainees to become truly proficient in this field. Hence, simulated arthroscopic skills training could be an important learning opportunity for residents and fellows.

Current simulators are limited to mainly the knee and shoulder modules and do not include some of the commonly performed operations such as meniscectomy, rotator cuff repair, or even loose body removal. It is clear that simulation-based arthroscopic skills training needs to be integrated into the educational curriculum. However, the types of simulator devices and software, joints on which to focus, and procedures to be practiced using arthroscopy simulators are still waiting to be defined and standardized. Cost factors will be another limitation. As an example, the cost of a high-fidelity simulator can be as high as 100000 USD including the device, software, and maintenance.

After defining the skills for which training with simulators will be most effective, programs to educate and certify simulation lab instructors to supervise trainees during simulation-based skills training could be of value. Although such an initiative could only become relevant after a standard simulation based curriculum is established, this may also aid in achieving uniformity among educational programs nationwide.

Time, duration, and frequency of simulation-based skills training

Although surgical simulation in orthopaedic skills training has been recognized as a necessity, and the Accreditation Council on Graduate Medical Education recommends simulation training during residency education, specifics with regard to time, duration, and frequency of practicing with simulators are left to program directors to determine what they think is best for their residents[2,8]. Since July 2013, orthopaedic residency programs in the United States have been required to incorporate laboratory-based surgical skills training into the curriculum during the first year of residency. Currently, some orthopaedic residency programs have included a one-month period of an intensive skills training course, or boot camp, into their curriculum before interns begin their training. There are existing concerns regarding the effectiveness of short-term intensive skills training, and the degree to which skills learned in these courses are retained and achieve the goal of improved integration into the actual OR is uncertain[3]. Hence, some residency programs in the United States have decided to spread these skills training courses throughout the entire internship year *via* one or two days of simulation-based training every week. Further research is required to prove the superiority of either method in surgical skills training during residency.

Due to the tremendous number of surgical skills and procedures that must be learned after the first year of residency, incorporation of simulation-based skills training into the latter years of residency should positively influence the development of trainees' skills. Choosing the time and duration of simulation-based training as well as determining the optimal time period for reinforcing the learned skills by repeating the simulated courses are of primary concern. Although more simulation-based surgical skills training may result in better learning for residents, this would also require more time spent in education and thus away from clinical service, which might be an obstacle to conducting lab-based training for extended periods during residency. The fellowship period might be a convenient time for practicing skills that are more advanced and specific to subspecialties and offer greater opportunities for dedicated time. However, fellowship programs may vary in terms of their goals and objectives for training, and standardized educational curriculum adjustments for simulation-based training during the fellowship period do not appear to be realistic at this stage. Also more advanced skills training is necessary at the fellowship level requiring higher fidelity simulations which may be cost prohibitive for many fellowship programs.

Proficiency-based-progression training

A notable simulation-based surgical skills training approach, which was recently proposed, is proficiency-based-progression (PBP). This approach can be defined as training based on a benchmark that has been established by expert performance. The benchmark that the novice must achieve is set by the mean performance scores of experts who undergo the same course (curriculum). Thus, the training is not completed in a given amount of time but rather continues until the benchmark scores are met for two consecutive trials. In addition, tasks are presented in a progressively increasing level of difficulty. The trainees are allowed to proceed to the next step only after the previous and easier task is accomplished proficiently. This notion also matches the Dreyfus and Dreyfus model of progression of skills performance from novice to master[9]. In a prospective randomized blinded study, Angelo *et al*[5] demonstrated that the PBP protocol, when coupled with the use of a shoulder model simulator and validated metrics, produces superior arthroscopic Bankart repair skills when compared with traditional and simulator-enhanced training methods. It is evident that the integration of simulation-based surgical skills training into educational curriculum using such novel approaches will be more beneficial if certain factors, such as which skills require focus and at what point during the training they should be implemented, could be determined and organized beforehand.

MEASUREMENT OF SKILLS LEARNED IN SIMULATORS

In the process of simulation-based surgical skills training, measurement of trainees' progress in performing surgical procedures and assessment of their levels of proficiency is vital. As Rear Admiral Dr. Grace Hopper stated, "One accurate measurement is worth a thousand expert opinions"[10]. Traditional assessment of surgical proficiency, which has been based on both the observations and personal opinions of experts regarding trainees' performances, will need to be replaced with valid, objective, and standardized techniques for the measurement of the skills learned using simulators.

Current measurement methods include questionnaires, objective structured assessment of technical skills (OSATS) and global rating scale of performance (GRS) scoring systems, structured assessments using video recording, motion tracking, and direct metric measurement of task performance. Although questionnaires can be practical and low-cost assessment tools, their inherent shortcomings are subjectivity and unfeasibility in terms of standardization. Further, comfort or knowledge questionnaires as proficiency measures in surgical procedures are not validated instruments[11]. OSATS is performed by independent observers, who evaluate a trainee's performance objectively using a checklist of specific surgical maneuvers that have been deemed essential to the procedure (*e.g*., measuring the screw length with depth gauge, verifying screw lengths, ensuring that screws securely engage the far cortex, *etc*.); GRS aims to measure characteristic surgical behaviors during the performance of any given procedure (*e.g*., respect for soft tissues, fluidity of movements, familiarity with the instruments, *etc*.)[2,12]. Hence, subjective criteria included in GRS result in limitations including ambiguity, poor inter-rater reliability, and frequent bias. Video-based feedback is a practical method that enables the assessment of surgical performance using the same measurement tools as OSATS or GRS at a later, convenient time for the rater[13]. However, this means that the shortcomings associated with OSATS and GRS are also relevant to the video-based assessment of simulated surgical skills. Motion tracking and analysis systems can be mounted to surgical tools and attached to or worn on the hands as sensors[14]. They can also be built within a simulator to track and analyze instrument tip trajectory data[15]. Although motion analysis systems might be an objective and valid tool for assessing surgical skills in terms of precision and economy of movements during the performance of simulated surgical procedures, the impact of these metrics on a trainee's skill transfer to the OR has yet to be proven[16,17]. Directly measuring a concrete aspect of a skill using universal metric measurements holds promise for improving reliability, validity, clinical relevance, and applicability in large-scale studies or high-stakes board exams, while decreasing time and expense. Examples of such parameters include the mechanical strength of a knot or a fracture fixation construct; accuracy of reduction; or time to completion of a skill task[18-20].

The abovementioned measurement methods can be used alone or in combination based on the preferences of each research group or institution. Therefore, heterogeneity exists in the literature in terms of available evidence to draw conclusions. Formation of standardized measurement protocols using reliable, valid, and objective metrics are essential before a simulation-based orthopaedic surgery education curriculum can become standard.

STANDARDIZATION OF SIMULATION-BASED CURRICULUM AMONG RESIDENCY AND FELLOWSHIP PROGRAMS

Although simulation-based surgical skills training in dedicated laboratories is already a requirement to learn basic surgical skills during residency in United States, there are no guidelines that each residency program is required to follow. Moreover, there is no requirement to implement simulation-based training in the fellowship period, during which more advanced procedural skills, such as arthroscopic treatment of intraarticular pathologies, are taught.

As an example for standardized curriculum change, the ABOS and the Orthopaedic RRC have taken initial steps by requiring simulation based training during the PGY 1 year. Organizations that focus on education such as American Orthopaedic Association/Council of Orthopaedic Residency Directors, American Academy of Orthopaedic Surgeons or subspecialty societies could develop a more robust simulation curriculum for later years in training. However further mandatory requirements will be necessary to widely incorporate simulation in to curriculum and to uniformly advance the field. It is likely that the accrediting and certifying bodies will want to see solutions to some of the other issues identified in this article before mandating further requirements. It is clear that proposing initiatives is easier said than done. However, improving surgical education and human health is worthy of the required intensive efforts.

CONCLUSION

Orthopaedic surgery requires the comprehensive integration of simulation-based surgical skills training into its educational curriculum. Although efforts are being made toward transitioning into simulation-based educational curriculum, orthopaedic surgery lagged behind other surgical disciplines in simulation. Current obstacles that require further work and research include definition of the areas that need simulation-based skills training in orthopaedic surgery, choosing the optimal time period in orthopaedic training for exposure to simulators; the

correct amount of such exposure; using objective, valid, and reliable metrics to measure the impact of the training on the development and progress of surgical skills; and standardization of the simulation-based curriculum both nationwide and internationally. A successful transition into simulation-based surgical skills training in the orthopaedic educational curriculum will depend on efficacious solutions to these obstacles.

REFERENCES

1 **Roberts KE**, Bell RL, Duffy AJ. Evolution of surgical skills training. *World J Gastroenterol* 2006; **12**: 3219-3224 [PMID: 16718842 DOI: 10.3748/wjg.v12.i20.3219]

2 **Atesok K**, Mabrey JD, Jazrawi LM, Egol KA. Surgical simulation in orthopaedic skills training. *J Am Acad Orthop Surg* 2012; **20**: 410-422 [PMID: 22751160 DOI: 10.5435/JAAOS-20-06-410]

3 **Atesok K**, Satava RM, Van Heest A, Hogan MV, Pedowitz RA, Fu FH, Sitnikov I, Marsh JL, Hurwitz SR. Retention of Skills After Simulation-based Training in Orthopaedic Surgery. *J Am Acad Orthop Surg* 2016; **24**: 505-514 [PMID: 27348146 DOI: 10.5435/JAAOS-D-15-00440]

4 **Seymour NE**, Gallagher AG, Roman SA, O'Brien MK, Bansal VK, Andersen DK, Satava RM. Virtual reality training improves operating room performance: results of a randomized, double-blinded study. *Ann Surg* 2002; **236**: 458-463; discussion 463-464 [PMID: 12368674 DOI: 10.1097/00000658-200210000-00008]

5 **Angelo RL**, Ryu RK, Pedowitz RA, Beach W, Burns J, Dodds J, Field L, Getelman M, Hobgood R, McIntyre L, Gallagher AG. A Proficiency-Based Progression Training Curriculum Coupled With a Model Simulator Results in the Acquisition of a Superior Arthroscopic Bankart Skill Set. *Arthroscopy* 2015; **31**: 1854-1871 [PMID: 26341047 DOI: 10.1016/j.arthro.2015.07.001]

6 **Slade Shantz JA**, Leiter JR, Gottschalk T, MacDonald PB. The internal validity of arthroscopic simulators and their effectiveness in arthroscopic education. *Knee Surg Sports Traumatol Arthrosc* 2014; **22**: 33-40 [PMID: 23052120 DOI: 10.1007/s00167-012-2228-7]

7 **Howells NR**, Gill HS, Carr AJ, Price AJ, Rees JL. Transferring simulated arthroscopic skills to the operating theatre: a randomised blinded study. *J Bone Joint Surg Br* 2008; **90**: 494-499 [PMID: 18378926 DOI: 10.1302/0301-620X.90B4.20414]

8 **Flannery MT**, Villarreal KF. Training using simulation in internal medicine residencies: an educational perspective. *Am J Med Sci* 2015; **349**: 276-278 [PMID: 25705970 DOI: 10.1097/MAJ.0000000000000406]

9 **Dreyfus SE**. The Five-Stage Model of Adult Skill Acquisition. Bulletin of Science, *Technology Society* 2004; **24**: 177-181 [DOI: 10.1177/0270467604264992]

10 **Grace Hopper Quotes**. Accessed August 28, 2016. Available from: URL: http://womenshistory.about.com/od/quotes/a/grace_hopper.htm

11 **Beth Grossman L**, Komatsu DE, Badalamente MA, Braunstein AM, Hurst LC. Microsurgical Simulation Exercise for Surgical Training. *J Surg Educ* 2016; **73**: 116-120 [PMID: 26762839 DOI: 10.1016/j.jsurg.2015.09.003]

12 **Alvand A**, Logishetty K, Middleton R, Khan T, Jackson WF, Price AJ, Rees JL. Validating a global rating scale to monitor individual resident learning curves during arthroscopic knee meniscal repair. *Arthroscopy* 2013; **29**: 906-912 [PMID: 23628663 DOI: 10.1016/j.arthro.2013.01.026]

13 **Karam MD**, Thomas GW, Koehler DM, Westerlind BO, Lafferty PM, Ohrt GT, Marsh JL, Van Heest AE, Anderson DD. Surgical Coaching from Head-Mounted Video in the Training of Fluoroscopically Guided Articular Fracture Surgery. *J Bone Joint Surg Am* 2015; **97**: 1031-1039 [PMID: 26085538 DOI: 10.2106/JBJS.N.00748]

14 **Clinkard D**, Holden M, Ungi T, Messenger D, Davison C, Fichtinger G, McGraw R. The development and validation of hand motion analysis to evaluate competency in central line catheterization. *Acad Emerg Med* 2015; **22**: 212-218 [PMID: 25676530 DOI: 10.1111/acem.12590]

15 **Howells NR**, Brinsden MD, Gill RS, Carr AJ, Rees JL. Motion analysis: a validated method for showing skill levels in arthroscopy. *Arthroscopy* 2008; **24**: 335-342 [PMID: 18308187 DOI: 10.1016/j.arthro.2007.08.033]

16 **Stefanidis D**, Yonce TC, Korndorffer JR, Phillips R, Coker A. Does the incorporation of motion metrics into the existing FLS metrics lead to improved skill acquisition on simulators? A single blinded, randomized controlled trial. *Ann Surg* 2013; **258**: 46-52 [PMID: 23470570 DOI: 10.1097/SLA.0b013e318285f531]

17 **Kowalewski KF**, Hendrie JD, Schmidt MW, Garrow CR, Bruckner T, Proctor T, Paul S, Adigüzel D, Bodenstedt S, Erben A, Kenngott H, Erben Y, Speidel S, Müller-Stich BP, Nickel F. Development and validation of a sensor- and expert model-based training system for laparoscopic surgery: the iSurgeon. *Surg Endosc* 2016; Epub ahead of print [PMID: 27604368]

18 **Yehyawi TM**, Thomas TP, Ohrt GT, Marsh JL, Karam MD, Brown TD, Anderson DD. A simulation trainer for complex articular fracture surgery. *J Bone Joint Surg Am* 2013; **95**: e92 [PMID: 23824397 DOI: 10.2106/JBJS.L.00554]

19 **Kho JY**, Johns BD, Thomas GW, Karam MD, Marsh JL, Anderson DD. A Hybrid Reality Radiation-Free Simulator for Teaching Wire Navigation Skills. *J Orthop Trauma* 2015; **29**: e385-e390 [PMID: 26165262 DOI: 10.1097/BOT.0000000000000372]

20 **Zendejas B**, Brydges R, Hamstra SJ, Cook DA. State of the evidence on simulation-based training for laparoscopic surgery: a systematic review. *Ann Surg* 2013; **257**: 586-593 [PMID: 23407298 DOI: 10.1097/SLA.0b013e318288c40b]

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EDITORIAL

Growing spine deformities: Are magnetic rods the final answer?

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Abstract

Treatment paradigms for Early Onset Scoliosis have changed from fusion to fusionless methods as the harmful effects of early fusion on the growing spine and thorax were realized. Magnetic rods are a recent addition to fusionless technology for controlling scoliosis in a growing spine. The clinical evidence base on magnet driven growth rods (MDGR) has accumulated over the last 4 years. It has implications for reduction in the number of repeat surgeries required with similar complications as the traditional growth rods (TGR) and at a higher initial cost. However in terms of patient psyche and avoidance of repeat surgeries which are necessary with the TGR, MDGR treatment works out less expensive in the long run with definitely better patient comfort. The authors look at the available literature coupled with their own experience to discuss the current status, limitations and future prospects for this type of technology.

Key words: Growing spine; Magnet driven growth rods; Magnetic growth rods; Growth rods; Early Onset Scoliosis

Core tip: This editorial focuses on the current status of magnet driven growth rods in the management of Early Onset Scoliosis (EOS). The editorial gives a background of this technology vis a vis the traditional growth rods and looks at the advantages, limitations and complications associated with the magnetic growth rods. Also its effects on lung function and cost comparison with the traditional growth rods is made. The authors attempt to answer the question "Are magnetic growth rods the final answer for EOS?" in the light of the world literature and personal experience on the above subject.

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Progressive Early-Onset Scoliosis (EOS) has remained a management challenge for decades with surgical management themes changing from early operative fusion to the more recent fusionless surgeries. With this there has been an increased interest to find an ideal tool to reach the goal with minimal complications. Desirable characteristics include ease of instrumentation without age restrictions, minimum number of surgeries for curve control or reduction with minimum hardware problems. The advantages and disadvantages of various growth friendly instruments are noted in Table 1.

EVOLUTION OF A NEW IMPLANT

The thought of achieving distraction without repeat surgical interventions started with Takaso *et al*[1]. In 1998 they devised a growing rod that could be elongated with a remote controller. The rod contained a motor with remote control receiver (placed in the abdominal cavity). In their experimental study on induced scoliosis in beagle dogs they could achieve correction of curves by 3 weekly distractions using external remote controller non-invasively with the study animal awake. The limitations of the instrument were size of the outer cylinder of the rod (16 mm) and the site for placement of the remote control receiver.

BEGINNING OF MAGNETIC ERA (MAGNET CONTROLLED GROWING RODS, MCGR)

The very first report of a magnetic rod being used for scoliosis dates back to 2004 when Jean Dubousset and Arnaud developed and used the Phenix device. Arnaud Souberian a French aeronautical engineer adopted the idea from expandable rod for bone tumors[2,3].

The Phenix device consisted of a magnetically controlled extensible rod that was distracted by placing a permanent magnet on the skin over the spine at home. It was first used in 8 paralytic patients. The clinical outcomes of this device were extremely limited. Miladi *et al*[4] reported a limited human experience on them.

Akbarnia *et al*[5] in 2009 presented the first technical note on Ellipse Technology Inc Device, wherein an implantable magnetic rod was distracted by external adjustment device. It was aimed at providing distraction to the spine by non-surgical means.

The next breakthrough came in 2012 when Akbarnia *et al*[5] published their report on MAGEC rod in an experimental study on Yucatan pigs[6]. In this well-designed study, the authors implanted the MAGEC rods designed by Ellipse technologies and compared the results with a sham group. The rod consisted of an actuator that had a magnet and could not be contoured. The proximal and distal parts could be contoured. Distraction was carried out at 7 mm/wk for 7 wk with the help of an external adjustment device. At the end of 10 wk of the study they found a significant difference in the vertebral unit height in experimental (MAGEC rod) as compared to sham group. There were no rod related complications. Histological data of the para-aortic lymph nodes revealed inflammatory cells in 2/5 in experimental and 1/3 in sham group. No abnormalities were found in liver, spleen and kidney biopsies.

The post implant removal magnetic resonance imaging (MRI) showed healthy discs and the cord was found to be normal. They could achieve 80% of distraction given by the external adjustment device.

INDICATIONS

Magnetic rods have been designed for EOS of varied etiologies including neuromuscular, idiopathic, congenital, *etc*. The indications can be extended to a slightly elder age group up to 12 years in selected cases. Because of the limitations of size of the rod most studies have used the rods after 3 to 4 years of age with scoliosis involving the thoracic spine predominantly. It can be used for the more rigid congenital varieties, the results of distraction may not be favorable, but the fact that the rod can act as an internal brace in itself can be of help in maintaining curvature.

MAGNET CONTROLLED GROWING RODS IN THE RECENT ERA

Many studies have been published in last couple of years showing its efficacy in humans covering various aspects of EOS.

In the very first publication on the experience of MAGEC in humans, Cheung *et al*[7] described the outcomes in 2 (one of Marfan's and other AIS) of the 5 patients who completed 2 years of follow-up. Length of instrumented segment increased by mean of 1.9 mm with each distraction (1.5-2 mm/mo). There were no implant related complications and no patient complained of pain. All the patients were satisfied with the procedure and had a good functional outcome as per the SRS-30 questionnaire. There was only one instance of loss of distraction that was rectified with the rod design.

Subsequent 3 years have seen a burst of papers on MAGEC exploring its efficacy. The first multicenter study of 33 patients by Akbarnia *et al*[8] documented results in 14 cases of EOS (idiopathic, neuromuscular, congenital and neurofibromatosis) treated with MAGEC rod instrumentation. The mean age was 8 year and 10 mo. They compared the results of single *vs* dual rods. The mean improvement in Cobb angles was 46% and 48% respectively in single and dual rods respectively. There was no significant difference in both groups in the average T1-T12 growth but the difference was significant in T1-S1 growth. Partial loss of distraction was the most common complication after 11 of 68 distractions (2 in dual and 9 in single rods). The loss was regained and maintained in subsequent distractions. No other implant related complications were noted. In none of the cases

Table 1 Advantages and disadvantages of various growth friendly instruments

Modality	Advantages	Disadvantages
Traditional growth rods/VEPTR	Fusionless surgery	Repeat surgical distractions, psychological issues
Shilla	Fusionless surgery, no repeat surgeries	Long term results awaited Growth potential dependent
Staple/tether	Less invasive, no repeat surgeries	Limited indications, lesser degree of severity

VEPTR: Vertical Expandable Prosthetic Titanium Rib.

proximal junctional kyphosis was seen[8].

A second landmark paper came from Dannawi *et al*[9] in 2013 with 34 children (mean age 8 years) of EOS with mean Cobb's angle of 69 degrees. At a mean follow-up of 15 mo (12 to 18 mo), both groups single and dual rods, had a statistically significant improvement in mean pre-operative, immediate post operative and final cobb angles and also significant increase in the mean T1-S1 distance. No patient developed a post-operative fusion. The complications met were: Superficial infection and rod breakage in 2 (one in each group), loss of distraction in 2 patients with single rod (rectified subsequently) and hook pull out in one patient with dual rod. Trimming of rod was done in one with hardware prominence. Overall complications were fewer as compared to conventional growth rods.

Hickey in their comparative study of MCGR (magnet controlled growing rods) implantation in primary (mean age 4.5 year, mean Cobb 74 degrees) *vs* revision cases (mean age 10.9 years, Cobb 45 degrees) of EOS found encouraging results in term of maintenance of Cobb angle with comparable increase in the spinal growth (6 mm/year in primary, 12 mm/year in revision cases)[10]. Of the two complications in primary procedure one was rod fracture and the other was proximal screw back out. In the revision group there was loss of distraction in one and failure of distraction in another.

La Rosa *et al*[11], Ridderbusch *et al*[12] and Yılmaz *et al*[13] in their case series of EOS with MCGR found it efficacious in allowing non invasive distraction without repeat surgeries. It achieved spinal growth comparable to conventional growth rod techniques.

Teoh *et al*[14] with the longest follow-up study till date could get a 43% correction of scoliosis in primary cases whereas it was only 2% in the conversion case, but the curves were maintained till the last follow-up.

IMPROVEMENT IN PULMONARY FUNCTION

Yoon *et al*[15], in a study of the effects of MAGEC rod instrumentation on pulmonary function in cases with neuromuscular scoliosis, compared pre-operative FVC and FEV1 to the post-operative values. They found a significant improvement in the post-operative values; they felt that there may not be longitudinal improvement in the function because of the natural course of the neuromuscular etiology, but the benefits of avoidance of repeat anaesthesia and surgery remain.

Harshavardhana *et al*[16] in a prospective study of 26 patients of EOS of various etiologies found the Magnet Driven Growth Rods (MdGR) to be effective in reducing the number of complications and distraction surgeries. They quoted a spectacular improvement of PFT in neuromuscular cases with reduced incidence of chest infections and emergency room admissions for pulmonary ailments.

DISTRACTION FREQUENCY

Three monthly *vs* small more frequent: Akbarnia *et al*[17] studied the effect of frequency of distraction on the outcomes of MCGR. In the more frequent distraction group (weekly to 2 mo) there were more complications of failure of rod distraction and proximal junctional kyphosis as compared to rod breakage and proximal foundation failure which were seen in other group that underwent distraction every 3 to 6 mo.

CONVERSION FROM TRADITIONAL GROWTH RODS TO MAGEC

Keskinen *et al*[18] compared the efficacy of using MdGR in primary *vs* conversion from previously operated traditional growth rods (TGR) and found that scoliosis can be equally controlled after conversion from TGR to MdGR, but the growth from baseline is less in conversion group.

The longest follow-up study (minimum longest follow-up of 44 mo) by Teoh *et al*[14] quotes that the mid term results of MAGEC are not as promising as the short term results. Single rod construct should be avoided and they indicated a caution in using MAGEC in revision cases.

COMPLICATIONS

Choi *et al*[19] in a retrospective multi-centric study of MCGR proposed a classification of complications related to the procedure. Of the 115 operated patients 54 had a minimum 1-year follow-up and were analyzed. They classified complications as wound/implant related and early (< 6 mo) or late > 6 mo. Implant related: (1) rod breakage; (2) failure of lengthening requiring revision surgery; and (3) anchor pull outs. Wound related complications: Surgical site infection (deep) requiring additional surgical intervention.

They summarized complications as: (1) 42% had atleast 1 complication; (2) 15% revision surgery, atleast one; (3) 11% rod breakage (33% early, 66% late); (4) 11% (6)

failure of lengthening, 4 distracted in subsequent visits, 2 rods were exchanged; (5) 13% anchor point problems; and (6) 3.7% (2) deep infection, one each early (drainage and antibiotic)/late (rod penetration, requiring removal of one of the dual rods).

In the longest follow-up study till date Teoh *et al*[14] reported 75% (6/8) patients required revision surgeries, 4 of which were for rod problems and one for proximal junctional kyphosis. Rod failure occurred mainly after 3 years (average 39 mo). All single rod constructs required revision procedure for failure.

Harshavardhana *et al*[16] encountered complications that include 3 single and 1 dual rod breakage, one superficial infection, four cases had proximal junctional kyphosis and distal anchor failure in two patients.

HURDLES

With MCGR emerging as the new hope for EOS as seen from the published articles and early results, it brings along with it its own sets of issues to be tackled. Some limitations are as follows: (1) radiation hazard due to frequent X-rays for monitoring the distraction; (2) MRI compatibility: Due to presence of internal magnet in the rod; and (3) cost.

ULTRASOUND FOR MEASURING DISTRACTION

In an effort to reduce radiation exposure due to repeated X-rays for measuring distractions, Stokes *et al*[20] and Cheung *et al*[21] found a good inter observer and intra observer variability in using ultrasound *vs* X-rays for measurement of distraction of the MCGR's, thus reducing the radiation hazard of frequent radiographs for monitoring distractions. This technique requires training, attention to details and rejection of sub-optimal images. Errors can occur during acquisition of images and selection of reference points. The limitations of this technique are the inability to assess the spinal alignment and integrity of construct. Therefore X-rays can be done at 6 monthly interval to assess these parameters.

MRI COMPATIBILITY

Sturm *et al*[22] in a review article on the management of EOS mention the efficacy of MAGEC and also state that there is no evidence that the electromagnetic field causes any persistent or major side effect with repeated distractions. Although stiffness, spontaneous fusions and diminished returns will also be observed with this technique, avoidance of multiple surgeries is a colossal advantage over TGR.

Budd *et al*[23] presenting their experimental study stated the safety of MRI with the MAGEC rods *in-situ*, *i.e.*, the lengthening mechanism was not triggered. They found no reduction or enhancement in the ability of the rods to lengthen but the rods did produce an artifact in imaging the spine.

COST AS COMPARED TO TGR

Charroin *et al*[24] compared the expenses in TGR *vs* MCGR over a period of 4 years based on a simulation model using assumptions obtained from literature search or their local experience. They found that MCGR procedure induces a strong expense at start, then costs evolve gradually because of the difference of TGR strategy. Despite its major unit cost, their results show that the use of MCGR could lead to lower direct costs with a time horizon of 4 years. Also improvement of quality of life could be indirectly evaluated considering that about 2 surgeries and hospital stays per patient-year could be avoided using MCGR. The limitations of the study included: (1) the basis of estimation of costs, *i.e.*, a simulation model; (2) not taking into account outpatient direct costs and indirect costs such as parent's time off work; and (3) assumptions of long term results of MCGR based on the short term, few published series. Jenks *et al*[25] found equal efficacy of both but the added advantage of MAGEC being a robust cost saving at the end of 6 years. Thus NICE issued a positive recommendation for the use of MAGEC for EOS. Similar recommendations were made by Rolton *et al*[26], Armoiry *et al*[27], with a significant cost saving at the end of 5 years.

WHAT IS THE EVIDENCE?

Evidence based: TGR vs MAGEC

In the first case matched study between traditional growth rods (TGR) and MCGR in 2014 by Akbarnia *et al*[28] they compared 12 MCGR patients to 12 case matched TGR patients. The average follow-up for TGR was 1.6 year more as compared to MCGR who had 2.5 year mean follow-up. Major curve correction, annual T1-T12 and T1-S1 growth was similar in both groups. Incidence of unplanned surgical revisions were similar in both groups but the MCGR patients had 57 fewer surgical procedures. Most of the complications were related to implant failure. In the MCGR group loss of distraction was commonest, 63%, and in the TGR it was anchor pull out and rod breakage.

Jenks *et al*[25] in a meta-analysis of the published literature made provisional recommendations for NICE (National Institute for Health and Care Excellence). These were: (1) MAGEC would avoid repeat surgeries and reduce complications and have benefit for physical and psychological aspects of patient and family; (2) indicated for use in children between ages of 2 to 11; and (3) the system is cost saving as compared to conventional growth rods from about three years after the index procedure.

Figueiredo *et al*[29] based on a systematic review of 6 papers found MCGR to be a safe and effective technique and an alternative to traditional growth rods. There were limitations due to the limitations of existing literature and

Table 2 Single centre series of 10 patients operated by the senior surgeon

Parameter	Mean
Age	10.6 yr
Pre operative Cobb angle	83.1°
Last follow-up	65°
No. distraction/patients	3.4
External remote controller distraction	12.15 mm
Actual distraction	8.9 mm (73.25%)
Follow-up	14.3 mo
Correction mean	18.3°
Percentage correction	21.62%

potential bias in literature due to this novel technique being in early phases.

The shortcomings of MAGEC

The results of MAGEC are promising but follow-up is short and the device technology does not guard against the risk of gradual stiffening of the spine between lengthening sessions and the limitation of the force of magnetic rod to overcome the scoliosis related stiffness in one or two years of use[30].

With the newer long-term studies coming up, we are now coming across specific complications of growing rods *viz*: (1) failure of distraction; (2) fatigue failure of implant; (3) proximal junctional kyphosis; (4) loss of sagittal balance due to non-contourable long actuator; (5) less reliable results on conversion from traditional growth rods to MCGR; and (6) more reliability on dual rods.

In a study on sagittal profile following MCGR in EOS, Akbarnia *et al*[31] showed that the thoracic kyphosis was reduced in cases with pre-existing thoracic kyphosis more than 40 degrees and had no effect on other regional sagittal parameters.

Inaparthy *et al*[32] reported incidence of proximal junctional kyphosis (PJK) in 28% cases of EOS operated with MCGR. It was common in males, all the cases were syndromic in etiology and 50% of them were conversion from traditional growth rods. But the presence of PJK was not an indication for further surgery.

AUTHOR'S EXPERIENCE

We have been using the MAGEC (Ellipse Technologies) since November 2014. In our single centre series of 10 patients operated by the senior surgeon (Dr. Ashok N Johari), 9 cases were of congenital etiology and one neurogenic with associated syringomyelia without neurodeficit. All the patients were females. The data is as shown in Table 2. The mean age at surgery was 10.6 years range (8-13 years). The mean pre operative Cobb's angle was 83.1° and post-operative was 65°, with a mean correction of 21.62%. This correction was maintained till the last follow-up of a mean 14.3 mo (7-21 mo). There were 3.4 distractions per patient with 73.25% (8.9/12.15 mms) distraction achieved *in-situ*.

No patient had any intra-operative complications or neurodeficit post-operatively but we had difficulties instrumenting the spine due to the complex anatomy of the congenital deformities and severe degrees of curvatures. The rods needed significant contouring and almost always we had to use hybrid constructs (hooks and pedicle screws). We had one rod breakage intra-operatively which was managed by using a rod to rod connector from the routine spine instrumentation inventory.

The patients were advised continuous bracing and distraction started 3 mo later at 3 mo interval. We had problems in distraction in one patient which was recovered in subsequent distraction under a setting of mild sedation in operation theatre as the patient was very apprehensive. Later on she had a smooth course of distraction. All the patients were satisfied with the procedure and none complained of pain during distraction.

SO, ARE MAGNETIC RODS THE FINAL ANSWER?

Problems similar to traditional growth rods like infection, anchors site failure/break outs persist with MCGR, except for elimination of repeat surgeries and its consequences. Although MCGR has reduced the number of planned surgeries for distraction, there are incidences of un-planned visits to operation theatre for its own reasons.

These issues need to be addressed before we give a final verdict on MAGEC. The technology still has scope for improvement. Due to its novel approach this technique kindles many a hopes and with traditional growth rods as the only competitor, MAGEC is here to stay till the next major breakthrough in instrumentation techniques.

REFERENCES

1 **Takaso M**, Moriya H, Kitahara H, Minami S, Takahashi K, Isobe K, Yamagata M, Otsuka Y, Nakata Y, Inoue M. New remote-controlled growing-rod spinal instrumentation possibly applicable for scoliosis in young children. *J Orthop Sci* 1998; **3**: 336-340 [PMID: 9811986 DOI: 10.1007/s007760050062]

2 International Congress on Early Onset Scoliosis and Growing Spine, November 7-8, 2008, Montreal, Quebec. Chairman: Behrooz A Akbarnia, MD. *J Child Orthop* 2009; **3**: 145-168 [PMID: 19308626 DOI: 10.1007/s11832-008-0152-7]

3 **Wick JM**, Konze J. A magnetic approach to treating progressive early-onset scoliosis. *AORN J* 2012; **96**: 163-173 [PMID: 22840505 DOI: 10.1016/aorn.2012.05.008]

4 **Miladi L**, Dubousset J. Magnetic powered extensible rod for thorax or spine. In: Akbarnia BA, Yazici M, Thompson GH, eds. The Growing Spine: Management of Spinal Disorders in Young Children. Heidelberg, Berlin, Germany: Springer-Verlag, 2010

5 **Akbarnia BA**, Mundis G, Salari P, Walker B, Pool S, Chang A. A technical report on the Ellipse Technologies device: a remotely expandable device for non-invasive lengthening of growing rod. *J Child Orthop* 2009; **3**: 530-531

6 **Akbarnia BA**, Mundis GM, Salari P, Yaszay B, Pawelek JB. Innovation in growing rod technique: a study of safety and efficacy of a magnetically controlled growing rod in a porcine model. *Spine* (Phila Pa 1976) 2012; **37**: 1109-1114 [PMID: 22146279 DOI: 10.1097/BRS.0b013e318240ff67]

7 **Cheung KM**, Cheung JP, Samartzis D, Mak KC, Wong YW, Cheung WY, Akbarnia BA, Luk KD. Magnetically controlled growing rods for severe spinal curvature in young children: a prospective case series. *Lancet* 2012; **379**: 1967-1974 [PMID: 22520264 DOI: 10.1016/S0140-6736(12)60112-3]

8 **Akbarnia BA**, Cheung K, Noordeen H, Elsebaie H, Yazici M, Dannawi Z, Kabirian N. Next generation of growth-sparing techniques: preliminary clinical results of a magnetically controlled growing rod in 14 patients with early-onset scoliosis. *Spine* (Phila Pa 1976) 2013; **38**: 665-670 [PMID: 23060057 DOI: 10.1097/BRS.0b013e3182773560]

9 **Dannawi Z**, Altaf F, Harshavardhana NS, El Sebaie H, Noordeen H. Early results of a remotely-operated magnetic growth rod in early-onset scoliosis. *Bone Joint J* 2013; **95-B**: 75-80 [PMID: 23307677]

10 **Hickey BA**, Towriss C, Baxter G, Yasso S, James S, Jones A, Howes J, Davies P, Ahuja S. Early experience of MAGEC magnetic growing rods in the treatment of early onset scoliosis. *Eur Spine J* 2014; **23** Suppl 1: S61-S65 [PMID: 24413746 DOI: 10.1007/s00586-013-3163-0]

11 **La Rosa G**, Oggiano L, Ruzzini L. Magnetically Controlled Growing Rods for the Management of Early-onset Scoliosis: A Preliminary Report. *J Pediatr Orthop* 2017; **32**: 79-85 [PMID: 26192879 DOI: 10.1097/BPO.0000000000000597]

12 **Ridderbusch K**, Rupprecht M, Kunkel P, Hagemann C, Stücker R. Preliminary Results of Magnetically Controlled Growing Rods for Early Onset Scoliosis. *J Pediatr Orthop* 2016 May 13; Epub ahead of print [PMID: 27182837 DOI: 10.1097/BPO.0000000000000752]

13 **Yılmaz B**, Ekşi MŞ, Işik S, Özcan-Ekşi EE, Toktaş ZO, Konya D. Magnetically Controlled Growing Rod in Early-Onset Scoliosis: A Minimum of 2-Year Follow-Up. *Pediatr Neurosurg* 2016; **51**: 292-296 [PMID: 27497928 DOI: 10.1159/000448048]

14 **Teoh KH**, Winson DM, James SH, Jones A, Howes J, Davies PR, Ahuja S. Do magnetic growing rods have lower complication rates compared with conventional growing rods? *Spine J* 2016; **16**: S40-S44 [PMID: 26850175 DOI: 10.1016/j.spinee.2015.12.099]

15 **Yoon WW**, Sedra F, Shah S, Wallis C, Muntoni F, Noordeen H. Improvement of pulmonary function in children with early-onset scoliosis using magnetic growth rods. *Spine* (Phila Pa 1976) 2014; **39**: 1196-1202 [PMID: 24825149 DOI: 10.1097/BRS.0000000000000383]

16 **Harshavardhana NS**, Fahmy A, Noordeen H. Surgical results of magnet driven growing rods (MdGR) for early-onset scoliosis (EOS): Single center experience of five years. *Spine Deformity* 2015; **3**: 622 [DOI: 10.1016/j.spine.2015.07.218]

17 **Akbarnia BA**, Cheung KMC, Kwan K, Samartzis D, Alanay A, Ferguson J, Thakr C, Panteliadis P, Nnadi C, Helenius I, Yazicic M, Demirkiran G. Effects of frequency of distraction in magnetically controlled growing rod (McGR) lengthening on outcomes and complications. *Spine J* 2016; **16**: S45-S63 [DOI: 10.1016/j.spinee.2016.01.057]

18 **Keskinen H**, Helenius I, Nnadi C, Cheung K, Ferguson J, Mundis G, Pawelek J, Akbarnia BA. Preliminary comparison of primary and conversion surgery with magnetically controlled growing rods in children with early onset scoliosis. *Eur Spine J* 2016; **25**: 3294-3300 [PMID: 27160822 DOI: 10.1007/s00586-016-4597-y]

19 **Choi E**, Yazsay B, Mundis G, Hosseini P, Pawelek J, Alanay A, Berk H, Cheung K, Demirkiran G, Ferguson J, Greggi T, Helenius I, La Rosa G, Senkoylu A, Akbarnia BA. Implant Complications After Magnetically Controlled Growing Rods for Early Onset Scoliosis: A Multicenter Retrospective Review. *J Pediatr Orthop* 2016 Jun 18; Epub ahead of print [PMID: 27328123 DOI: 10.1097/BPO.0000000000000803]

20 **Stokes OM**, O'Donovan EJ, Samartzis D, Bow CH, Luk KD, Cheung KM. Reducing radiation exposure in early-onset scoliosis surgery patients: novel use of ultrasonography to measure lengthening in magnetically-controlled growing rods. *Spine J* 2014; **14**: 2397-2404 [PMID: 24486476 DOI: 10.1016/j.spinee.2014.01.039]

21 **Cheung JP**, Bow C, Samartzis D, Ganal-Antonio AK, Cheung KM. Clinical utility of ultrasound to prospectively monitor distraction of magnetically controlled growing rods. *Spine J* 2016; **16**: 204-209 [PMID: 26523963 DOI: 10.1016/j.spinee.2015.10.044]

22 **Sturm PF**, Anadio JM, Dede O. Recent advances in the management of early onset scoliosis. *Orthop Clin North Am* 2014; **45**: 501-514 [PMID: 25199421 DOI: 10.1016/j.ocl.2014.06.010]

23 **Budd HR**, Stokes OM, Meakin J, Fulford J, Hutton M. Safety and compatibility of magnetic-controlled growing rods and magnetic resonance imaging. *Eur Spine J* 2016; **25**: 578-582 [PMID: 26272372 DOI: 10.1007/s00586-015-4178-5]

24 **Charroin C**, Abelin-Genevois K, Cunin V, Berthiller J, Constant H, Kohler R, Aulagner G, Serrier H, Armoiry X. Direct costs associated with the management of progressive early onset scoliosis: estimations based on gold standard technique or with magnetically controlled growing rods. *Orthop Traumatol Surg Res* 2014; **100**: 469-474 [PMID: 25128440 DOI: 10.1016/j.otsr.2014.05.006]

25 **Jenks M**, Craig J, Higgins J, Willits I, Barata T, Wood H, Kimpton C, Sims A. The MAGEC system for spinal lengthening in children with scoliosis: A NICE Medical Technology Guidance. *Appl Health Econ Health Policy* 2014; **12**: 587-599 [PMID: 25172432 DOI: 10.1007/s40258-014-0127-4]

26 **Rolton D**, Richards J, Nnadi C. Magnetic controlled growth rods versus conventional growing rod systems in the treatment of early onset scoliosis: a cost comparison. *Eur Spine J* 2015; **24**: 1457-1461 [PMID: 25433541 DOI: 10.1007/s00586-014-3699-7]

27 **Armoiry X**, Abelin-Genevois K, Charroin C, Aulagner G, Cunin V. Magnetically controlled growing rods for scoliosis in children. *Lancet* 2012; **380**: 1229 [PMID: 23040859 DOI: 10.1016/S0140-6736(12)61713-9]

28 **Akbarnia BA**, Pawelek JB, Cheung KMC, Demirkiran G, Elsebaie H, Emans JB, Johnston CE, Mundis GM, Noordeen H, Skaggs DL, Sponseller PD, Thompson GH, Yaszay B, Yazici M, Growing Spine Study Group. Traditional Growth Rods vs magnetically controlled growing rods for the surgical treatment of early-onset scoliosis: a case matched 2 year study. *Spine Deformity* 2014; **2**: 493-497 [DOI: 10.1016/j.jspd.2014.09.050]

29 **Figueiredo N**, Kananeh SF, Siqueira HH, Figueiredo RC, Al Sebai MW. The use of magnetically controlled growing rod device for pediatric scoliosis. *Neurosciences* (Riyadh) 2016; **21**: 17-25 [PMID: 26818162 DOI: 10.17712/nsj.2016.1.20150266]

30 **Cunin V**. Early-onset scoliosis: current treatment. *Orthop Traumatol Surg Res* 2015; **101**: S109-S118 [PMID: 25623270 DOI: 10.1016/J.OTSR.2014.06.032]

31 **Akbarnia BA**, Cheung KMC, Kwan K, Samartzis D, Ferguson J, Tkakar Chrishan, Panteliadis P, Nnadi C, Helenius I, Yazici M, Demirkiran GH, Alanay A. The effect of magnetically controlled growing rod on the sagittal profile in early onset scoliosis patients. Posters. *Spine J* 2016; **16**: S72-S93 [DOI: 10.1016/j.spinee.2016.01.112]

32 **Inaparthy P**, Queruz JC, Bhagawati D, Thakar C, Subramanian T, Nnadi C. Incidence of proximal junctional kyphosis with magnetic expansion control rods in early onset scoliosis. *Eur Spine J* 2016; **25**: 3308-3315 [PMID: 27435487 DOI: 10.1007/s00586-016-4693-z]

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THERAPEUTIC ADVANCES

Syndesmotic *Internal*Brace™ for anatomic distal tibiofibular ligament augmentation

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Author contributions: Regauer M had the idea of syndesmotic *Internal*Brace™, was the treating physician and was responsible for writing the paper and design of illustrations and figures; Mackay G had invented the general *Internal*Brace™ technique and revised the article critically for important intellectual content and correct English language as a native speaker; Lange M was responsible for acquisition of data and helped to design the illustrations and figures; Kammerlander C and Böcker W revised the article critically for important intellectual content and were responsible for the final approval of the version to be published.

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Abstract

Reconstruction of unstable syndesmotic injuries is not trivial, and there is no generally accepted treatment guidelines. Thus, there still remain considerable controversies regarding diagnosis, classification and treatment of syndesmotic injuries. Syndesmotic malreduction is the most common indication for early re-operation after ankle fracture surgery, and widening of the ankle mortise by only 1 mm decreases the contact area of the tibiotalar joint by 42%. Outcome of ankle fractures with syndesmosis injury is worse than without, even after surgical syndesmotic stabilization. This may be due to a high incidence of syndesmotic malreduction revealed by increasing postoperative computed tomography controls. Therefore, even open visualization of the syndesmosis during the reduction maneuver has been recommended. Thus, the most important clinical predictor of outcome is consistently reported as accuracy of anatomic reduction of the injured syndesmosis. In this context the TightRope® system is reported to have advantages compared to classical syndesmotic screws. However, rotational instability of the distal fibula cannot be safely limited by use of 1 or even 2 TightRopes®. Therefore, we developed a new syndesmotic *Internal*Brace™ technique for improved anatomic distal tibiofibular ligament augmentation to protect healing of the injured native ligaments. The *Internal*Brace™ technique was developed by *Gordon Mackay* from Scotland in 2012 using SwiveLocks® for knotless aperture fixation of a FiberTape® at the anatomic footprints of the augmented ligaments, and augmentation of the anterior talofibular ligament, the

deltoid ligament, the spring ligament and the medial collateral ligaments of the knee have been published so far. According to the individual injury pattern, patients can either be treated by the new syndesmotic *Interna*/Brace™ technique alone as a single anterior stabilization, or in combination with one posteriorly directed TightRope® as a double stabilization, or in combination with one TightRope® and a posterolateral malleolar screw fixation as a triple stabilization. Moreover, the syndesmotic *Interna*/Brace™ technique is suitable for anatomic refixation of displaced bony avulsion fragments too small for screw fixation and for indirect reduction of small posterolateral tibial avulsion fragments by anatomic reduction of the anterior syndesmosis with an *Interna*/Brace™ after osteosynthesis of the distal fibula. In this paper, comprehensively illustrated clinical examples show that anatomic reconstruction with rotational stabilization of the syndesmosis can be realized by use of our new syndesmotic *Interna*/Brace™ technique. A clinical trial for evaluation of the functional outcomes has been started at our hospital.

Key words: Syndesmosis injury; Rotational instability; Stabilization; Anatomic repair; *Interna*/Brace™; Surgical technique

Core tip: Reconstruction of unstable syndesmotic injuries is not trivial, and there are no generally accepted treatment guidelines. The TightRope® system is reported to have advantages compared to classical syndesmotic screws. However, rotational instability of the distal fibula is not safely eliminated by use of 1 or even 2 TightRopes®. Therefore, we developed a new syndesmotic *Interna*/Brace™ technique using SwiveLocks® for knotless aperture fixation of a FiberTape® at the anatomic footprints of the injured ligaments for improved anatomic distal tibiofibular ligament augmentation to protect healing of the injured native ligaments.

Regauer M, Mackay G, Lange M, Kammerlander C, Böcker W. Syndesmotic *Interna*/Brace™ for anatomic distal tibiofibular ligament augmentation. *World J Orthop* 2017; 8(4): 301-309 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i4/301.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i4.301

INTRODUCTION

The ligaments stabilizing the syndesmosis prevent excess fibular motion in multiple directions: Anterior-posterior translation, lateral translation, cranio-caudal translation, and internal and external rotation[1]. Appropriate fibular position and limited rotation are necessary for normal syndesmotic function and talar position within the ankle mortise[2]. Reconstruction of unstable syndesmotic injuries is not trivial, and there is no generally accepted treatment guidelines[1,3,4]. Thus, there still remains considerable controversies regarding diagnosis, classification and treatment of syndesmotic injuries[1,5]. Syndesmotic malreduction is the most common indication for early re-operation after ankle fracture surgery, and widening of the ankle mortise by only 1 mm decreases the contact area of the tibiotalar joint by 42%[6-9]. Syndesmotic instability is a strong predictor for less favorable clinical outcomes of ankle fractures, even after surgical syndesmotic stabilization. This may be due to a high incidence of syndesmotic malreduction revealed by increasing postoperative computed tomography (CT) controls[10-14]. Therefore, even open visualization of the syndesmosis during the reduction maneuver has been recommended[13]. Thus, the most important clinical predictor of outcome is consistently reported as accuracy of anatomic reduction of the injured syndesmosis[12,14,15].

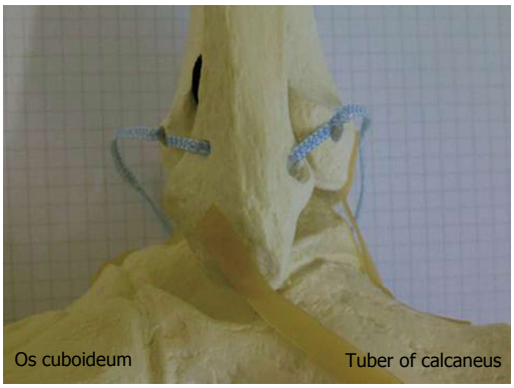

Figure 1 Lateral view on a skeletal model of a left ankle joint: Anatomic augmentation of the anterior and posterior tibiofibular ligament by use of an *Internal*BraceTM technique is simulated.

In this context the TightRope® system (Arthrex®, Naples, United States) is repeatedly reported to have advantages compared to classical syndesmotic screws[12,16-18]. However, rotational instability of the distal fibula cannot be safely limited by standard use of 1 or even 2 TightRopes® as shown by Teramoto *et al*[18] who tried to imitate anatomy by use of different directions of the TightRopes®.

Therefore, we developed a new syndesmotic *Internal*-Brace™ technique using SwiveLocks® (Arthrex®, Naples, United States) for knotless aperture fixation of a FiberTape® (Arthrex®, Naples, United States) directly at the anatomic footprints of the injured ligaments for an optimized imitation of the anatomy of the anterior and posterior syndesmosis to protect healing of the injured native ligaments. Figure 1 shows a simulation of an anatomic augmentation of the anterior and posterior tibiofibular ligament by use of a syndesmotic *Interna*/Brace™ technique in a skeletal model of a left ankle joint.

SYNDESMOTIC *INTERNAL*BRACE™ - THEORY AND PRINCIPLES

The *Internal*Brace™ technique was developed by *Gordon*

Mackay from Scotland in 2012 using SwiveLocks® for knotless aperture fixation of a FiberTape® at the anatomic footprints of the augmented ligaments, and augmentation of the anterior talofibular ligament[19-22], the deltoid ligament[3], the spring ligament[23], and the medial collateral and cruciate ligaments of the knee have been published so far[24-28].

The primary aim of an *Internal*Brace™ is repair of vital tissue rather than reconstruction or replacement with non-vital tendon transplants[3]. Ligament healing should be standard rather than replacement, as the original footprints of ligaments tend to be much larger than tendon grafts could replace. So an important advantage of the the *Internal*Brace™ technique is preservation of proprioception instead of cutting out the ligament remnants. An *Internal*Brace™ acts as a check-rein or as a corner stone to stability just like a seat-belt, and thus the *Internal*Brace™ supports early mobilization of a repaired ligament and allows the natural tissues to progressively strengthen[3,25]. In analogy to fracture repair, an *Internal*Brace™ applies AO principles to soft tissues.

The FiberTape® is a braided ultra-high-molecular-weight polyethylene/polyester suture tape which has an ultimate tensile strength of about 750 N[3]. Until June 2014, when we started to use this new technique, about 732000 FiberTapes® have been sold, and a total of only 95 complications due to FiberTapes® have been reported so far (internal information by Arthrex). According to *Peter Miller* FiberTapes® have been recognized to be "incorporated" after 4 mo in revision shoulder surgery. Taken as a whole, FiberTapes® can be considered very safe implants. Alternative applications of FiberTapes®, SwiveLocks® or the *Internal*Brace™ technique, respectively, are augmentation of the anterolateral ligament of the knee, additional AC-joint stabilization in the horizontal plane, augmentation of the ulnar collateral ligaments for elbow stabilization, or minimally invasive repair of ruptured Achilles tendons[3,29,30].

SYNDESMOTIC *INTERNAL*BRACE™ - SURGICAL TECHNIQUE

Primary feasibility studies in human cadaver models showed that the syndesmotic *Internal*Brace™ technique can be performed easily in a minimally invasive fashion (Figures 2 and 3). A longitudinal incision about 15 mm long was performed at the level of the ankle joint line just a few millimeters anterior and posterior of the distal fibula. An aiming drill guide was used to insert a k-wire into the distal fibula from the anterior to the posterior footprint of the syndesmotic ligaments for creating a bone tunnel using a 2.7 mm cannulated drill (Figure 2A). A FiberTape® was inserted through the bone tunnel until the middle of the tape was inside the tunnel. The FiberTape® was then locked securely inside the bone tunnel of the distal fibula by use of an interference screw (SwiveLock® 3.5 mm) to avoid movements of the tape inside the tunnel with potential sawing effects (Figure 2B). Using the existing approaches, 3.4 mm bone tunnels were drilled at the tibial footprints of the anterior and posterior syndesmotic ligaments identified by fluoroscopy, and after adequate tapping of the bone tunnels and correct positioning of the distal fibula, both free ends of the FiberTape® were fixed into the bone tunnels with a 4.75 mm SwiveLock® (Figure 2C-F). Control of the minimally invasively performed positioning of the implants was possible by extensive opening of the cadaver situs. The view from anterolateral (Figure 3A) and from posterolateral (Figure 3B) on the left ankle joint reveals correct placement of the four anchors for anatomic reduction and augmentation of the anterior and posterior tibiofibular ligaments. Based on these positive results of the feasibility studies we started to use this technique in patients.

According to the individual injury pattern, patients were either treated by the new syndesmotic *Internal*Brace™ technique alone as a single anterior stabilization (Figure 4), or in combination with one posteriorly directed TightRope® as a double stabilization (Figures 5 and 6), or in combination with one TightRope® and a posterolateral malleolar screw fixation as a triple stabilization (Figure 7).

SINGLE ANTERIOR STABILIZATION

Figure 4 shows the clinical example of a 32-year-old female soccer player with acute injury of the anterior syndesmosis after supination-inversion sprain of the right ankle (Figure 4A). We sutured the torn ligament (Figure 4B) and performed a single stabilization of the anterior syndesmosis with a 3.5 mm SwiveLock® at the fibular and a 4.75 mm SwiveLock® at the tibial footprint, respectively (Figure 4C). In case of open surgery, the fibular and tibial footprints can be identified by direct visualization just following the fibers of the injured ligament. Here it is important to avoid distal malpositioning of the SwiveLocks to prevent impinging of the FiberTape® on the anterolateral aspect of the talus. To avoid over-constraining of the anterior syndesmosis a hemostat clamp can be put under the FiberTape® during tensioning. After surgery we performed a CT scan to verify anatomic positioning of the ankle mortise and correct screw placement (Figure 4D).

DOUBLE STABILIZATION

Figure 5 shows a double stabilization with an anterior *Internal*Brace™ and one posteriorly directed TightRope® resulting in a perfect indirect reduction of the small posterolateral avulsion fragment. The 45-year-old male patient sustained a type B ankle fracture with postero-lateral subluxation of the talus due to an avulsion of the posterolateral malleolus (Figures 6A, C, E and G). After standard plate osteosynthesis of the distal fibula the syndesmosis remained unstable, especially when performing external rotation or posterior translation of the distal fibula. Due to the multidirectional instability of

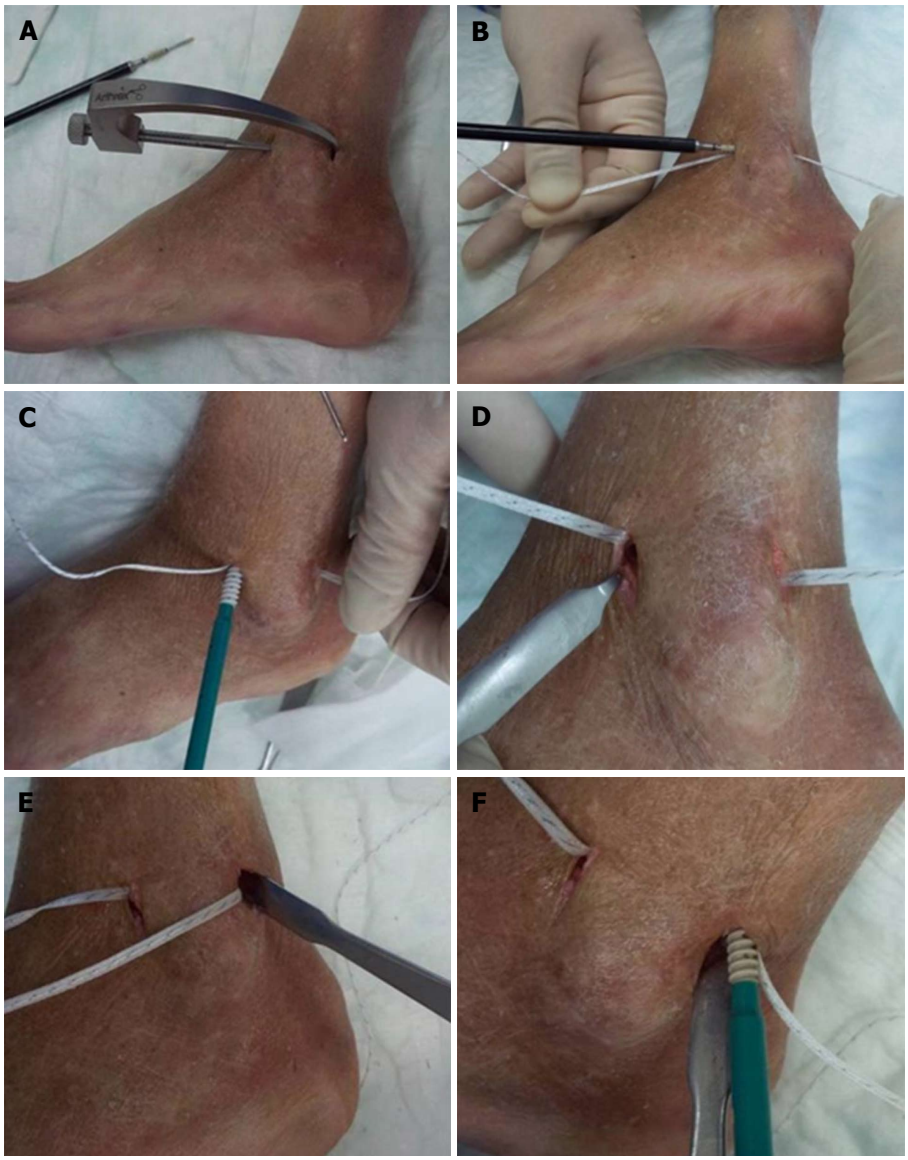

Figure 2 Minimally invasive anatomic augmentation of the anterior and posterior syndesmosis in a cadaver model (A-F). Note: The FiberTape® has to be locked securely inside the bone tunnel of the distal fibula by use of an interference screw to avoid movements of the Tape inside the tunnel with potential sawing effects.

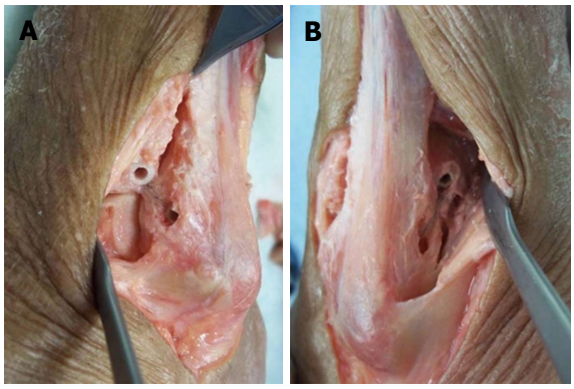

Figure 3 Control of the positioning of the implants by extensive opening of the cadaver situs. View from anterolateral (A) and from posterolateral (B) on a left ankle joint: correct placement of the four anchors for anatomic reduction and augmentation of the anterior and posterior tibiofibular ligament.

the syndesmosis a double stabilization was performed. Here the sequence of stabilization is important: First the anterior stabilization should be performed ensuring anatomic positioning of the distal fibula under direct visualization so that the posteriorly directed second stabilization using the TightRope® will not lead to malreduction. In contrast, not directing the TightRope® posteriorly could lead to malreduction in kind of anterior displacement or malrotation of the distal fibula. To protect the neurovascular bundle the surgeon has to check under fluoroscopy if the aiming k-wire enters the tibia on the lateral side and comes out of the tibia at the medial side, and before overdrilling the k-wire the surgeon has to ensure that the k-wire comes out of the tibia at the medial side anterior to the tendon of the posterior tibial muscle. Figure 6 shows the comparison of preoperative

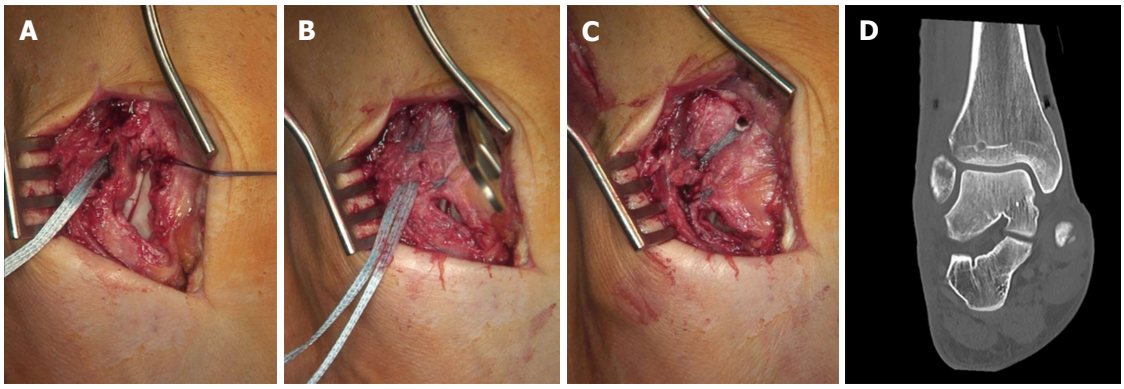

Figure 4 Syndesmotic *Internal*Brace™ for anterior single stabilization after suturing of the disrupted anterior syndesmotic ligament (A-D).

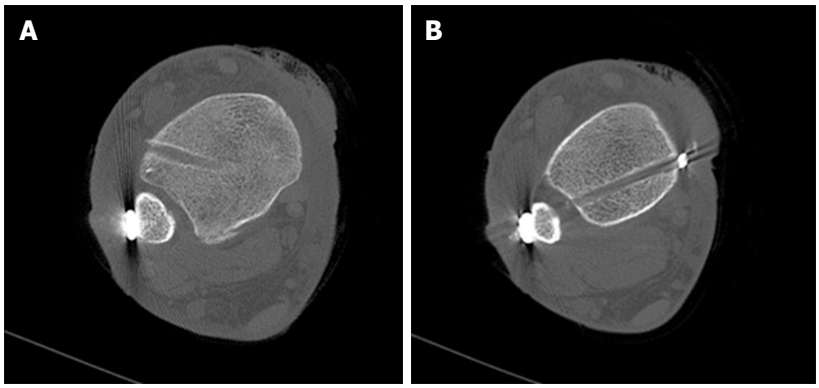

Figure 5 Syndesmotic *Internal*Brace™ for double stabilization by combination with a slightly posteriorly running TightRope® for indirect reduction (A) and stabilization (B) of the fracture of the posterior malleolus.

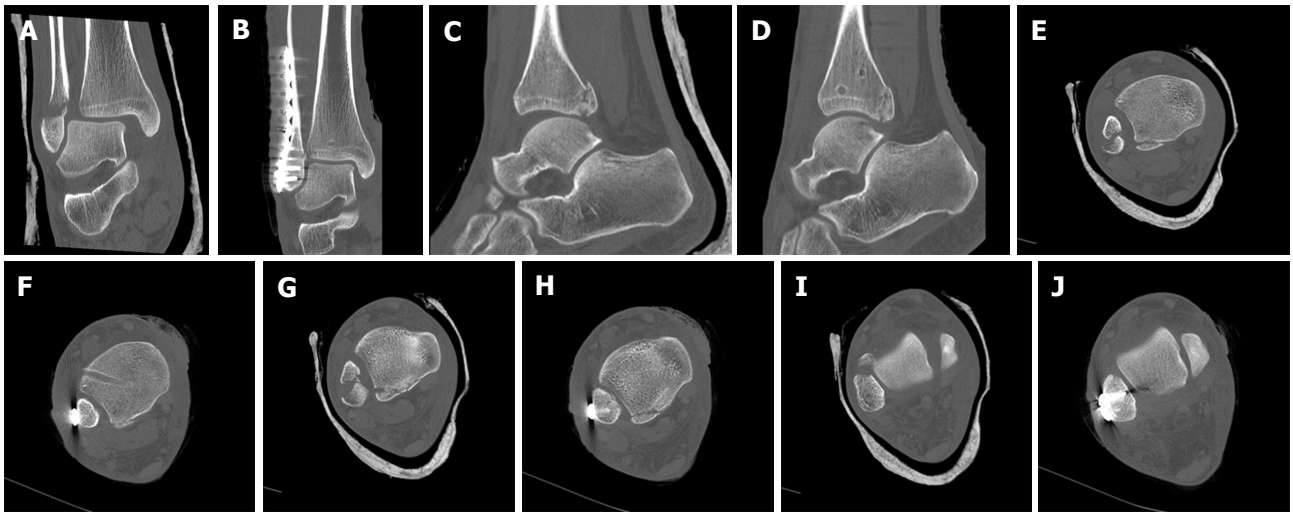

Figure 6 Syndesmotic *Internal*Brace™ for double stabilization. Comparison of preoperative (A, C, E, G, I) and postoperative (B, D, F, H, J) CT scans. Note: anatomic positioning (F, H) and rotation (J) of the distal fibula and indirect anatomic reduction of the fracture of the posterior malleolus (D, F, H).

(left) and postoperative (right) CT scans revealing anatomic positioning (Figure 6F, H) and rotation (Figure 6J) of the distal fibula and indirect anatomic reduction of the fracture of the posterior malleolus (Figure 6D, F and H).

TRIPLE STABILIZATION

Figure 7 shows a syndesmotic *Internal*Brace™ for triple stabilization with an additional posterolateral screw. The 27-year-old male patient sustained a type C Maisonneuve ankle fracture during a mountain bike accident. The anterior syndesmosis was disrupted and the posterolateral malleolus was fractured. The high fibular fracture did not need osteosynthesis. In a first step, the posterior malleolus was directly refixed with a lag screw *via* a posterolateral approach (Figure 7A). Then

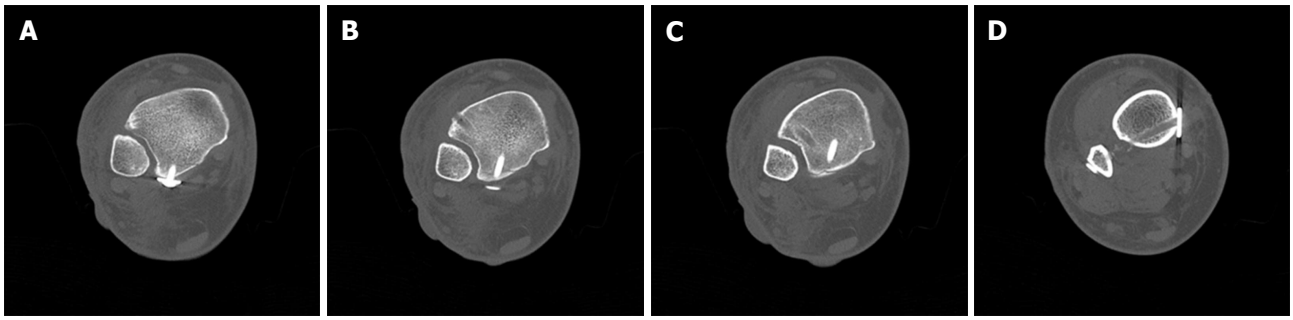

Figure 7 Syndesmotic *Internal*Brace™ for triple stabilization. The posterior malleolus was first directly refixed with a lag screw (A), then the anterior syndesmosis was augmented with an InternalBraceTM under direct view (B, C), and finally the posterolateral screw fixation was augmented by a slightly posteriorly directed TightRope® resulting in a perfect anatomical positioning of the highly unstable distal fibula (D).

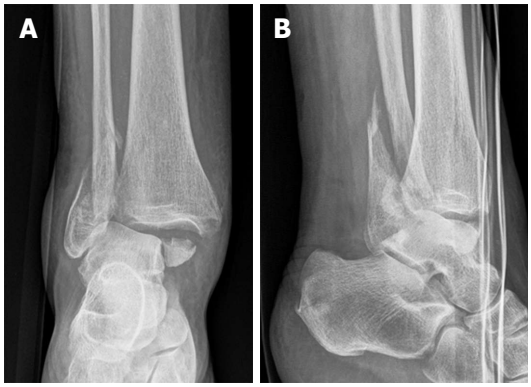

Figure 8 Trimalleolar dislocation fracture of a right ankle joint (A, B).

the anterior syndesmosis was augmented with an *Internal*Brace™ after anatomic reduction of the distal fibula under direct view *via* an anterolateral approach (Figure 7B and C). And finally, the posterolateral screw fixation was augmented by a slightly posteriorly directed TightRope® inserted at a level just above the tibial incisura, resulting in a perfect anatomical positioning of the distal fibula, which initially had been highly unstable due to the Maisonneuve fracture (Figure 7D).

Moreover, we found that the syndesmotic *Internal*-Brace™ technique is quite suitable for anatomic refixation and stabilization of displaced bony avulsion fragments too small for screw fixation. For example, Figure 8 shows X-rays of a 43-year-old male patient who sustained a trimalleolar dislocation fracture of the right ankle joint during a motor bike accident. After immediate closed reduction and cast immobilization, CT scans of the ankle showed tibial avulsion of the anterior tibiofibular ligament with dislocation of a bone fragment (black arrow) too small for screw fixation (Figure 9A). Furthermore, complete closed reduction was not possible due to a small bone fragment (white arrow) interposed between distal tibia and fibula (Figure 9B). Figure 9C and d reveal a displaced avulsion of a small fragment of the posterolateral malleolus. Due to the fracture pattern the patient was treated by open surgery (Figure 10).

The distal fibula and the anterolateral ankle joint were exposed by a lateral approach. Note the small

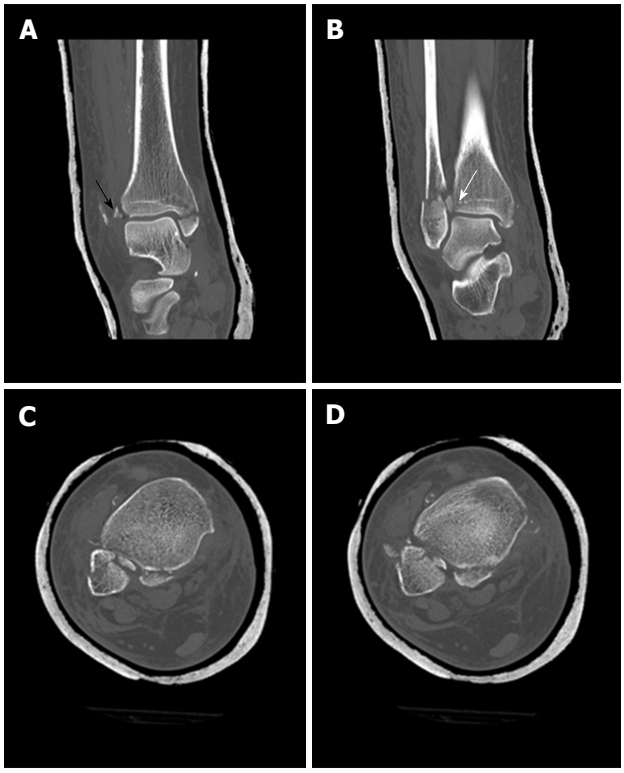

Figure 9 Computed tomography scans of the ankle from Figure 8 showing tibial avulsion of the anterior tibiofibular ligament with dislocation of a bone fragment (black arrow) too small for screw fixation (A), complete closed reduction was not possible due to a small bone fragment (white arrow) interposed between distal tibia and fibula (B), displaced avulsion of a small fragment of the posterolateral malleolus (C, D).

bony tibial avulsion fragment of the anterior tibiofibular ligament (black arrow) and the corresponding avulsion site (white arrow) at the tubercule de Chaput (Figure 10A). After reduction of the avulsion fragment the whole ligament proved to be intact (Figure 10B). After insertion of a FiberTape® about 4 mm proximal and medial of the avulsion site (Figure 10C) with a 4.75 mm SwiveLock®, standard osteosynthesis of the distal fibula was performed using an anatomic preformed locking plate (Arthrex®, Naples, United States). The reduced tibial avulsion fragment was then stabilized with a FiberTape® fixed by the tibial 4.75 mm SwiveLock® and by knots

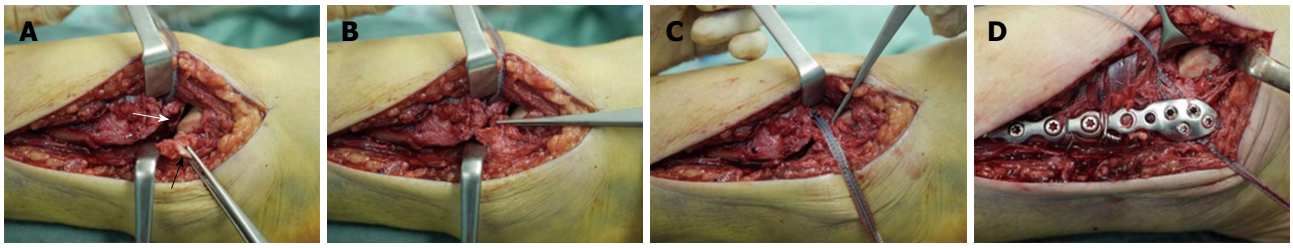

Figure 10 Surgical treatment of the patient from Figure 8. Note the small bony tibial avulsion fragment of the anterior tibiofibular ligament (black arrow) and the corresponding avulsion site (white arrow) at the tubercule de Chaput (A). After reduction of the avulsion fragment the whole ligament proved to be intact (B). Insertion of a FiberTape® about 4 mm proximal and medial of the avulsion site with a 4.75 mm SwiveLock® (C). Standard osteosynthesis of the distal fibula was performed using an anatomic preformed locking plate (Arthrex®, Naples, United States). The reduced tibial avulsion fragment was then stabilized with a FiberTape® fixed by the tibial 4.75 mm SwiveLock® and by knots under the osteosynthesis plate (D).

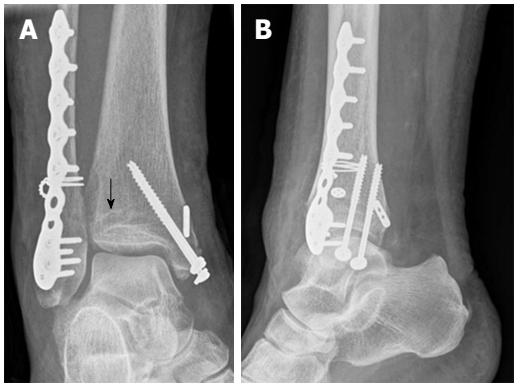

Figure 11 Postoperative X-rays of the ankle from Figure 8 showing anatomic reduction of the syndesmotic injury (A, B). The tibial bone tunnel for the InternalBraceTM visible (black arrow).

under the osteosynthesis plate.

Postoperative X-rays of the ankle showed anatomic reduction of the syndesmotic injury (Figure 11). The tibial bone tunnel for the *Internal*Brace™ is clearly visible (black arrow). Postoperative CT scans in Figure 12 revealed anatomic reduction of the tibial avulsion (white arrows) of the anterior tibiofibular ligament (Figure 12A and C) as well as anatomic reduction of the ankle mortise (Figure 12D). The tibial bone tunnel (black arrows) for the *Internal*Brace™ is clearly visible (Figure 12A and B).

In the field of surgical treatment for unstable syndesmotic injuries, intraoperative testing of the stability of the syndesmosis still remains a major problem, and a normal classical hook test is not sufficient to exclude a clinically relevant syndesmotic instability[31]. Figure 13 shows an example of an intraoperative testing of syndesmotic stability after distal fibula plating of a type B ankle fracture: The classical hook test (Figure 13A and B) shows no lateral translation of the distal fibula while pulling the distal fibula laterally and pushing the distal tibia medially, indicating a normal result without syndesmotic instability. However, the same ankle joint shows relevant rotational instability of the anterior tibiofibular ligament (Figure 13C and D) indicating the need for surgical stabilization. Intraoperative testing of syndesmotic rotational stability under direct visualization after distal fibula plating using a mounted drill bit for locking screws is shown in Figure 14. The ankle joint

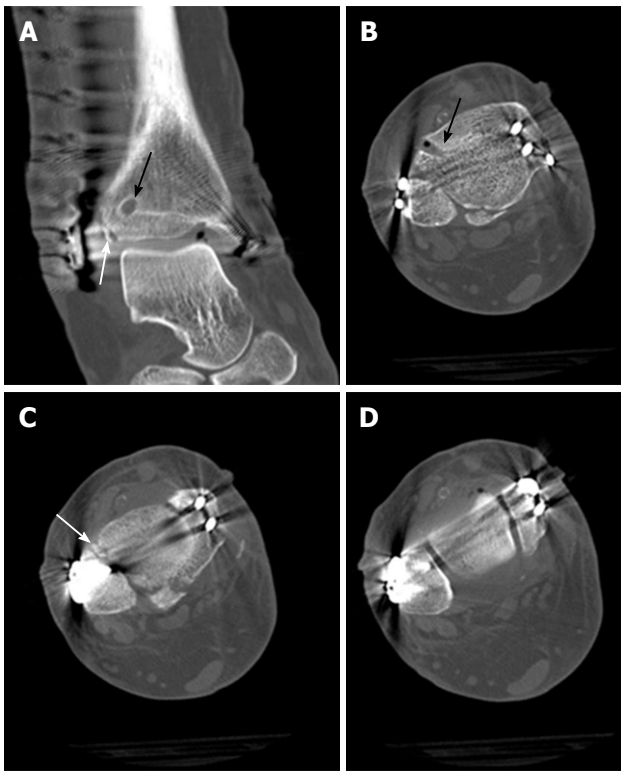

Figure 12 Postoperative computed tomography scans of the ankle from Figure 8 showing anatomic reduction of the tibial avulsion (white arrows) of the anterior tibiofibular ligament (A, C) as well as anatomic reduction of the ankle mortise (D); the tibial bone tunnel (black arrows) for the *Internal*Brace™ is clearly visible (A, B).

shows relevant external rotational instability of the anterior tibiofibular ligament (Figure 14B) indicating the need for surgical stabilization. Note the clear opening of the star figure (white arrow) normally built by the tibiofibular, tibiotalar and talofibular joint lines (black arrow) by external rotation of the distal fibula (Figure 14B). Due to the well-known problems of fluoroscopic intraoperative stability testing of the syndesmosis reported in the current literature, an open visualization of the syndesmosis during the reduction maneuver and stability testing has recently been recommended[13]. Disadvantages of the described procedures are higher costs of implants and may be an increased surgical time compared to using classical syndesmotic screws.

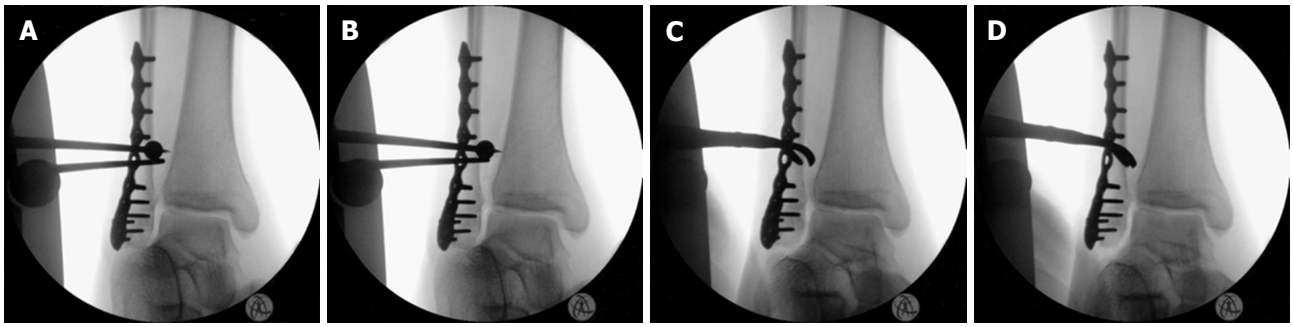

Figure 13 Intraoperative testing of syndesmotic stability after distal fibular plating: The classical hook test (A, B) shows no lateral translation of the distal fibula while pulling the distal fibula laterally and pushing the distal tibia medially, indicating a normal result without syndesmotic instability, however, the same ankle joint shows relevant rotational instability of the anterior tibiofibular ligament (C, D) indicating the need for surgical stabilization.

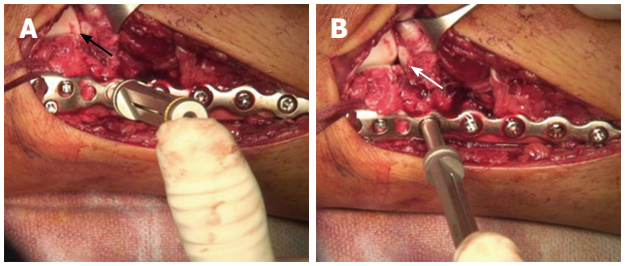

Figure 14 Intraoperative testing of syndesmotic stability after distal fibular plating using a mounted drill bit for locking screws: The ankle joint shows relevant external rotational instability of the anterior tibiofibular ligament (B) indicating the need for surgical stabilization. Note opening (white arrow in B) of the star figure (black arrow in A) normally built by the tibiofibular, tibiotalar and talofibular joint lines by external rotation of the distal fibula (B).

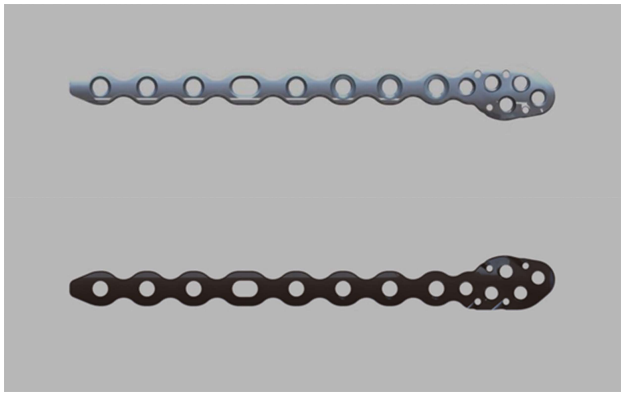

Figure 15 Prototype of a new syndesmosis plate (Arthrex, Naples, United States) with suture holes especially designed for augmentation of the anterior and posterior syndesmosis.

OVER THE HORIZON

Our preliminary clinical results indicate that anatomic reconstruction with rotational stabilization of the syndesmosis can be realized regularly by use of the reported new syndesmotic *Internal*Brace™ technique. A clinical trial for prospective evaluation of the functional outcomes has just been started at our hospital.

And - based on our positive results - a new syndesmosis plate is currently developed with added suture holes for easier mounting of the FiberTapes® for performing a syndesmotic *Internal*Brace™.

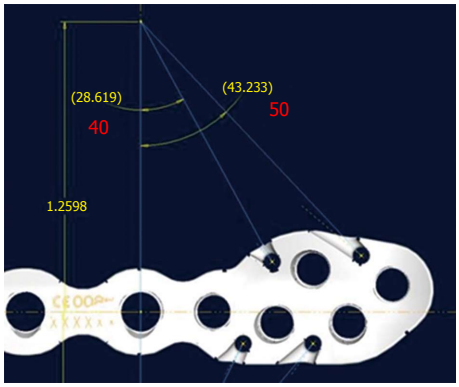

Figure 16 Prototype of a new syndesmosis plate with four suture holes, each combined with a specially designed notch at the inside surface exactly in line with the potential course of the inserted and tensioned FiberTape®.

Figure 15 shows the current prototype of the new syndesmosis plate (Arthrex®, Naples, United States) with suture holes at the distal part especially designed for augmentation of the anterior and posterior syndesmosis. The four suture holes are combined with a specially designed notch at the inside surface (Figure 16) exactly in line with the potential course of the inserted and tensioned FiberTape® to avoid impaired fitting of the plate to the distal fibula. As expected, this new syndesmosis plate will provide another step for improving anatomical stabilization of syndesmotic injuries.

REFERENCES

1 **Hunt KJ**. Syndesmosis injuries. *Curr Rev Musculoskelet Med* 2013; **6**: 304-312 [PMID: 23949902 DOI: 10.1007/s12178-013-9184-9]
2 **Jelinek JA**, Porter DA. Management of unstable ankle fractures and syndesmosis injuries in athletes. *Foot Ankle Clin* 2009; **14**: 277-298 [PMID: 19501807 DOI: 10.1016/j.fcl.2009.03.003]
3 **Mackay GM**, Blyth MJ, Anthony I, Hopper GP, Ribbans WJ. A review of ligament augmentation with the InternalBrace™: the surgical principle is described for the lateral ankle ligament and ACL repair in particular, and a comprehensive review of other surgical applications and techniques is presented. *Surg Technol Int* 2015; **26**: 239-255 [PMID: 26055016]
4 **Bava E**, Charlton T, Thordarson D. Ankle fracture syndesmosis fixation and management: the current practice of orthopedic surgeons. *Am J Orthop* (Belle Mead NJ) 2010; **39**: 242-246 [PMID: 20567742]
5 **van den Bekerom MP**. Diagnosing syndesmotic instability in ankle fractures. *World J Orthop* 2011; **2**: 51-56 [PMID: 22474636

DOI: 10.5312/wjo.v2.i7.51]
6 **Ovaska MT**, Mäkinen TJ, Madanat R, Kiljunen V, Lindahl J. A comprehensive analysis of patients with malreduced ankle fractures undergoing re-operation. *Int Orthop* 2014; **38**: 83-88 [PMID: 24252973 DOI: 10.1007/s00264-013-2168-y]
7 **Hermans JJ**, Beumer A, de Jong TA, Kleinrensink GJ. Anatomy of the distal tibiofibular syndesmosis in adults: a pictorial essay with a multimodality approach. *J Anat* 2010; **217**: 633-645 [PMID: 21108526 DOI: 10.1111/j.1469-7580.2010.01302.x]
8 **Harris J**, Fallat L. Effects of isolated Weber B fibular fractures on the tibiotalar contact area. *J Foot Ankle Surg* 2004; **43**: 3-9 [PMID: 14752757 DOI: 10.1053/j.jfas.2003.11.008]
9 **Ramsey PL**, Hamilton W. Changes in tibiotalar area of contact caused by lateral talar shift. *J Bone Joint Surg Am* 1976; **58**: 356-357 [PMID: 1262367]
10 **Knops SP**, Kohn MA, Hansen EN, Matityahu A, Marmor M. Rotational malreduction of the syndesmosis: reliability and accuracy of computed tomography measurement methods. *Foot Ankle Int* 2013; **34**: 1403-1410 [PMID: 23667049 DOI: 10.1177/1071100713489286]
11 **Gardner MJ**, Demetrakopoulos D, Briggs SM, Helfet DL, Lorich DG. Malreduction of the tibiofibular syndesmosis in ankle fractures. *Foot Ankle Int* 2006; **27**: 788-792 [PMID: 17054878]
12 **Naqvi GA**, Cunningham P, Lynch B, Galvin R, Awan N. Fixation of ankle syndesmotic injuries: comparison of tightrope fixation and syndesmotic screw fixation for accuracy of syndesmotic reduction. *Am J Sports Med* 2012; **40**: 2828-2835 [PMID: 23051785 DOI: 10.1177/0363546512461480]
13 **Sagi HC**, Shah AR, Sanders RW. The functional consequence of syndesmotic joint malreduction at a minimum 2-year follow-up. *J Orthop Trauma* 2012; **26**: 439-443 [PMID: 22357084 DOI: 10.1097/BOT.0b013e31822a526a]
14 **Egol KA**, Pahk B, Walsh M, Tejwani NC, Davidovitch RI, Koval KJ. Outcome after unstable ankle fracture: effect of syndesmotic stabilization. *J Orthop Trauma* 2010; **24**: 7-11 [PMID: 20035171 DOI: 10.1097/BOT.0b013e3181b1542c]
15 **Weening B**, Bhandari M. Predictors of functional outcome following transsyndesmotic screw fixation of ankle fractures. *J Orthop Trauma* 2005; **19**: 102-108 [PMID: 15677926]
16 **Klitzman R**, Zhao H, Zhang LQ, Strohmeyer G, Vora A. Suture-button versus screw fixation of the syndesmosis: a biomechanical analysis. *Foot Ankle Int* 2010; **31**: 69-75 [PMID: 20067726 DOI: 10.3113/FAI.2010.0069]
17 **Coetzee J,** Eberling P. Treatment of syndesmosis disruptions with TightRope fixation. *Tech Foot Ankle Surg* 2008; **7**: 196-201
18 **Teramoto A**, Suzuki D, Kamiya T, Chikenji T, Watanabe K, Yamashita T. Comparison of different fixation methods of the suture-button implant for tibiofibular syndesmosis injuries. *Am J Sports Med* 2011; **39**: 2226-2232 [PMID: 21768530 DOI: 10.1177/0363546511413455]
19 **Yoo JS**, Yang EA. Clinical results of an arthroscopic modified Brostrom operation with and without an internal brace. *J Orthop Traumatol* 2016; **17**: 353-360 [PMID: 27108426 DOI: 10.1007/s10195-016-0406-y]
20 **Waldrop NE**, Wijdicks CA, Jansson KS, LaPrade RF, Clanton TO. Anatomic suture anchor versus the Broström technique for anterior talofibular ligament repair: a biomechanical comparison. *Am J Sports Med* 2012; **40**: 2590-2596 [PMID: 22962291 DOI: 10.1177/0363546512458420]
21 **Viens NA**, Wijdicks CA, Campbell KJ, Laprade RF, Clanton TO. Anterior talofibular ligament ruptures, part 1: biomechanical comparison of augmented Broström repair techniques with the intact anterior talofibular ligament. *Am J Sports Med* 2014; **42**: 405-411 [PMID: 24275864 DOI: 10.1177/0363546513510141]
22 **Clanton TO**, Viens NA, Campbell KJ, Laprade RF, Wijdicks CA. Anterior talofibular ligament ruptures, part 2: biomechanical comparison of anterior talofibular ligament reconstruction using semitendinosus allografts with the intact ligament. *Am J Sports Med* 2014; **42**: 412-416 [PMID: 24280308 DOI: 10.1177/0363546513509963]
23 **Acevedo J**, Vora A. Anatomical reconstruction of the spring ligament complex: "internal brace" augmentation. *Foot Ankle Spec* 2013; **6**: 441-445 [PMID: 23925791 DOI: 10.1177/1938640013499404]
24 **Gilmer BB**, Crall T, DeLong J, Kubo T, Mackay G, Jani SS. Biomechanical Analysis of Internal Bracing for Treatment of Medial Knee Injuries. *Orthopedics* 2016; **39**: e532-e537 [PMID: 27135459 DOI: 10.3928/01477447-20160427-13]
25 **Lubowitz JH,** MacKay G, Gilmer B. Knee medial collateral ligament and posteromedial corner anatomic repair with internal bracing. *Arthrosc Tech* 2014; **3**: e505-508
26 **Heitmann M**, Dratzidis A, Jagodzinski M, Wohlmuth P, Hurschler C, Püschel K, Giannakos A, Preiss A, Frosch KH. [Ligament bracing--augmented cruciate ligament sutures: biomechanical studies of a new treatment concept]. *Unfallchirurg* 2014; **117**: 650-657 [PMID: 24893725 DOI: 10.1007/s00113-014-2563-x]
27 **Heitmann M**, Gerau M, Hötzel J, Giannakos A, Frosch KH, Preiss A. [Ligament bracing--augmented primary suture repair in multiligamentous knee injuries]. *Oper Orthop Traumatol* 2014; **26**: 19-29 [PMID: 24553686 DOI: 10.1007/s00064-013-0263-2]
28 **Smith JO**, Yasen SK, Palmer HC, Lord BR, Britton EM, Wilson AJ. Paediatric ACL repair reinforced with temporary internal bracing. *Knee Surg Sports Traumatol Arthrosc* 2016; **24**: 1845-1851 [PMID: 27141865 DOI: 10.1007/s00167-016-4150-x]
29 **McWilliam JR**, Mackay G. The Internal Brace for Midsubstance Achilles Ruptures. *Foot Ankle Int* 2016; **37**: 794-800 [PMID: 27440059 DOI: 10.1177/1071100716653373]
30 **Cisneros LN**, Reiriz JS. Management of acute unstable acromioclavicular joint injuries. *Eur J Orthop Surg Traumatol* 2016; **26**: 817-830 [PMID: 27541311]
31 **Candal-Couto JJ**, Burrow D, Bromage S, Briggs PJ. Instability of the tibio-fibular syndesmosis: have we been pulling in the wrong direction? *Injury* 2004; **35**: 814-818 [PMID: 15246807 DOI: 10.1016/j.injury.2003.10.013]

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ORIGINAL ARTICLE

Basic Study

Posterior interosseous nerve localization within the proximal forearm - a patient normalized parameter

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Author contributions: Kamineni S and Deane AS designed the research; Kamineni S, Norgren CR and Davidson EM performed the research; Kamineni S and Kamineni EP analyzed the data; Kamineni S, Norgren CR, Kamineni EP and Davidson EM wrote the paper; all authors performed dissection.

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Conflict-of-interest statement: None.

Data sharing statement: None.

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Abstract

AIM

To provide a "patient-normalized" parameter in the proximal forearm.

METHODS

Sixty-three cadaveric upper extremities from thirty-five cadavers were studied. A muscle splitting approach was utilized to locate the posterior interosseous nerve (PIN) at the point where it emerges from beneath the supinator. The supinator was carefully incised to expose the midpoint length of the nerve as it passes into the forearm while preserving the associated fascial connections, thereby preserving the relationship of the nerve with the muscle. We measured the transepicondylar distance (TED), PIN distance in the forearm's neutral rotation position, pronation position, supination position, and the nerve width. Two individuals performed measurements using a digital caliper with inter-observer and intra-observer blinding. The results were analyzed with the Wilcoxon-Mann-Whitney test for paired samples.

RESULTS

In pronation, the PIN was within two confidence intervals of 1.0 TED in 95% of cases (range 0.7-1.3 TED); in neutral, within two confidence intervals of 0.84 TED in 95% of cases (range 0.5-1.1 TED); in supination,

within two confidence intervals of 0.72 TED in 95% of cases (range 0.5-0.9 TED). The mean PIN distance from the lateral epicondyle was 100% of TED in a pronated forearm, 84% in neutral, and 72% in supination. Predictive accuracy was highest in supination; in all cases the majority of specimens (90.47%-95.23%) are within 2 cm of the forearm position-specific percentage of TED. When comparing right to left sides for TEDs with the signed Wilcoxon-Mann-Whitney test for paired samples as well as a significance test (with normal distribution), the *P*-value was 0.0357 (significance - 0.05) indicating a significant difference between the two sides.

CONCLUSION

This "patient normalized" parameter localizes the PIN crossing a line drawn between the lateral epicondyle and the radial styloid. Accurate PIN localization will aid in diagnosis, injections, and surgical approaches.

Key words: Posterior interosseous nerve; Radial nerve; Transepicondylar distance; Radial tunnel syndrome; Supinator syndrome

Core tip: We present a "patient normalized" parameter that localizes posterior interosseous nerve (PIN) crossing point with a line interconnecting the lateral epicondyle and the radial styloid, with the "70-85-100" rule. The mean PIN distance from the lateral epicondyle was 100% of transepicondylar distance (TED) in a pronated forearm, 85% in neutral, and 70% in supination. Predictive accuracy was highest in supination; in all cases the majority of specimens (90.47%-95.23%) are within 2 cm of the forearm position-specific percentage of TED. Non-invasive accurate PIN localization will aid in diagnosis, injections, surgical approaches, and understanding neurological symptoms in the forearm.

Kamineni S, Norgren CR, Davidson EM, Kamineni EP, Deane AS. Posterior interosseous nerve localization within the proximal forearm - a patient normalized parameter. *World J Orthop* 2017; 8(4): 310-316 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i4/310.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i4.310

INTRODUCTION

The radial nerve's localization has been the subject of much concern due to the potential for pathologic[1,2], traumatic[3,4], and iatrogenic[5-7] injuries. Radial nerve localization has been described relative to a distance from various bony landmarks: The acromion and lateral epicondyle[8] proximal to the elbow and the bicipital tuberosity distal to the elbow[9]. The deep radial nerve [posterior interosseous nerve (PIN)] has proven more difficult to localize distal to the elbow. Accurately localizing PIN in the proximal forearm is important when diagnosing nerve compression with physical examination, placing injections at the site of the nerve, accurately exposing the nerve during a surgical exposure[10], and reducing the incidence of iatrogenic nerve injury during surgical interventions[11-17]. Specifically, the surgical repair of open and closed injuries to the elbow/forearm, relief of entrapment neuropathies, and implantation of fixation devices for fracture stabilization all require intimate knowledge of PIN anatomy[8,10,13,17,18]. The general course of PIN has previously been described in detail in relation to muscular anatomy and by using absolute measurement from a bony landmark[8,9,11,14,16,19,20]. These descriptors serve a useful function for the general anatomic understanding of PIN location, but have their limitations. They are limited because muscular anatomy must be defined first, which limits its usefulness to surgical interventions with this capacity, such as open surgical dissection. Descriptors utilizing a specific measurement from a bony landmark can be difficult to use clinically due to body habitus or because the bony landmark is outside of the surgical field. An absolute measurement does not normalize for a particular individual and can lead to erroneous localization. This latter issue is based on the wide range of variability in body sizes. Thus, localization of PIN in the proximal forearm utilizing a patient-normalized parameter is advantageous when dealing with an individual person.

Surgical landmarks traditionally used to localize PIN in the forearm (such as the bicipital tuberosity, articular surface of the posterior supinator head, and the entry and exit points of the supinator muscle) require invasive surgical exploration of the area for accurate use of the parameter[9,11,14,20,21]. The establishment of a non-invasive parameter using external anatomical landmarks would be beneficial by localizing PIN without invasive dissection and could potentially reduce the incidence of iatrogenic PIN injury.

We propose that the transepicondylar distance (TED) are, utilized as a body size descriptor and normalizing feature, can be used as a non-invasive parameter for PIN localization in the proximal forearm. In this study, we calculate PIN distance from the lateral humeral epicondyle as a percentage of TED and examine the predictive accuracy of this parameter in localizing PIN in three forearm positions: Pronation, supination, and neutral. We expect this information will be useful to guide surgical techniques in a more patient-specific manner, which may ultimately reduce surgical morbidities.

MATERIALS AND METHODS

Approval was obtained from the Department of Anatomy in the College of Medicine at our University to collect morphometric data describing PIN position from cadavers. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation.

Cadaver preparation

Skin was removed from 35 cadavers utilizing 63 upper extremities. A muscle splitting approach was utilized to locate PIN at the point where it emerges from beneath the supinator. The supinator was carefully incised to expose the midpoint length of the nerve as it passes into the forearm while preserving the associated fascial connections, thereby preserving the relationship of the nerve with the muscle.

Measurements

TED: The medial and lateral epicondyles of the humerus were palpated to identify the maximum medial and lateral extensions of the humeral epicondyles. The distance between these points was measured using Mityoto digital calipers. Maximum TED was measured on three separate occasions by two separate observers for a total of six measurements.

PIN distance: The distance between the lateral humeral epicondyle apex and the proximal and distal borders of PIN were recorded for each cadaver with the forearm in a pronated, supinated and neutral position along an interconnecting line between the lateral epicondyle and radial styloid tip ("epi-styloid line"). PIN position was measured by establishing the position of the lateral humeral epicondyle and then extending a length of inelastic string (0.5 mm diameter) from that point to the radial styloid process, following the surface contour of the forearm. Distances were recorded from the lateral epicondyle to the proximal intersection of PIN with the string and between the lateral epicondyle and the distal intersection of PIN with the guide string. Proximal and distal PIN positions were each measured on three separate occasions by two observers for a total of six proximal and six distal PIN measurements. PIN distance from the epicondyle was recorded as the distance from the epicondyle to the midpoint between the proximal and distal intersection of PIN with the guide string.

PIN width: The total difference between the proximal and distal intersection of PIN with the guide string.

Summary descriptive statistics (*i.e*., mean, standard deviation, range) were calculated for all individual PIN distance measurements and for all individual PIN distance measurements when calculated as a percentage of TED. We conducted the signed Wilcoxon-Mann-Whitney test for paired samples as well as a significance test (with normal distribution) for paired samples in order to compare difference between right and left sides of TED lengths, pronated position, supinated position, and neutral position. The distances of PIN from the lateral epicondyle, with respect to TED, were plotted with 95%CIs, using normal, long normal, Weibull, and Gamma distributions.

RESULTS

The mean TED for all elbows was 63.59 mm (range 53.0-80 mm). The mean left elbow TED was 62.92 mm (range 53-80 mm), and the mean right TED was 63.97 mm (range 54-77 mm). When comparing right to left sides for TEDs with the signed Wilcoxon-Mann-Whitney test for paired samples as well as a significance test (with normal distribution), the *P*-value was 0.0357 (significance - 0.05) indicating a significant difference between the two sides. However, when comparing the measurements by different observers, as a measure of inter-observer differences of measurements taken, all *P*-values were greater than 0.29 indicating no significance was detected.

Mean radial nerve distances from the lateral epicondyle were greatest when the forearm was in a pronated position [63 mm (range 34.5-80.6 mm)] and least when the forearm was in a supinated position [45.7 mm (33-61.9 mm)]. Mean radial nerve distances when the forearm was in a neutral position [53.5 mm (34.3-70.6 mm)] was intermediate to the values reported for the pronated and supinated forearm (Figure 1).

We calculated the location of PIN along the epi-styloid line as a percentage of TED for that same specimen. In neutral forearm rotation the radial nerve was located at 85% of TED [range 65% (4.1 cm) to 105% (6.6 cm) TED]. In supination it was located at 70% of TED [range 50% (3.15 cm) to 90% (5.7 cm) TED], and in pronation was 100% of TED [range 70% (4.4 cm) to 120% (7.6 cm) TED] (Figure 2).

Radial nerve width (*i.e.*, the distance between the proximal and distal intersection of the nerve with the guide string) was observed to vary across cadavers. Figure 3 represents boxplots of sample median, standard deviation and range for all forearm positions in both the left and right upper limb (Figure 3).

Mean PIN distance as a percentage of TED was greatest when the forearm is pronated (98.7%-101.4%) and least when the forearm was supinated (71.7%-72.6%). Mean PIN distance as a percentage of TED when the forearm was in a neutral position (84.4%-84.7%) were intermediate to the values reported for the pronated and supinated forearm.

PIN distances recorded when the forearm was pronated, supinated, and in neutral rotation were used to predict PIN position relative to the lateral epicondyle. The mean distance between the lateral epicondyle and proximal intersection of PIN and guide string was used to establish predictive lengths for each of the three forearm positions. When the forearm was pronated the mean PIN distance was 100% of TED. In the supinated position the mean PIN distance was 70% of TED. When the arm is in a neutral position the mean posterior interosseous distance was approximately 85% of TED. These percentages were applied to the individual cadavers to establish a "Predictive Value" for PIN localization.

When the arm was pronated PIN was located within 1.5 cm of 1.0 × TED in 71.43% of the specimens and within 2 cm in 90.47% of specimens. The predictive accuracy was highest when the arm was supinated. PIN was identified within 1 cm of 0.7 × TED in 73.01% of

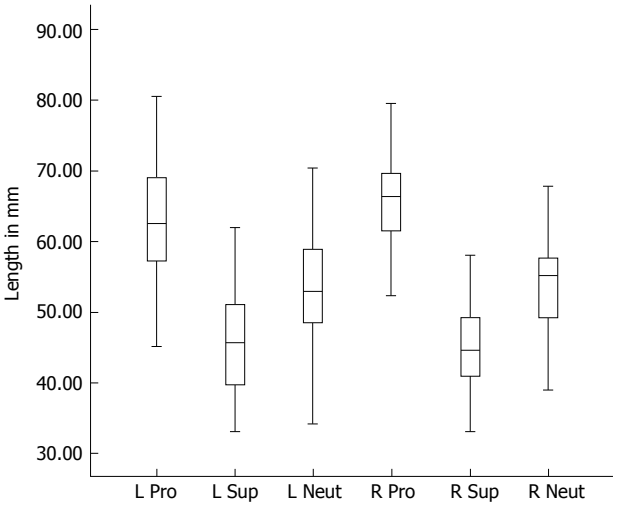

Figure 1 Boxplots of the distance from the humeral epicondyle to the midpoint of the radial nerve (mm) for the left and right forearm in pronated, supinated and neutral positions. Cross bars represent the median value for each group, while the boxes show the 50% confidence interval and the whiskers extend to the highest and lowest values. L: left; R: Right; Pro: Pronated; Sup: Supinated; Neut: Neutral.

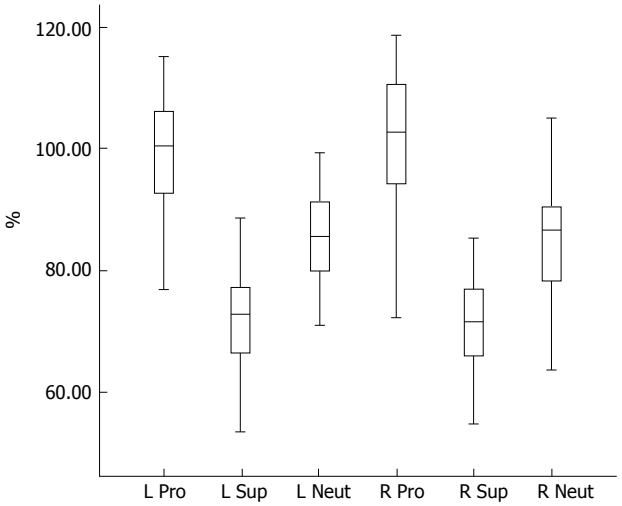

Figure 2 Boxplots of the distance from the humeral epicondyle to the midpoint of the radial nerve (mm) for the left and right forearm in pronated, supinated and neutral positions as expressed as a percentage of transepicondylar distance breadth. Crossbars represent the median value for each group, while the boxes show the 50% confidence interval and the whiskers extend to the highest and lowest values. L: left; R: Right; Pro: Pronated; Sup: Supinated; Neut: Neutral.

cadavers, and within 1.5 cm in 85.7% of cadavers and within 2 cm in 95.23% of cadavers. When the forearm was in neutral rotation PIN was within 1 cm of 0.85 × TED in 63.5% of specimens, 1.5 cm in 84.12%, and within 2 cm in 93.7% of proximal forearms.

DISCUSSION

Our study introduces a non-invasive, patient-normalized parameter for localizing PIN in the proximal forearm within 2 cm of the predicted distance from the lateral humeral epicondyle with 90%-95% accuracy in three positions of forearm rotation. TED has previously been utilized to normalize radial nerve localization proximal to the elbow, to help prevent radial nerve injury when placing pins/screws[22], as has the bicipital tuberosity[9] distal to the elbow. We have demonstrated that the mean PIN distance relative to TED is approximately 85% in neutral (Figure 4), 70% when supinated (Figure 5), and 100% when pronated (Figure 6).

There are several potential limitations to consider when evaluating this "70-85-100" guideline. These issues include the use of cadavers, variable branching patterns, inter-individual differences, and the value of this parameter compared to using absolute values for localization of PIN.

Anatomical investigations often use cadavers for data collection, but some studies use formalin-embalmed cadavers while others use fresh specimens. While it is unclear how the embalming process would significantly alter anatomical relationships, Artico *et al*[8] postulated that differences in the distances of PIN to various landmarks in their study *vs* other literature can be explained by the use of either fresh cadaver specimens or formalin-embalmed cadavers. While fresh cadaver specimens likely preserve normal anatomy more accurately than embalmed ones, we believe the relatively large sample size of our study (n = 63) increases the power of our data such that the correlations we have found are true. However, future research with fresh cadaver specimens may be valuable in supporting or refuting our findings.

There were significant variations in the branching patterns of the deep PIN within the supinator muscle that made localization less precise even though care was taken during the dissection to preserve as much surrounding fascial tissue as possible with minimal disruption of anatomical relationships. This is reflected by the wide ranges of PIN widths (Figure 3) as determined by the distance from the lateral epicondyle to the proximal and distal edges of where the guide string crossed PIN. The inclusion of some, but not all, branches as part of the main PIN trunk led to some subjective interpretation of which branches were "too far" or "too small" to include. Variability in nerve sizes and branching patterns contributed to a wide range of widths which could affect the calculated mean distances of the "midpoint" of the nerve to the lateral epicondyle. A suggestion for future research would be to focus on the "safe zone" of where surgical incisions are less likely to damage PIN or any of its branches as opposed to direct PIN localization.

Intra-individual variation between right and left upper extremities is not well predicted by our "70-85-100" rule. Despite the fact that most people have similar right and left TED's, this does not necessarily mean that their PINs have symmetric courses. Benham *et al*[23] found that there were significant intra-individual differences between the right and left limb in the distance from the

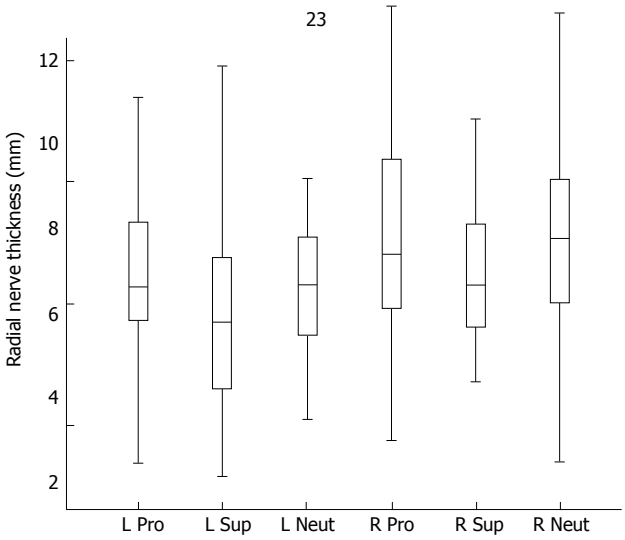

Figure 3 Boxplots of the distance from the proximal to the distal intersection of the radial nerve and the guide string for the left and right forearm in pronated, supinated and neutral positions. Crossbars represent the median value for each group, while the boxes show the 50% confidence interval and the whiskers extend to the highest and lowest values. L: left; R: Right; Pro: Pronated; Sup: Supinated; Neut: Neutral.

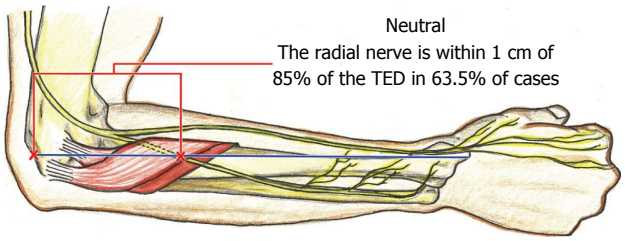

Figure 4 Pictoral depiction of the location of the posterior interosseous nerve, along the longitudinal line drawn from the lateral epicondyle to the radial styloid, at 85% transepicondylar distance, with the forearm in neutral rotation. TED: Transepicondylar distance.

lateral epicondyle to the bifurcation point of PIN into its superficial and deep branches. While this finding may have important clinical implications, it may not be relevant for deep PIN localization because their study uses a different point of measurement and our study found no significant difference between the right and left measurements in any of the three forearm positions. While intra-individual variation may exist at the bifurcation point of the superficial and deep PIN branches, it does not likely play a role in the localization of the deep PIN within the supinator muscle.

TED was measured after skin removal, which resulted in an over-estimation when assessing PIN *in situ*. However, our method provides a good estimation of PIN localization as the effect of skin thickness is likely negligible when using the parameter non-surgically (skin intact state).

Although our proposed localizing parameter is patient-normalized using TED, it may not be any more specific than using the absolute values provided by previous research. It is important to note that our "70-85-100" rule

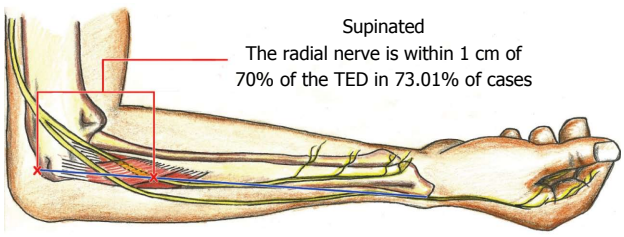

Figure 5 Pictoral depiction of the location of the posterior interosseous nerve, along the longitudinal line drawn from the lateral epicondyle to the radial styloid, at 70 transepicondylar distance, with the forearm in supination. TED: Transepicondylar distance.

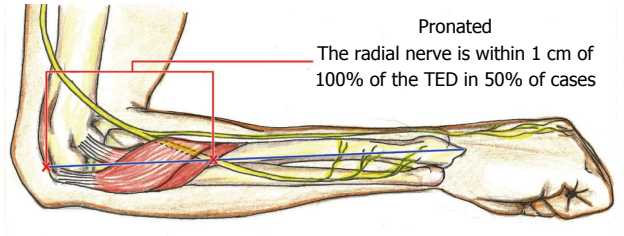

Figure 6 Pictoral depiction of the location of the posterior interosseous nerve, along the longitudinal line drawn from the lateral epicondyle to the radial styloid, at 100% transepicondylar distance, with the forearm in pronation. TED: Transepicondylar distance.

predicts the location of PIN within 1 cm in only 50% of cases when pronated, 63.5% when neutral, and 73.1% when supinated. Only when the range is increased to 2 cm does it include 90%-95% of cases, which is no more specific or accurate than the average values and ranges calculated from numerous specimens. For example, Strauch *et al*[11] found the average distance from the posterior interosseous tuberosity to PIN is 2.3 cm with a total range of only 1.4 cm (1.8 cm-3.2 cm). Witt *et al*[9] discovered the distance from the first branches of PIN to the articular surface of the posterior interosseous head are 6.0 cm ± 1 cm (range 4.0-8.4 cm). Thomas *et al*[14] reported that the bifurcation of PIN into its superficial and deep branches is 8.0 cm ± 1.9 cm distal to the lateral intermuscular septum and 3.6 cm ± 0.7 cm proximal to the leading edge of the supinator (Arcade of Froshe). While these studies use different landmarks, they all have ranges of < 2 cm when reporting absolute values for localizing PIN. Therefore, our patient-normalized parameter may be no more specific or individualized than absolute values for localizing PIN, but it still has the advantage of being non-invasive.

Our study has limitations that should be considered when utilizing it in the clinical setting. These were cadaveric specimens which may differ from patients in their musculoskeletal relationships as a consequence of the preservation procedure. The line connecting the lateral epicondyle and radial styloid was not a projected straight line, but a straight line following the contour of the forearm and may be influenced by the individual bulk of the forearm, which was not investigated in this study. Previous trauma or surgical procedures in the

territory could influence this parameter.

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COMMENTS

Background

The authors describe a simple method, based on cadaveric data and corroborated in clinical practice, of locating the posterior interosseous nerve (PIN) in the proximal forearm. The location of the PIN can be simply summarized by the 70-85-100 rule. They have demonstrated that the location of the PIN from the lateral epicondyle, in terms of the patient's transepicondylar distance (TED) is approximately 70%TED with forearm supination, 85%TED in neutral forearm rotation, and 100%TED when pronated. This will help clinicians to localize the PIN when dealing with a proximal forearm painful differential diagnosis, injections around the PIN for diagnostic and therapeutic purposes, and when surgically approaching the PIN for a decompressive operation.

Research frontiers

The PIN is increasingly recognized as a differential diagnosis and a coexistent pathology in tennis elbow. The ability to locate the PIN accurately in relation to the patient's own anatomy is a very important step towards an accurate diagnosis.

Innovations and breakthroughs

The significant innovation of the study is that they are able to locate the PIN by "normalizing" their measurement to the patient's own anatomy. The authors' normalizing parameter is the TED, which can easily be measured by the clinician.

Applications

The practical application of their study is that it accurately locates the PIN, it normalizes the location of this nerve to the patient's own anatomy, helps in the diagnosis of lateral elbow and forearm pain, improves the localization of diagnostic and therapeutic injections around the PIN, and helps the surgeon decrease in the size of the incision when decompressing the PIN.

Terminology

TED: The distance between the most prominent part of the medial and lateral epicondyle.

Peer-review

This is a very well presented study.

REFERENCES

1 **Jou IM**, Wang HN, Wang PH, Yong IS, Su WR. Compression of the radial nerve at the elbow by a ganglion: two case reports. *J Med Case Rep* 2009; **3**: 7258 [PMID: 19830153 DOI: 10.4076/1752-1947-3-7258]
2 **Nelson G**. Radial nerve compression due to lipoma. *J Vis Commun Med* 2007; **30**: 191-192 [PMID: 18266144 DOI: 10.1080/17453050701822836]
3 **Chesser TJ**, Leslie IJ. Radial nerve entrapment by the lateral intermuscular septum after trauma. *J Orthop Trauma* 2000; **14**: 65-66 [PMID: 10630806 DOI: 10.1097/00005131-200001000-00013]
4 **Banskota A**, Volz RG. Traumatic laceration of the radial nerve following supracondylar fracture of the elbow. A case report. *Clin Orthop Relat Res* 1984; (**184**): 150-152 [PMID: 6705338 DOI: 10.1097/00003086-198404000-00022]
5 **Haapaniemi T**, Berggren M, Adolfsson L. Complete transection of the median and radial nerves during arthroscopic release of post-traumatic elbow contracture. *Arthroscopy* 1999; **15**: 784-787 [PMID: 10524831 DOI: 10.1016/s0749-8063(99)70015-0]
6 **Caldwell JM**, Kim HM, Levine WN. Radial nerve injury associated with application of a hinged elbow external fixator: a report of 2 cases. *J Shoulder Elbow Surg* 2013; **22**: e12-e16 [PMID: 23352546 DOI: 10.1016/j.jse.2012.11.012]
7 **Marcu DM**, Balts J, McCarthy JJ, Kozin SH, Noonan KJ. Iatrogenic radial nerve injury with cannulated fixation of medial epicondyle fractures in the pediatric humerus: a report of 2 cases. *J Pediatr Orthop* 2011; **31**: e13-e16 [PMID: 21307699 DOI: 10.1097/BPO.0b013e318209287d]
8 **Artico M**, Telera S, Tiengo C, Stecco C, Macchi V, Porzionato A, Vigato E, Parenti A, De Caro R. Surgical anatomy of the radial nerve at the elbow. *Surg Radiol Anat* 2009; **31**: 101-106 [PMID: 18795220 DOI: 10.1007/s00276-008-0412-8]
9 **Witt JD**, Kamineni S. The posterior interosseous nerve and the posterolateral approach to the proximal radius. *J Bone Joint Surg Br* 1998; **80**: 240-242 [PMID: 9546452 DOI: 10.1302/0301-620x.80b2.8036]
10 **Ducic I**, Felder JM, Quadri HS. Common nerve decompressions of the upper extremity: reliable exposure using shorter incisions. *Ann Plast Surg* 2012; **68**: 606-609 [PMID: 22643103 DOI: 10.1097/SAP.0b013e31824b3e68]
11 **Strauch RJ**, Rosenwasser MP, Glazer PA. Surgical exposure of the dorsal proximal third of the radius: how vulnerable is the posterior interosseous nerve? *J Shoulder Elbow Surg* 1996; **5**: 342-346 [PMID: 8933455 DOI: 10.1016/S1058-2746(96)80064-4]
12 **Tabor OB**, Bosse MJ, Sims SH, Kellam JF. Iatrogenic posterior interosseous nerve injury: is transosseous static locked nailing of the radius feasible? *J Orthop Trauma* 1995; **9**: 427-429 [PMID: 8537847 DOI: 10.1097/00005131-199505000-00011]
13 **Catalano LW**, Zlotolow DA, Hitchcock PB, Shah SN, Barron OA. Surgical exposures of the radius and ulna. *J Am Acad Orthop Surg* 2011; **19**: 430-438 [PMID: 21724922]
14 **Thomas SJ**, Yakin DE, Parry BR, Lubahn JD. The anatomical relationship between the posterior interosseous nerve and the supinator muscle. *J Hand Surg Am* 2000; **25**: 936-941 [PMID: 11040309 DOI: 10.1053/jhsu.2000.16360]
15 **Lindenhovius AL**, Felsch Q, Ring D, Kloen P. The long-term outcome of open reduction and internal fixation of stable displaced isolated partial articular fractures of the radial head. *J Trauma* 2009; **67**: 143-146 [PMID: 19590324 DOI: 10.1097/TA.0b013e31818234d6]
16 **Heidari N**, Kraus T, Weinberg AM, Weiglein AH, Grechenig W. The risk injury to the posterior interosseous nerve in standard approaches to the proximal radius: a cadaver study. *Surg Radiol Anat* 2011; **33**: 353-357 [PMID: 20803014 DOI: 10.1007/s00276-010-0718-1]
17 **Tornetta P**, Hochwald N, Bono C, Grossman M. Anatomy of the posterior interosseous nerve in relation to fixation of the radial head. *Clin Orthop Relat Res* 1997; (**345**): 215-218 [PMID: 9418643 DOI: 10.1097/00003086-199712000-00031]
18 **Clavert P**, Lutz JC, Adam P, Wolfram-Gabel R, Liverneaux P, Kahn JL. Frohse's arcade is not the exclusive compression site of the radial nerve in its tunnel. *Orthop Traumatol Surg Res* 2009; **95**: 114-118 [PMID: 19297265 DOI: 10.1016/j.otsr.2008.11.001]
19 **Diliberti T**, Botte MJ, Abrams RA. Anatomical considerations regarding the posterior interosseous nerve during posterolateral approaches to the proximal part of the radius. *J Bone Joint Surg Am* 2000; **82**: 809-813 [PMID: 10859100 DOI: 10.2106/00004623-200006000-00007]
20 **Tubbs RS**, Salter EG, Wellons JC, Blount JP, Oakes WJ. Superficial surgical landmarks for identifying the posterior interosseous nerve. *J Neurosurg* 2006; **104**: 796-799 [PMID: 16703886 DOI: 10.3171/jns.2006.104.5.796]
21 **Prasartritha T**, Liupolvanish P, Rojanakit A. A study of the posterior interosseous nerve (PIN) and the radial tunnel in 30 Thai cadavers. *J Hand Surg Am* 1993; **18**: 107-112 [PMID: 8423293 DOI: 10.1016/0363-5023(93)90253-y]

22 **Kamineni S**, Ankem H, Patten DK. Anatomic relationship of the radial nerve to the elbow joint: clinical implications of safe pin placement. *Clin Anat* 2009; **22**: 684-688 [PMID: 19637299 DOI: 10.1002/ca.20831]

23 **Benham A**, Introwicz B, Waterfield J, Sim J, Derricott H, Mahon M. Intra-individual variations in the bifurcation of the radial nerve and the length of the posterior interosseous nerve. *Man Ther* 2012; **17**: 22-26 [PMID: 21903444 DOI: 10.1016/j.math.2011.07.009]

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ORIGINAL ARTICLE

Basic Study

Effect of a specialized injury prevention program on static balance, dynamic balance and kicking accuracy of young soccer players

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Author contributions: Dunsky A designed and coordinated the research, and wrote the paper; Barzilay I performed the majority of experiments; Fox O analyzed the data.

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Conflict-of-interest statement: The authors declare no conflict of interest.

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Abstract

AIM

To study the effect of balance intervention program using the "FIFA 11+" program on static and dynamic balance and kicking accuracy of young soccer players.

METHODS

Twenty young soccer players were allocated to experimental (n = 10) or control (n = 10) groups. The experimental group performed the "FIFA 11+" program three times a week for six weeks. The control group performed their normal warm-up routine. The primary outcomes were measured pre and post intervention, and assessed kicking accuracy, static balance and dynamic balance.

RESULTS

No differences were found in kicking accuracy following intervention, for both groups, however, static balance improved significantly among the experimental group with significant interaction with the control group, and with high effect size. In addition, the dynamic balance of the left leg of the experimental group, with medium effect size for interaction between groups.

CONCLUSION

The large effect size of balance improvement that was observed following six weeks of intervention sessions, implies that soccer trainers and coaches should consider the inclusion of "FIFA 11+" as components of programs aimed at improving balance ability/control in young soccer players, as improvement in balance abilities may prevent injuries.

Key words: Soccer; Injury prevention; Balance; Warm-up; Kicking accuracy

Core tip: The implementation of "FIFA 11+" for six weeks of intervention, led to a large effect size of balance improvement among young soccer players. As improvement in balance abilities may prevent injuries, soccer trainers and coaches should consider the inclusion of "FIFA 11+" as a component of training programs in young soccer players.

Dunsky A, Barzilay I, Fox O. Effect of a specialized injury prevention program on static balance, dynamic balance and kicking accuracy of young soccer players. *World J Orthop* 2017; 8(4): 317-321 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i4/317.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i4.317

INTRODUCTION

Soccer is a sport requiring a plethora of technical skills as well as static, semi-dynamic and dynamic balance. Most of these skills, such as passing, juggling the ball in the air, dribbling or receiving the ball, are achieved through standing on one leg. Balance plays a pivotal role in the harsh conditions, such as pushing opponents, slippery grass, changes to the ball's orbit, moving, facing footballers during a football game[1].

Balance ability has been found to be significantly related to several performances in sport, such as shooting accuracy of archers, pitching accuracy of baseball pitchers, maximum skating speed during ice hockey, and putting accuracy of golfers[2]. While the relationship between balance and accuracy of ball kicking in soccer is randomly reported, it is well known that good balance seems to be effective in neuromuscular control performance[1], and is considered a distinctive characteristic of high level soccer players at the same time[3]. In addition, soccer players have been proved to surpass basketball players in static and dynamic balance and do not differ from gymnasts or dancers[2].

Playing soccer, as with any other sport, entails some risk of injury. With more than 240 million amateur soccer players worldwide, it has the highest participation rate in the world, and it accounts for more than 10% of sport injuries requiring medical attention in adolescents[4,5]. Based on those facts, injury prevention programs should be of major importance for soccer coaches and trainers. Considerable reductions in the number of injured players, ranging between 30% and 70%, have been observed among the teams that implemented the FIFA 11+ program[6].

As poor balance has been correlated to increased risk of injury in athletes[7], it was suggested that a program based on balance improvement may reduce the risk of injury[8].

One suggested program was the "FIFA 11+", which is a complete warm-up package that combines cardiovascular activation and preventive neuromuscular exercises. The key element of the program is the promotion of proper neuromuscular control during all exercises ensuring correct posture and body control, thus it is mainly based on balance control. Recently the "FIFA 11+" was found to induced improvements in neuromuscular control in amateur football players[8], however in another study it was found to have no significant effect on vertical jump tests, sprint running and soccer skill tests in comparison to control condition[9].

To the best of our knowledge, no studies have examined the changes in accuracy of ball kicking among young soccer players induced by the "FIFA 11+". Therefore, the main aim of this study was to examine whether implementing the "FIFA11+" for six weeks as a routine warm-up can improve kicking accuracy as well as static and dynamic balance abilities in young soccer players.

Table 1 Descriptive statistics for anthropometric data of the participants (means and standard deviations)

Variable	Experimental	Control
Age (yr)	12.91 ± 0.26	12.75 ± 0.3
Height (cm)	153.6 ± 7.58	149.7 ± 7.45
Weight (kg)	44.8 ± 6.33	40.7 ± 6.5
Right leg length (cm)	80.4 ± 4.95	76.8 ± 5.05
Left leg length (cm)	79.7 ± 4.57	77.1 ± 4.86

MATERIALS AND METHODS

The study was approved by the Zinman College of Physical Education and Sport Sciences Institutional Review Board.

Participants

Twenty young soccer players who agreed to participate, and had confirmation from their parents, were selected to take part in the study, and were allocated into two groups by their football group for convenience of training routine.

Inclusion criteria for the players were: (1) male amateur players competing in the Official Amateur Championships of the Israeli Football Federation; (2) supervised training 3 times a week for 90 min; (3) no major recent injuries; and (4) good physical condition for completing the baseline measurements.

Descriptive statistics for the group are presented in Table 1.

Intervention

Experimental group: The players completed "The FIFA 11+" (for details see the manual and instructions freely

1	3	1
3	5	3
1	3	1

Figure 1 Scoring grid for the kicking-accuracy protocol.

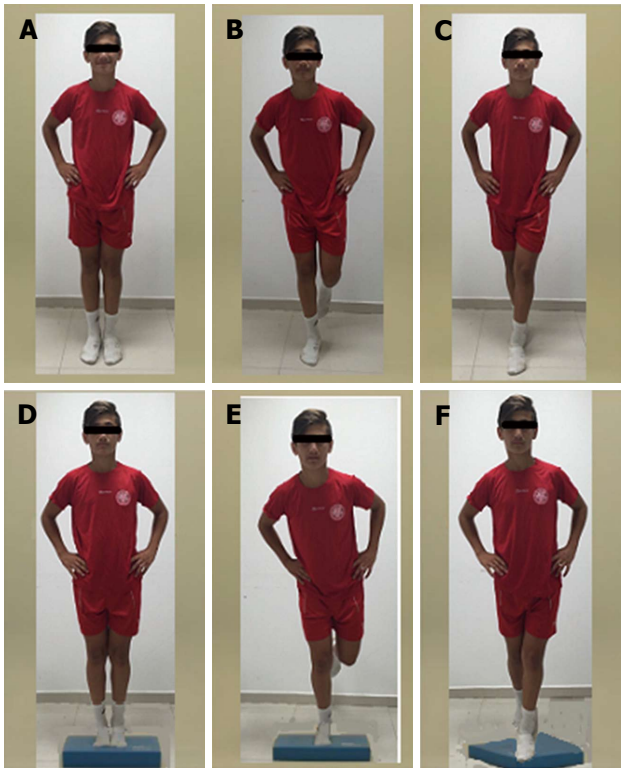

Figure 2 Stances used in Balance Error Scoring System. A: Double-leg stance; B: Single-leg stance; C: Tandem stance; D: Double-leg stance with foam; E: Single leg on foam; F: Tandem stance on foam.

available on the official website: http://f-marc.com/fifa-11-kids/) three times a week for six weeks substituting their normal warm-up routine. In brief, the protocol includes three parts: 8 min of running exercises, 10 min of strength, plyometric and balance exercises, and 2 min of explosive running exercises. From week one to two players performed the level 1, from week three to four they performed the level 2 and from week five to six they performed the level 3.

Control group: The control group received a normal warm-up routine while matching the duration of the "FIFA 11+" (20-25 min). This routine involved a combination of running, stretching, technical exercises with the ball and small-sided games.

The guidance of both groups were performed by the fitness coach who is familiar with the "FIFA 11+".

Assessments

Kicking accuracy: This test was performed based on Currell *et al*[10]. A goalmouth was split into nine equal targets by a series of ropes. Each target was allocated a different score: The center was worth 5 points, around the center 3 points and the corners 1 point (Figure 1). Participants had 10 attempts from 16 m away, using their preferred foot and with the ball being stationary. On the completion of one kick the next immediately followed.

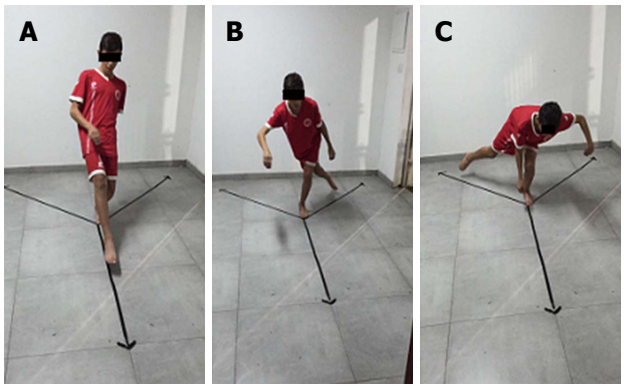

Figure 3 Postures used in the Y Balance Test. A: Y-balance anterior reach; B: Y-balance posteromedial reach; C: Y-balance posterolateral reach.

Balance ability: Static balance - Balance Error Scoring System[11]. This test consists of three stances: Double-leg stance (hands on the hips and feet together), single-leg stance (standing on the non-dominant leg with hands on hips), and a tandem stance (non-dominant foot behind the dominant foot) in a heel-to-toe fashion (Figure 2). The stances are performed on a firm surface and on a foam surface with the eyes closed, with errors counted during each 20-s trial. An error is defined as opening eyes, lifting hands off hips, stepping, stumbling or falling out of position, lifting forefoot or heel, abducting the hip by more than 30°, or failing to return to the test position in more than 5 s. Dynamic balance - The Y Balance Test (YBT) assesses range of motion (ROM), strength, and neuromuscular control of the lower extremity and was chosen to assess the participants' lower limb balance as prior studies have demonstrated its utility as a clinical test to assess for lower limb balance deficits in the athletic population[12]. The participant reaches with one foot in the anterior, posteromedial, and posterolateral directions while standing on the other foot on a centralized stance platform. The test is performed barefoot with both left and right limbs (Figure 3). Following the protocol, each participant was required to perform six practice trials before the three data-collection trials. With the stance-foot toes immediately behind the start line, the participant was instructed to reach as far as he could while maintaining his balance. Each participant was instructed that any of the following activities would constitute a failed attempt, after which an additional trial would be performed: (1) touching the reach foot down before returning to the stance platform under control; or (2) losing balance before returning under control to bilateral stance. The reach distance in each direction was normalized to the limb length (*i.e.*, inferior anterosuperior iliac spine to inferior medial malleolus). The sum of three normalized reach distances was then averaged and

Table 2 Means, standard deviations and analysis of variance comparing performance for kicking accuracy, static balance and dynamic balance

Variable	Experimental		Control		Cohen's *d*
	Pre	Post	Pre	Post	
kicking accuracy	2.69 ± 0.54	3.06 ± 0.72	2.5 ± 0.51	2.82 ± 0.38	0.11
Static balance - BESS	3.52 ± 0.78	3.35 ± 1.04	1.72 ± 0.66	2.94 ± 1.17[1]	1.92
Dynamic balance - YBT-R	0.98 ± 0.07	1.03 ± 0.07	0.97 ± 0.06	1.00 ± 0.04	0.31
Dynamic balance - YBT-L	0.98 ± 0.08	1.04 ± 0.07[2]	0.97 ± 0.06	1.01 ± 0.04	0.32

[1]Significant interaction ($F_{1,18} = 21.05$, $P < 0.01$); [2]Significant improvement ($t = 1.78$, $P = 0.05$). BESS: Balance Error Scoring System; YBT-R: Y Balance Test Right leg; YBT-L: Y Balance Test Left leg.

multiplied by 100 to generate a composite score[3].

Statistical analysis

A repeated measures ANOVA model was employed in order to determine possible statistically significant differences between the measurements and between the experimental and control group.

RESULTS

Both groups showed excellent adherence during the intervention period. More specifically, participants of the experimental group expressed their high enthusiastic about the "FIFA 11+" program, and asked their coach to continue with it.

The differences in kicking accuracy and balance assessments between pre and post intervention for the experimental group and the control group are presented in Table 2. No differences were found in kicking accuracy following intervention, for both groups, however, static balance improved significantly among the experimental group with significant interaction with the control group, and with high effect size. In addition, the dynamic balance of the left leg of the experimental group, with medium effect size for interaction between groups.

DISCUSSION

The results of this study show that the integration of "FIFA 11+" program for six weeks improved both static as well as dynamic balance ability, among young soccer players, but it did not improve the accuracy of kicking. The "FIFA 11+" has been developed for improving neuromuscular control[8], which explains the improvement in balance control among the experimental group in the current study, and also in other studies[8,13]. In addition, the implementation of "FIFA 11+" led to reductions in the number of injured players, ranging between 30% and 70%[6].

Improvement in balance control as measured by the YBT is considered to be important for soccer players, since it is based on the combination of ROM, movement abilities, strength, and proprioception[3]. Thus, improvements found in that assessment may imply better performances during soccer game.

In addition, some researchers investigated the effects of balance training on injury rates reduction concerning soccer players, since soccer is a contact sport associated with a large number of injuries involving adult as well as young players[14]. In that matter, it was found that balance training was associated with reduced number of injuries among soccer players[15,16]. However, Malliou *et al*[15] suggested that for better results of injury prevention, proprioceptive training should be incorporated with the balance training. It is important to mention in this matter, that the prevention of muscular injuries seems multifactorial and would imply nutrition and hydration to optimize performances and recovery, type of grounds, climatic conditions, or still stretching and strengthening protocols to restore limbs muscle imbalance[17], thus, the posibility to predict injuries or to prevent injuries may still considered to be inconclusive.

The fact that the accuracy of kicking was not changed significantly may be explained by the short duration of the intervention, since we found some improvement in that variable, however it was not significant. It is possible that longer period of intervention would lead to significant improvement in kicking accuracy, based on the fact that kicking requires control and exploitation of large reactive forces while the performer preserves stability over a narrow base of support[18].

Another possible explanation for the lack of changes in kicking accuracy is based on the "FIFA 11+" protocol. It is possible that if training protocols were designed to not just prevent injuries but also increase performance, they would lead to higher potential for athlete compliance[9]. The "FIFA 11+" does not contain specific accuracy exercises, however based on the correlations that were found between kicking accuracy and single-leg balance[18], it was suggested that improved balance would lead to improved accuracy. Still, no significant improvement was seen in kicking accuracy among the experimental group in comparison to the control group.

In the current study, the large effect size of balance improvement that was observed following six weeks of intervention sessions implies that soccer trainers and coaches should consider the inclusion "FIFA 11+" as components of programs aimed at improving balance ability/control in young soccer players, as improvement in balance abilities may prevent injuries.

COMMENTS

Background

Playing soccer entails some risk of injury and it accounts for more than 10% of sport injuries requiring medical attention in adolescents. As poor balance has been correlated to increased risk of injury in athletes, it was suggested that a program based on balance improvement might reduce the risk of injury.

Research frontiers

The "FIFA 11+", which is a complete warm-up package that combines cardiovascular activation and preventive neuromuscular exercises, was found to induce improvements in neuromuscular control in amateur football players. The key element of the program is the promotion of proper neuromuscular control during all exercises ensuring correct posture and body control, thus it is mainly based on balance control.

Innovations and breakthroughs

To the best of our knowledge, no studies have examined the changes in both balance as well as accuracy of ball kicking among young soccer players induced by the "FIFA 11+". The major result of the study implies a large effect size of balance improvement following six weeks of intervention sessions, with no significant change in kicking accuracy.

Applications

The large effect size of balance improvement that was observed following six weeks of intervention sessions, implies that soccer trainers and coaches should consider the inclusion of "FIFA 11+" as components of programs aimed at improving balance ability/control in young soccer players, as improvement in balance abilities may prevent injuries.

Terminology

The "FIFA 11+" program - A warm-up program that includes three parts: 8 min of running exercises, 10 min of strength, plyometric and balance exercises, and 2 min of explosive running exercises.

Peer-review

The review has a good level of quality and it is very interesting and adequate.

REFERENCES

1 **Evangelos B,** Georgios K, Konstantinos A, Gissis I, Papadopoulos C, Aristomenis S. Proprioception and balance training can improve amateur soccer players' technical skills. *J Phys Educ Sport* 2012; **12:** 81-89

2 **Hrysomallis C**. Balance ability and athletic performance. *Sports Med* 2011; **41**: 221-232 [PMID: 21395364 DOI: 10.2165/11538560-000000000-00000]

3 **Butler RJ**, Southers C, Gorman PP, Kiesel KB, Plisky PJ. Differences in soccer players' dynamic balance across levels of competition. *J Athl Train* 2012; **47**: 616-620 [PMID: 23182008 DOI: 10.4085/1062-6050-47.5.14]

4 **Emery CA**, Meeuwisse WH, McAllister JR. Survey of sport participation and sport injury in Calgary and area high schools. *Clin J Sport Med* 2006; **16**: 20-26 [PMID: 16377971 DOI: 10.1097/01.jsm.0000184638.72075.b7]

5 **Gstöttner M,** Neher A, Scholtz A, Millonig M, Lembert S, Raschner C. Balance ability and muscle response of the preferred and nonpreferred leg in soccer players. *Motor Control* 2009; **13:** 218-231

6 **Barengo NC**, Meneses-Echávez JF, Ramírez-Vélez R, Cohen DD, Tovar G, Bautista JE. The impact of the FIFA 11+ training program on injury prevention in football players: a systematic review. *Int J Environ Res Public Health* 2014; **11**: 11986-12000 [PMID: 25415209 DOI: 10.3390/ijerph111111986]

7 **Koenig JP,** Puckree T. Injury prevalence, stability and balance among female adolescent. *AJPHERD* 2015; **21:** 92-102

8 **Impellizzeri FM**, Bizzini M, Dvorak J, Pellegrini B, Schena F, Junge A. Physiological and performance responses to the FIFA 11+ (part 2): a randomised controlled trial on the training effects. *J Sports Sci* 2013; **31**: 1491-1502 [PMID: 23855764 DOI: 10.1080/02640414.2013.802926]

9 **Steffen K**, Bakka HM, Myklebust G, Bahr R. Performance aspects of an injury prevention program: a ten-week intervention in adolescent female football players. *Scand J Med Sci Sports* 2008; **18**: 596-604 [PMID: 18208424 DOI: 10.1111/j.1600-0838.2007.00708.x]

10 **Currell K**, Conway S, Jeukendrup AE. Carbohydrate ingestion improves performance of a new reliable test of soccer performance. *Int J Sport Nutr Exerc Metab* 2009; **19**: 34-46 [PMID: 19403952]

11 **Hill C.** Balance Error Scoring System (BESS). *Univ North Carolina's Sport Med Res Lab* 2007: 7

12 **Hudson C**, Garrison JC, Pollard K. Y-balance normative data for female collegiate volleyball players. *Phys Ther Sport* 2016; **22**: 61-65 [PMID: 27583650 DOI: 10.1016/j.ptsp.2016.05.009]

13 **Brito J,** Figueiredo P, Fernandes L, Seabra A, Soares J.M, Krustrup P, Rebelo A. Isokinetic strength effects of FIFA's "the 11 " injury prevention training programme. *Isokinet Exerc Sci* 2010; **18:** 211-215

14 **Peterson L**, Junge A, Chomiak J, Graf-Baumann T, Dvorak J. Incidence of football injuries and complaints in different age groups and skill-level groups. *Am J Sports Med* 2000; **28**: S51-S57 [PMID: 11032108]

15 **Malliou P,** Gioftsidou A, Pafis G, Beneka A, Godolias G. Proprioceptive training (balance exercises) reduces lower extremity injuries in young soccer players. *J Back Musculoskelet Rehabil* 2004; **17**: 101-104 [DOI: 10.3233/BMR-2004-173-403]

16 **Söderman K**, Werner S, Pietilä T, Engström B, Alfredson H. Balance board training: prevention of traumatic injuries of the lower extremities in female soccer players? A prospective randomized intervention study. *Knee Surg Sports Traumatol Arthrosc* 2000; **8**: 356-363 [PMID: 11147154 DOI: 10.1007/s001670000147]

17 **Orchard J**. Is there a relationship between ground and climatic conditions and injuries in football? *Sports Med* 2002; **32**: 419-432 [PMID: 12015804]

18 **Chew-Bullock TS**, Anderson DI, Hamel KA, Gorelick ML, Wallace SA, Sidaway B. Kicking performance in relation to balance ability over the support leg. *Hum Mov Sci* 2012; **31**: 1615-1623 [PMID: 22939850 DOI: 10.1016/j.humov.2012.07.001]

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ORIGINAL ARTICLE

Case Control Study

Abnormal ground reaction forces lead to a general decline in gait speed in knee osteoarthritis patients

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Author contributions: Wiik AV and Cobb J designed the study; Wiik AV collected the clinical data; Wiik AV and Brevadt M analysed the data; Wiik AV, Aqil A, Brevadt M, Jones G and Cobb J interpreted and wrote the report.

Institutional review board statement: Ethical approval was sought and gained prior to commencement of the trial through the research ethics committee (10/H0807/101). All investigations were conducted in conformity with ethical principles of research, and informed consent for participation in the study was obtained. This work was performed at, Imperial College London, Charing Cross Campus, United Kingdom.

Informed consent statement: All study participants provided informed written consent prior to study enrolment.

Conflict-of-interest statement: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Data sharing statement: Extended dataset available from the corresponding author.

Manuscript source: Invited manuscript

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Abstract

AIM

To analyse ground reaction forces at higher speeds using another method to be more sensitive in assessing significant gait abnormalities.

METHODS

A total of 44 subjects, consisting of 24 knee osteoarthritis (OA) patients and 20 healthy controls were analysed. The knee OA patients were recruited from an orthopaedic clinic that were awaiting knee replacement. All subjects had their gait patterns during stance phase at top walking speed assessed on a validated treadmill instrumented with tandem force plates. Temporal measurements and ground reaction forces (GRFs) along with a novel impulse technique were collected for both limbs and a symmetry ratio was applied to all variables to assess inter-limb asymmetry. All continuous variables for each group were compared using a student *t*-test and χ^2 analysis for categorical variables with significance set at $\alpha = 0.05$. Receiver operator characteristics curves were utilised to determine best discriminating ability.

RESULTS

The knee OA patients were older (66 ± 7 years *vs* 53 ±

9 years, P = 0.01) and heavier (body mass index: 31 ± 6 *vs* 23 ± 7, P < 0.001) but had a similar gender ratio when compared to the control group. Knee OA patients were predictably slower at top walking speed (1.37 ± 0.23 m/s *vs* 2.00 ± 0.20 m/s, P < 0.0001) with shorter mean step length (79 ± 12 cm *vs* 99 ± 8 cm, P < 0.0001) and broader gait width (14 ± 5 cm *vs* 11 ± 3 cm, P = 0.015) than controls without any known lower-limb joint disease. At a matched mean speed (1.37 ± 0.23 *vs* 1.34 ± 0.07), ground reaction results revealed that push-off forces and impulse were significantly (P < 0.0001) worse (18% and 12% respectively) for the knee OA patients when compared to the controls. Receiver operating characteristic curves analysis demonstrated total impulse to be the best discriminator of asymmetry, with an area under the curve of 0.902, with a cut-off of -3% and a specificity of 95% and sensitivity of 88%.

CONCLUSION

Abnormal GRFs in knee osteoarthritis are clearly evident at higher speeds. Analysing GRFs with another method may explain the general decline in knee OA patient's gait.

Key words: Gait; Treadmill; Ground reaction forces; Symmetry; Osteoarthritis; Knee

Core tip: Top walking speed may unmask significant abnormalities which would not be seen at slower walking speeds. The use of impulse rather than solitary peaks in the analysis of ground reaction forces may be more sensitive in detecting significant abnormalities in gait.

Wiik AV, Aqil A, Brevadt M, Jones G, Cobb J. Abnormal ground reaction forces lead to a general decline in gait speed in knee osteoarthritis patients. *World J Orthop* 2017; 8(4): 322-328 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i4/322.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i4.322

INTRODUCTION

Difficulty walking is one of the principal symptoms reported by patients with knee osteoarthritis (OA). Analysis of gait symmetry between right and left legs has been shown useful in identifying lower limb joint disease, particularly osteoarthritis[1]. Such data may be useful as a trigger for clinical intervention, given that significant asymmetry may lead to falls, injury to other joints and declining walking activity[2,3].

Previous studies analysing gait symmetry in OA are arguably limited in value by their use of slow speed gait protocols[4], with more recent studies demonstrating that slower speeds are employed as a protective mechanism by the patient, and can disguise the significant gait abnormalities apparent at higher speeds[5]. Furthermore, analysis at faster walking speeds may provide insight into why self-selected walking speed is reduced in knee OA patients, which is of particular interest given that a slow walking speed has been associated with decreased life expectancy[6].

Biomechanical (obesity, joint instability and malalignment) factors play an important role in the development of OA[7,8], and the vertical ground reaction force (GRF) measured in gait laboratories is a useful non-invasive surrogate of internal joint loading[9]. Although repeatable and well described, GRF results are surprisingly variable in the published literature, which is likely due to the uncontrolled variation in walking speed during assessments[5]. Analysing GRF symmetry offers a potential method of removing the effect introduced by variations in speed, given that the patient's normal limb acts as a control when compared to the diseased contralateral limb. Moreover, most studies only use single "peak" data points for GRF during the gait cycle[10], which may fail to capture the variation between subjects afforded by a more detailed analysis.

The aim of the study was to: (1) assess the gait patterns and symmetry of patients with knee OA at top walking speed with the aid of an instrumented treadmill; and (2) apply a new method of assessing ground reaction force symmetry. The null hypothesis was that top walking speed and a new method of analysis would show no differences.

MATERIALS AND METHODS

Participants

A total of 44 subjects, consisting of 24 knee OA patients and 20 healthy controls, were included in this study ethically approved by the joint research office (10/H0807/101). Patients with unilateral symptomatic knee OA awaiting knee arthroplasty were recruited from an orthopaedic knee clinic. All subjects had primary knee osteoarthritis and were cardio-vascularly fit, with no further lower limb or joint disease. Standard pre-operative knee radiographs of the OA patient group were used to assess disease severity using Kellgren and Lawrence (KL) grading[11]. In order to aid validity and interpretation of subsequent data, patients with neurological, medical or other lower limb conditions were excluded, as these variables may also have affected walking ability. This study utilised a control group comprising of healthy staff members, who were free from neurological or joint problems. Test subjects were recruited by a single research assistant. Gait analysis was undertaken using a blinded assessor to avoid testing bias.

Gait analysis and data collection

Gait analysis was performed using a validated treadmill instrumented with tandem piezo-electric force plates (Kistler Gaitway®, Kistler Instrument Corporation, Amherst NY). All participants gave informed consent before treadmill testing began. After an acclimatisation period at 4 km/h, speed was increased incrementally until top

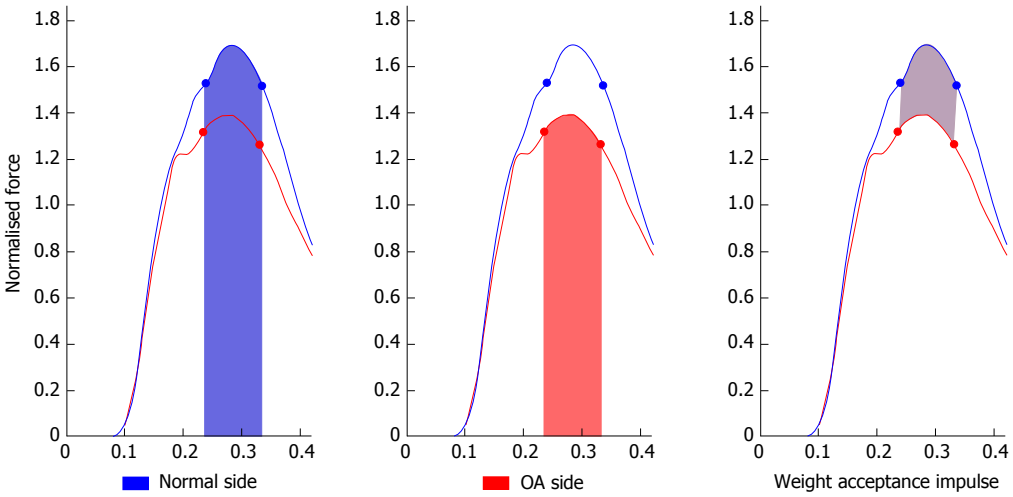

Figure 1 Impulse analysis during weight acceptance: Comparing the knee osteoarthritis limb to the contralateral normal side. OA: Osteoarthritis.

walking speed (TWS) performance had been attained. TWS was defined as the fastest speed a subject could walk without running. All walking measurements were collected without the aid of any props using a standardised testing protocol[12]. Vertical ground reaction forces, centre of pressure (COP) and temporal measurements were collected for both limbs with a sampling frequency of 100 Hz over 10 s. Gait data was subject to averaging by a custom written MATLAB software script as a 10 s interval normally recorded a minimum of 5 steps for each limb. A validated body weight normalising (BWN) was applied to the force results to correct for mass differences[13].

BWN force = Ground reaction force/(body mass × gravity)

The data was further divided into affected (A)/unaffected (UA) limb for the OA group, and right/left limb for the healthy controls. A previously described and validated symmetry ratio (SR)[14], was applied to all variables.

SR= [(XA/XUA) - 1] x 100%

SR values describe the percentage difference between limbs, with zero indicating complete symmetry. Negative values indicated worsening asymmetry with respect to the affected limb in the OA group and the right limb in the control group.

Impulse values were calculated from the vertical GRF data. Impulse takes into account both the magnitude of loading and duration of stance phase of a limb. The total and each phase peak of impulse was assessed on the "M" pattern force curve, comprising weight acceptance (WA) and push-off (PO) impulse. These peaks were identified using a MATLAB script to segment the data, with the limits of integration defined as 5% of force time either side of the maximum value. Figure 1 illustrates the calculation of weight acceptance impulse during stance phase between right and left legs. The same technique was also used for push-off and total impulse used the entire curve.

Statistical analysis

Statistical analysis was performed with SPSS (IBM SPSS Statistics, version 20). For continuous variables between the groups an independent *t*-test was used and for categorical variable (gender), a χ^2 test was used. A significance level of α = 0.05 was employed throughout. Shapiro-Wilk test showed the gait variables to be normally distributed. Variable data is presented as means with standard deviations.

Receiver operating characteristics (ROC) curves were utilised to determine which gait symmetry variables had the best discriminating ability. Categorisation of the area under the curve (AUC) was performed, with AUC above 0.7 determined as fair, above 0.8 good and above 0.9 as excellent discriminating ability[15].

OA patients' top walking speed results were predictably slower than the healthy group, and were hence also compared to the healthy group's preferred walking speed, which was more comparable.

RESULTS

Patient and control characteristics are provided in Table 1. The most common disease severity grade of OA was 2 using Kellgren and Lawrence system. Nineteen patients had medial tibiofemoral OA with an element of patellofemoral OA. Two patients had lateral tibiofemoral OA and remaining three had primarily patellofemoral OA. None of the patients had significant joint bone deformity and an intermediate grade of knee OA can be concluded.

Preferred and top walking speed for the knee OA patients was predictably and significantly slower (P < 0.0001) than the controls (1.09 m/s *vs* 1.34 m/s and 1.37 m/s *vs* 2.00 m/s respectively). Step length was also reduced at TWS (79 cm *vs* 99 cm, P < 0.0001), with a broader gait width (14 cm *vs* 11 cm, P = 0.015) as seen in Table 2. As ground reaction forces are partly speed dependent[16] (Figure 2), analysis comparing the knee OA

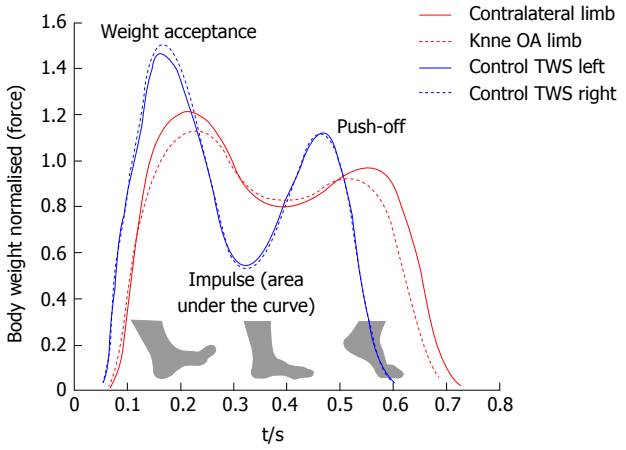

Figure 2 Mean gait patterns during stance phase of controls (blue) and knee osteoarthritis patients (red) at their top walking speed. OA: Osteoarthritis; TWS: Top walking speed.

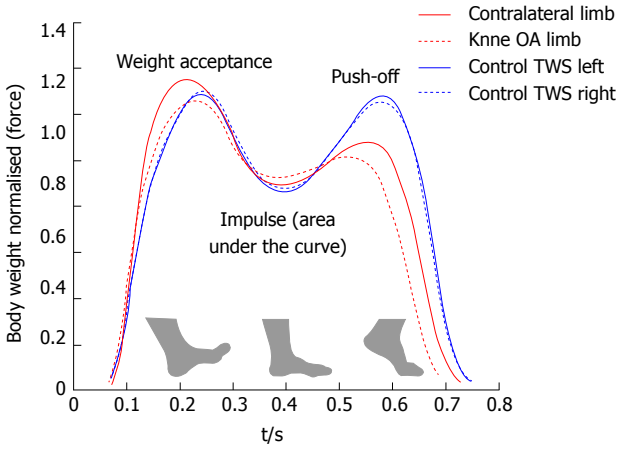

Figure 3 Mean gait patterns during stance phase of controls (blue) and knee osteoarthritis patients (red) at similar speeds. OA: Osteoarthritis; TWS: Top walking speed.

results to the control group's preferred walking speed was done given that they were similar (1.34 m/s *vs* 1.37 m/s $P = 0.56$). Push-off force and total impulse were significantly ($P < 0.0001$) less (22% and 12% respectively) than the controls (Table 2 and Figure 3). This was also seen at the knee OA preferred walking speed, but became more pronounced at top walking speed. The knee OA patients were also significantly more asymmetrical than the healthy controls, with the greatest difference between limbs (Table 2) seen during single limb stance time (8%, $P = 0.001$), push-off impulse (7%, $P = 0.050$) and total impulse (7%, $P < 0.0001$). ROC analysis of the gait symmetry variables (Table 3) at TWS demonstrated that total impulse (Figure 4) was the best discriminator of symmetry with an AUC of 0.902, with a cut-off of -3% and a specificity of 95% and sensitivity of 88%.

DISCUSSION

By analysing gait ground reaction forces and symmetry at top walking speed, this study set-out to determine

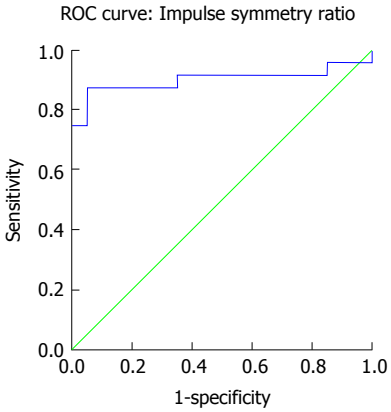

Figure 4 Receiver operating characteristics graph: Displaying the discriminating ability of total impulse symmetry ratio. ROC: Receiver operating characteristics.

Table 1 Subject characteristics

Subject	Control	Knee OA
Sex M:F	7:13	8:16
Age (yr)	52.5 (8.8)	65.5 (7.2)[1]
BMI	23.2 (6.6)	31.2 (6.1)[1]
Leg length (cm)	89.3 (5.6)	85.1 (5.9)[1]
Height (cm)	168.5 (7.5)	164.1 (7.9)
Total KL score	NA	2.5 (1.1)

[1]Significant difference between OA group *vs* control at PWS ($P < 0.05$). OA: Osteoarthritis; NA: Not available; PWS: Preferred walking speed; KL: Kellgren and Lawrence; BMI: Body mass index.

the changes in gait associated with the general decline in walking speed seen in patients with knee OA. In accordance with previous studies[17,18], compared to healthy controls the OA group walked more slowly and asymmetrically, with a wider based gait, and a shorter step length. Furthermore the study demonstrated that testing at top walking speed elicited differences in gait which would not ordinarily be detected at slower walking speeds.

Of most interest was that the OA patients had a significantly lower, and less symmetrical, push-off force and push-off impulse compared to healthy controls - suggesting a weakness during the terminal stance phase is a factor causing slower walking speeds. This may be secondary to loss of muscle power around the joint, a theory supported by Baert *et al*[19]'s finding of a 37% decrease in isometric knee extension power in early OA, and a 56% decrease in established OA patients, when compared to a matched control group. This loss may also be due to pain and the progressive attrition of muscle power due to the decreasing activity found in a biomechanically faulty knee. Nevertheless Bytyqi *et al*[20] demonstrated 11.6 degree loss during knee flexion/extension during comfortable walking in patients with OA when compared to controls which would further explain the importance of power and improved knee kinematics to achieve faster walking speed. This is of clinical value to surgeons and patients alike, given that it reinforces

Table 2 Temporospatial and normalised ground reaction results

Variable	Knee OA PWS		Symmetry ratio %	Control PWS		Symmetry ratio %	Knee OA TWS		Symmetry ratio %	Control TWS		Symmetry ratio %
	Affected (n = 24) Mean (SD)	Unaffected (n = 24) Mean (SD)	Mean (SD)	Right (n = 20) Mean (SD)	Left (n = 20) Mean (SD)	Mean (SD)	Affected (n = 24) Mean (SD)	Unaffected (n = 24) Mean (SD)	(n = 24) Mean (SD)	Right (n = 20) Mean (SD)	Left (n = 20) Mean (SD)	Mean (SD)
Speed (m/s)	1.09[1] (0.14)		NA	1.34 (0.07)		NA	1.37[2] (0.23)		NA	2.00 (0.20)		NA
Cadence (step/min)	113 (7)		NA	114 (10)		NA	123[1,2] (9)		NA	137 (11)		NA
Gait width (cm)	14.6 (4.2)[1]		NA	11.2 (3.2)		NA	14.2[1,2] (4.5)		NA	11.2 (3.0)		NA
Weight acceptance (BWN)	1.07[1] (0.08)	1.12[1] (0.10)	-4.0[1] (5.7)	1.18 (0.08)	1.18 (0.07)	0.7 (2.0)	1.18[2] (0.14)	1.26[1,2] (0.16)	-5.9 (5.7)[1,2]	1.55 (0.12)	1.52 (0.12)	2.6 (3.3)
Push-off (BWN)	1.00[1] (0.06)	1.02[1] (0.06)	-2.6 (5.2)	1.15 (0.09)	1.16 (0.08)	-1.5 (1.6)	0.95[1,2] (0.07)	1.00[1,2] (0.07)	-4.2 (6.0)[1,2]	1.16 (0.12)	1.17 (0.10)	-0.9 (3.5)
Total impulse (BWN/s)	0.53 (0.05)	0.57 (0.04)	-5.9[1] (5.6)	0.55 (0.05)	0.55 (0.05)	-0.2 (1.8)	0.49[1,2] (0.04)	0.53[1,2] (0.04)	-7.1 (6.2)[1,2]	0.46 (0.04)	0.46 (0.04)	-0.1 (1.6)
Weight acceptance impulse (BWN/s)	0.104[1] (0.008)	0.108 (0.010)	-3.4[1] (6.3)	0.112 (0.007)	0.112 (0.007)	0.9 (3.1)	0.113[2] (0.014)	0.120[2] (0.015)	-5.1 (6.6)[1,2]	0.146 (0.010)	0.142 (0.011)	3.5 (4.2)
Push off impulse (BWN/s)	0.098[1] (0.008)	0.098[1] (0.011)	0.6 (13.4)	0.111 (0.009)	0.114 (0.008)	-2.9 (2.6)	0.091[1,2] (0.008)	0.098[1,2](0.007)	-6.6 (8.0)[1,2]	0.110 (0.011)	0.111 (0.009)	-2.9 (4.7)
Step length (cm)	68[1] (10)	67[1] (9)	2.6 (6.5)	79 (6)	78 (5)	1.7 (2.5)	79 (12)[2]	78 (11)[2]	2.4 (6.2)	99 (8)	98 (8)	1.0 (1.9)
Step time (s)	0.53 (0.05)	0.54 (0.04)	-1.2 (7.5)	0.53 (0.05)	0.53 (0.04)	0.3 (3.1)	0.48[1,2] (0.03)	0.50[2] (0.05)	-4.0 (6.6)[1,2]	0.44 (.04)	0.44 (0.04)	-0.2 (3.5)
Contact time (s)	0.72 (0.05)	0.73[1] (0.05)	-2.4[1] (3.8)	0.68 (0.06)	0.69 (0.06)	-0.3 (1.7)	0.65[1,2] (0.05)	0.67[2] (0.07)	-3.4 (3.9)[1,2]	0.56 (0.05)	0.56 (0.05)	-0.3 (1.5)
Single limb stance time (s)	0.33[1] (0.04)	0.36 (0.04)	-7.0[1] (9.3)	0.38 (0.04)	0.38 (0.04)	-0.4 (3.5)	0.32[1] (0.02)	0.34[1] (0.03)	-7.5 (8.5)[1,2]	0.33 (0.04)	0.33 (0.03)	-0.3 (3.1)

The values are indicated as means ± standard deviation; [1]Significant difference between OA group *vs* control at PWS ($P < 0.05$); [2]Significant difference between OA group *vs* control at TWS ($P < 0.05$). PWS: Preferred walking speed; NA: Not available; TWS: Top walking speed; BWN: Body weight normalised; OA: Osteoarthritis.

the need for replacement surgery to be combined with physiotherapy aimed at restoring muscle strength and range of motion, and is consistent with the finding that gait and function can improve over time[21].

Another important study finding was the results of weight acceptance and weight acceptance impulse in the knee OA patients. Weight acceptance is the period during early stance phase at which the knee is fully extended and accepting the full weight. Whilst the weight acceptance of the affected limb in knee OA patients was comparable to healthy controls (1.18 *vs* 1.18 BWN and 0.113 *vs* 0.112 BWN/s respectively), they were in fact abnormal when compared to the unaffected leg in the same patient (1.18 *vs* 1.26 BWN and 0.113 *vs* 0.120 BWN/s). This likely indicates that these patients inherently have loaded their arthritic knee joint beyond than what would be expected at that speed at which now they are limping and trying to reduce load on it. Furthermore considering that the patient's body mass index (BMI) were 35% higher than the controls, the normalised force results underestimates the true gross force which is traveling through the OA patient's knee during walking. These findings may partly explain why their knee joints wore out in the first instance. Furthermore they are consistent with a study reporting significantly increased knee joint loads during walking in subjects with knee OA[22]. These observations may be of practical value, as a tool for measuring intervention which aim to retrain gait, avoid high weight acceptance forces and theoretically prevent further joint arthrosis from occurring.

The second main aim of the study was to assess the use of an area (impulse) below ground reaction force peaks, rather than just solitary points on the peak, as a novel method of assessing symmetry. In this regard, after single limb stance time, total impulse and push-off impulse displayed the largest asymmetries in knee OA patients. And ROC analysis identified the total impulse symmetry ratio as the best variable to discriminate between groups, with an AUC of 0.902 which is considered excellent. Weight acceptance impulse also proved to be a good discriminating measure, with an AUC of 0.852. Hodt-Billington recommended a 10% asymmetry criterion for pathological gait from their work comparing hip OA patients with healthy controls[1], whilst our results suggest a symmetry ratio criterion as low as 5% for total impulse. Nevertheless a 10% criterion should generally be recommended for parametric data as recommended by multiple studies[1,23,24]. Our results also demonstrate that healthy gait has a range of asymmetry which is parameter dependent and varies statistically depending on its confidence interval.

The limitation of this study relates to the control group, who were significantly lighter and younger, and walked with a significantly faster top speed. Fortuitously, the

Table 3 Area under curve results with confidence intervals demonstrating the discriminating ability of different variables

SR at TWS	AUC	CI	Significance
WA	0.898	0.800, 0.996	< 0.001
PO	0.683	0.521, 0.846	0.038
TI	0.902	0.797, 1.000	< 0.001
WAI	0.852	0.736, 0.968	< 0.001
POI	0.654	0.491, 0.817	0.081
ST	0.650	0.484, 0.816	0.090
CT	0.767	0.628, 0.905	0.003
SLST	0.767	0.628, 0.906	0.003

AUC: Area under curve; CI: Confidence intervals; SR: Symmetry ratio; WA: Weight acceptance; PO: Push-off; TI: Total impulse; WAI: Weight acceptance impulse; POI: Push-off impulse; ST: Stance time; CT: Contact time; SLST: Single limb stance time.

control group's preferred walking speed was similar to the OA group's top walking speed with identical step length (79 cm *vs* 79 cm), allowing for a fair and better comparison. Additionally the intended objective was not to determine which group was faster but rather, which factors caused them to be slower. Nevertheless a previous 3-D kinematic gait study looking at knee movements did not observe a difference in fast walking speed in knee OA patients despite them being almost 10 years older than the health controls[25]. And as previously discussed, by looking at asymmetry, in effect patients act as their own controls if they have one healthy, un-affected, knee. In common with many other gait studies, our OA group were significantly heavier than controls, which is unsurprising given that high BMI is a perhaps the greatest known risk factor for OA[5,25]. However, all ground reaction forces were normalised for body weight to minimise the bias introduced by this difference between groups. Lastly this is a cross-sectional study and it would have been interesting to see whether interventions such as physiotherapy, foot orthotics, or knee surgery could restore normal ground reaction forces and symmetry while walking.

In conclusion, this paper reconfirms the gait abnormalities seen with knee OA, but for the first time using ground reaction forces at top walking speed and a novel method of analysis. Reduced push-off and overall loading (impulse) are key factors in limiting the top walking speed of patients with OA. Higher than expected weight acceptance loads are potential causes for patients wearing out their joints. Furthermore OA patients demonstrate significant asymmetry in almost all parameters of gait biomechanics, with ROC analysis identifying total impulse as the variable with the best discriminating ability. Longitudinal studies are required, but these features may be useful in the screening and rehabilitation of patients at risk of developing, or with early knee arthrosis.

COMMENTS

Background

Knee osteoarthritis is an increasingly common condition. Understanding the loading characteristics of patients with knee osteoarthritis may help prevent or delay this condition from occurring.

Research frontiers

The gait assessment of patients with knee osteoarthritis has primarily been completed using slower speed protocols. The use of faster speeds on an instrumented treadmill has allowed us to better understand the loading patterns of patients with knee osteoarthritis.

Innovations and breakthroughs

This study demonstrated that faster speed detected differences which would not be seen at slower speed. Impulse and weight acceptance were the variables with the best discriminating ability.

Applications

Faster walking speed is recommended during gait analysis for patients with knee osteoarthritis.

Terminology

Ground reaction forces are the stance phase loading characteristics of the foot during gait.

Peer-review

This is an interesting paper that aims to evaluate the gait patterns in osteoarthritis patients at top walking speed. This is a well-designed and organized study that uses validated measurements and produces some important findings. The methodology used is appropriate and well presented.

REFERENCES

1 **Hodt-Billington C**, Helbostad JL, Vervaat W, Rognsvåg T, Moe-Nilssen R. Criteria of gait asymmetry in patients with hip osteoarthritis. *Physiother Theory Pract* 2012; **28**: 134-141 [PMID: 21722001 DOI: 10.3109/09593985.2011.574783]

2 **Patterson KK**, Parafianowicz I, Danells CJ, Closson V, Verrier MC, Staines WR, Black SE, McIlroy WE. Gait asymmetry in community-ambulating stroke survivors. *Arch Phys Med Rehabil* 2008; **89**: 304-310 [PMID: 18226655 DOI: 10.1016/j.apmr.2007.08.142]

3 **Jørgensen L**, Crabtree NJ, Reeve J, Jacobsen BK. Ambulatory level and asymmetrical weight bearing after stroke affects bone loss in the upper and lower part of the femoral neck differently: bone adaptation after decreased mechanical loading. *Bone* 2000; **27**: 701-707 [PMID: 11062359]

4 **Bejek Z**, Paróczai R, Illyés A, Kiss RM. The influence of walking speed on gait parameters in healthy people and in patients with osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2006; **14**: 612-622 [PMID: 16331521 DOI: 10.1007/s00167-005-0005-6]

5 **Zeni JA**, Higginson JS. Differences in gait parameters between healthy subjects and persons with moderate and severe knee osteoarthritis: a result of altered walking speed? *Clin Biomech* (Bristol, Avon) 2009; **24**: 372-378 [PMID: 19285768 DOI: 10.1016/j.clinbiomech.2009.02.001]

6 **Studenski S**, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, Brach J, Chandler J, Cawthon P, Connor EB, Nevitt M, Visser M, Kritchevsky S, Badinelli S, Harris T, Newman AB, Cauley J, Ferrucci L, Guralnik J. Gait speed and survival in older adults. *JAMA* 2011; **305**: 50-58 [PMID: 21205966 DOI: 10.1001/jama.2010.1923]

7 **Tanamas S**, Hanna FS, Cicuttini FM, Wluka AE, Berry P, Urquhart DM. Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. *Arthritis Rheum* 2009; **61**: 459-467 [PMID: 19333985 DOI: 10.1002/art.24336]

8 **Blagojevic M**, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2010; **18**: 24-33 [PMID: 19751691 DOI: 10.1016/j.joca.2009.08.010]

9 **Hunt MA**, Birmingham TB, Giffin JR, Jenkyn TR. Associations among knee adduction moment, frontal plane ground reaction

force, and lever arm during walking in patients with knee osteoarthritis. *J Biomech* 2006; **39**: 2213-2220 [PMID: 16168997 DOI: 10.1016/j.jbiomech.2005.07.002]
10 **McCrory JL**, White SC, Lifeso RM. Vertical ground reaction forces: objective measures of gait following hip arthroplasty. *Gait Posture* 2001; **14**: 104-109 [PMID: 11544061]
11 **KELLGREN JH**, LAWRENCE JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957; **16**: 494-502 [PMID: 13498604]
12 **Wiik AV**, Manning V, Strachan RK, Amis AA, Cobb JP. Unicompartmental knee arthroplasty enables near normal gait at higher speeds, unlike total knee arthroplasty. *J Arthroplasty* 2013; **28**: 176-178 [PMID: 24099573 DOI: 10.1016/j.arth.2013.07.036]
13 **Hof AL**. Scaling gait data to body size. *Gait Posture* 1996: 222-223 [DOI: 10.1016/0966-6362(95)01057-2]
14 **Patterson KK**, Gage WH, Brooks D, Black SE, McIlroy WE. Evaluation of gait symmetry after stroke: a comparison of current methods and recommendations for standardization. *Gait Posture* 2010; **31**: 241-246 [PMID: 19932621 DOI: 10.1016/j.gaitpost.2009.10.014]
15 **Hanley JA**, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; **143**: 29-36 [PMID: 7063747 DOI: 10.1148/radiology.143.1.7063747]
16 **Astephen Wilson JL**. Challenges in dealing with walking speed in knee osteoarthritis gait analyses. *Clin Biomech* (Bristol, Avon) 2012; **27**: 210-212 [PMID: 22019141 DOI: 10.1016/j.clinbiomech.2011.09.009]
17 **Debi R**, Mor A, Segal G, Debbi EM, Cohen MS, Igolnikov I, Bar Ziv Y, Benkovich V, Bernfeld B, Rozen N, Elbaz A. Differences in gait pattern parameters between medial and anterior knee pain in patients with osteoarthritis of the knee. *Clin Biomech* (Bristol, Avon) 2012; **27**: 584-587 [PMID: 22406298 DOI: 10.1016/j.clinbiomech.2012.02.002]
18 **Ornetti P**, Maillefert JF, Laroche D, Morisset C, Dougados M, Gossec L. Gait analysis as a quantifiable outcome measure in hip or knee osteoarthritis: a systematic review. *Joint Bone Spine* 2010; **77**: 421-425 [PMID: 20471899 DOI: 10.1016/j.jbspin.2009.12.009]
19 **Baert IA**, Jonkers I, Staes F, Luyten FP, Truijen S, Verschueren SM. Gait characteristics and lower limb muscle strength in women with early and established knee osteoarthritis. *Clin Biomech* (Bristol, Avon) 2013; **28**: 40-47 [PMID: 23159192 DOI: 10.1016/j.clinbiomech.2012.10.007]
20 **Bytyqi D**, Shabani B, Lustig S, Cheze L, Karahoda Gjurgjeala N, Neyret P. Gait knee kinematic alterations in medial osteoarthritis: three dimensional assessment. *Int Orthop* 2014; **38**: 1191-1198 [PMID: 24619388 DOI: 10.1007/s00264-014-2312-3]
21 **Taniguchi M**, Sawano S, Kugo M, Maegawa S, Kawasaki T, Ichihashi N. Physical Activity Promotes Gait Improvement in Patients With Total Knee Arthroplasty. *J Arthroplasty* 2016; **31**: 984-988 [PMID: 26707650 DOI: 10.1016/j.arth.2015.11.012]
22 **Baliunas AJ**, Hurwitz DE, Ryals AB, Karrar A, Case JP, Block JA, Andriacchi TP. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. *Osteoarthritis Cartilage* 2002; **10**: 573-579 [PMID: 12127838]
23 **Robinson RO**, Herzog W, Nigg BM. Use of force platform variables to quantify the effects of chiropractic manipulation on gait symmetry. *J Manipulative Physiol Ther* 1987; **10**: 172-176 [PMID: 2958572]
24 **Balasubramanian CK**, Bowden MG, Neptune RR, Kautz SA. Relationship between step length asymmetry and walking performance in subjects with chronic hemiparesis. *Arch Phys Med Rehabil* 2007; **88**: 43-49 [PMID: 17207674 DOI: 10.1016/j.apmr.2006.10.004]
25 **Landry SC**, McKean KA, Hubley-Kozey CL, Stanish WD, Deluzio KJ. Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed. *J Biomech* 2007; **40**: 1754-1761 [PMID: 17084845 DOI: 10.1016/j.jbiomech.2006.08.010]

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ORIGINAL ARTICLE

Retrospective Study

Variability in conflict of interest disclosures by physicians presenting trauma research

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Author contributions: Wong K and Yi PH designed the research; Wong K, Yi PH, Mohan R and Choo KJ contributed to data acquisition, analysis and interpretation; Wong K wrote the paper; all authors contributed to the drafting, critical revisions, and final approval of the manuscript.

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Abstract

AIM

To quantify the variability of financial disclosures by authors presenting orthopaedic trauma research.

METHODS

Self-reported authorship disclosure information published for the 2012 American Academy of Orthopaedic Surgeons (AAOS) and Orthopaedic Trauma Association (OTA) meetings was compiled from meeting programs. Both the AAOS and OTA required global disclosures for participants. Data collected included: (1) total number of presenters; (2) number of presenters with financial disclosures; (3) number of disclosures per author; (4) total number of companies supporting each author; and (5) specific type of disclosure. Disclosures made by authors presenting at more than one meeting were then compared for discrepancies.

RESULTS

Of the 5002 and 1168 authors presenting at the AAOS and OTA annual meetings, respectively, 1649 (33%) and 246 (21.9%) reported a financial disclosure ($P < 0.0001$). At the AAOS conference, the mean number of disclosures among presenters with disclosures was 4.01 with a range from 1 to 44. The majority of authors with disclosures reported three or more disclosures ($n = 876$, 53.1%). The most common cited disclosure

was as a paid consultant (51.5%) followed by research support (43.0%) and paid speaker (34.8%). Among the 256 physicians with financial disclosures presenting at the OTA conference, the mean number of disclosures was 4.03 with a range from 1 to 22. Similar to the AAOS conference, the majority of authors with any disclosures at the OTA conference reported three or more disclosures (n = 140, 54.7%). Most authors with a disclosure had three or more disclosures and the most common type of disclosure was paid consulting. At the OTA conference, the most commonly cited form of disclosure was paid consultant (54.3%) followed by research support (46.1%) and paid speaker (42.6%). Of the 346 researchers who presented at both meetings, 112 (32.4%) authors were found to have at least one disclosure discrepancy. Among authors with a discrepancy, 36 (32.1%) had three or more discrepancies.

CONCLUSION

There were variability and inconsistencies in financial disclosures by researchers presenting orthopaedic trauma research. Improved transparency of conflict of interest disclosures is warranted among trauma researchers presenting at national meetings.

Key words: Conflict of interest; Financial disclosures; Ethics; American Academy of Orthopaedic Surgeons; Orthopaedic Trauma Association

Core tip: Previous studies have demonstrated discrepancies in financial conflict of interest disclosures among physicians presenting research. The purpose of this study was to quantify the variability of self-reported financial disclosures by authors presenting at multiple trauma conferences during the same year. The disclosures published for the 2012 annual meetings of the American Academy of Orthopaedic Surgery and Orthopaedic Trauma Association were tabulated and disclosures made by authors presenting at both meetings were compared for discrepancies. Our results demonstrate variability in reported disclosures by authors presenting at multiple conferences within the same year. Further work is warranted to improve transparency of disclosures.

Wong K, Yi PH, Mohan R, Choo KJ. Variability in conflict of interest disclosures by physicians presenting trauma research. *World J Orthop* 2017; 8(4): 329-335 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i4/329.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i4.329

INTRODUCTION

Private industry has become an increasingly significant source of funding for physicians conducting research in recent years[1-3]. As industry investment in medical research grows however, conflict of interest (COI) has become a controversial topic in orthopaedic surgery. Many studies have suggested that close ties between industry and physicians may negatively influence the quality and integrity of clinical studies[4-6]. For example, industry funding is one of the strongest predictors for a favorable result in a product being studied[7-11]. Although industry funding has a potential to create bias, it has also been essential in achieving many advances in diagnosis and treatment in medicine[12], and as a result balancing the benefits and risks of industry relationships has become a divisive reality to deal with within the orthopaedic community.

Disclosures of conflict of interest have been called for by the American Academy of Orthopaedic Surgeons (AAOS) and other medical organizations in order to maintain research integrity[13-16]. Unfortunately, differences in what constitutes a COI as well as ambiguity between disclosure guidelines between different organizations can make it difficult for physicians to know exactly what to disclose[15,17]. Previous studies have shown variability in the COI disclosures by researchers presenting on spine surgery and sports medicine, possibly due to variability in disclosure policies[18,19]. In fact, some evidence suggests that inaccuracies in COI disclosure can be found throughout the field of orthopaedics as a whole[20]. To date, however, there has been no previous analysis of COI discrepancies within the subspecialty of orthopaedic trauma.

The purpose of the present study was: (1) to describe the COI disclosures of authors presenting research at both the AAOS and the OTA annual meetings; and (2) to quantify variability in COI disclosures of authors who presented orthopaedic trauma research. We hypothesized that there would be variability in the disclosure of physicians presenting research at the two conferences in the same given year.

MATERIALS AND METHODS

We recorded the disclosures from all authors who presented trauma research at two orthopedic conferences. The two conferences included in the study were the 2012 annual meeting for the AAOS and the 2012 annual meeting for the Orthopaedic Trauma Association (OTA). Self-reported disclosure data from the authors for each conference was collected from the printed meeting information, which is available online[21,22]. Since the 2012 AAOS abstract deadline was in June 2011 while the 2012 OTA conference abstract deadline was in February 2012, it is possible that industry support and COI for some authors may have changed during the time between the two conferences. However, it is common for industry sponsorships to last for years, especially when these partnerships involve clinical research[23,24]. Thus, for the purposes of this current study, it was assumed that changes, if any, would be minimal given the relatively short time between the two conference deadlines.

The disclosure policies for the AAOS and OTA con-

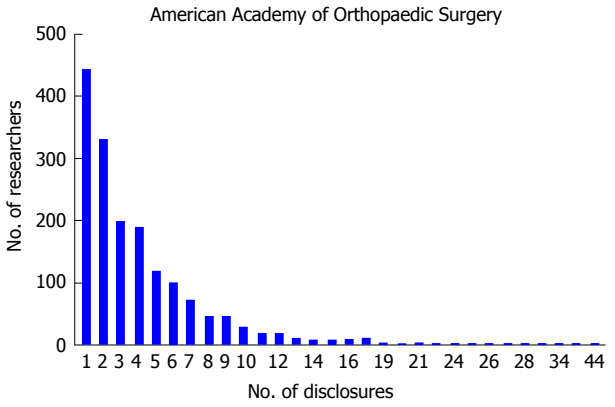

Figure 1 Total number of researchers reporting disclosures at the American Academy of Orthopaedic Surgery decreases as the total number of disclosures increases.

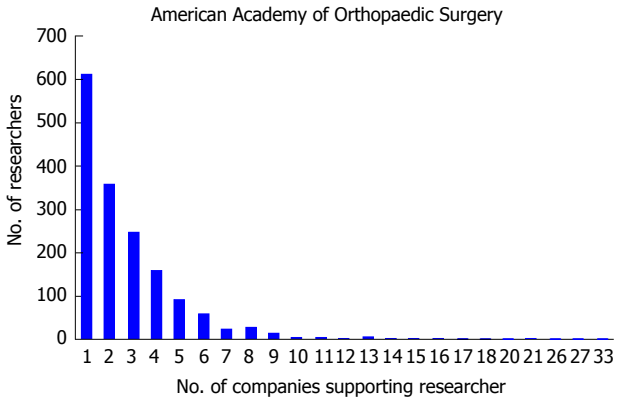

Figure 2 Number of researchers disclosing company/entity support at the American Academy of Orthopaedic Surgery decreases as the number of disclosures increases.

ferences were obtained from the AAOS and OTA websites[25]. Both the AAOS and OTA conferences required global disclosure (*i.e.,* presenters were required to disclose all financial relationships, regardless of relevance to their presentation). Because the guidelines between these two conferences were equivalent, we were able to compare the financial relationships reported by authors who attended both conferences in order to quantify any discrepancies present in the author's disclosures. Only authors who presented at both conferences were included in the present study for a total of 346 individuals. Researchers who presented at only one of the conferences were excluded from the study.

Pertinent characteristics recorded from each conference included: (1) total number of presenters; (2) number of presenters with financial disclosures; (3) number of disclosures per author (among authors with disclosures); (4) total number of companies/entities supporting each author (among authors with disclosures); and (5) percentage breakdown of each type of disclosure into 9 specific categories (*i.e.,* royalties, paid speaker, employee, paid consultant, nonpaid consultant, stock options, research support, other support, and publishers).

After recording disclosure data from each conference for eligible authors, the disclosures between the two conferences were then compared. First, the total number of authors with and without consistent number of disclosures was recorded. Next the individuals with inconsistent disclosures were categorized into two categories: (1) those who disclosed at least one financial relationship at one conference but no financial relationships at the other conference; and (2) those who disclosed at both conferences but with different number and type of disclosures.

RESULTS

The total number of research presenters at the AAOS annual meeting was 5002, and out of those who presented, 1649 (33.0%) had financial disclosures. The total number of presenters at the OTA annual meeting was 1168 and a total of 256 (21.9%) authors at the OTA meeting had financial disclosures. In total there were 6613 disclosures reported at the AAOS meeting and 1033 disclosures reported at the OTA meeting.

At the AAOS conference, the mean number of disclosures among presenters with disclosures was 4.01 with a range from 1 to 44. The majority of authors with disclosures reported three or more disclosures (n = 876, 53.1%); in contrast, only 443 (26.9%) researchers reported one disclosure and 330 (20.0%) of researchers reported two disclosures. Although the majority of authors reported three or more disclosures, the number of researchers reporting increasing number of disclosures progressively decreases (Figure 1). The mean number of companies/entities supporting researchers among those with disclosures was 2.88 with a range from 1 to 33 companies. Of those authors with support from companies, 612 (37.1%) researchers received support from only one company, 358 (21.7%) received support from two companies, and 679 (41.2%) received support from three or more companies. Similar to the total number of disclosures, the number of researchers disclosing company/entity support decreases as the number of disclosures increases (Figure 2). Among authors who provided specific types of disclosures, the most common cited disclosure was as a paid consultant (51.5%) followed by research support (43.0%) and paid speaker (34.8%). In descending order, the remaining disclosures include royalties (29.1%), stock options (27.9%), publisher (17.5%), unpaid consultant (11.7%), other support (11.0%), and employee (5.15%).

Among the 256 physicians with financial disclosures presenting at the OTA conference, the mean number of disclosures was 4.03 with a range from 1 to 22. Similar to the AAOS conference, the majority of authors with any disclosures reported three or more disclosures (n = 140, 54.7%), a total of 61 (23.8%) presenters reported only one disclosure and 55 (21.5%) of presenters reported two disclosures. Although the majority of authors who reported any disclosures at the OTA conference reported three or more financial affiliations, the number of re-

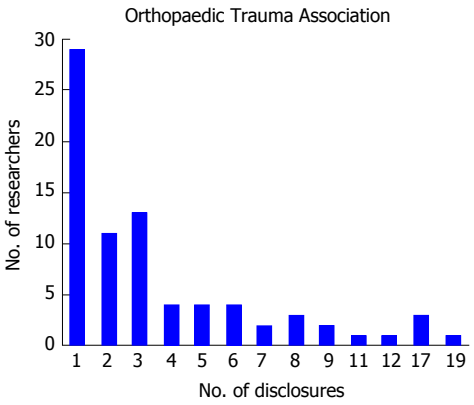

Figure 3 Total numbers of researchers reporting disclosures at the Orthopaedic Trauma Association decreases as the total number of disclosures increases.

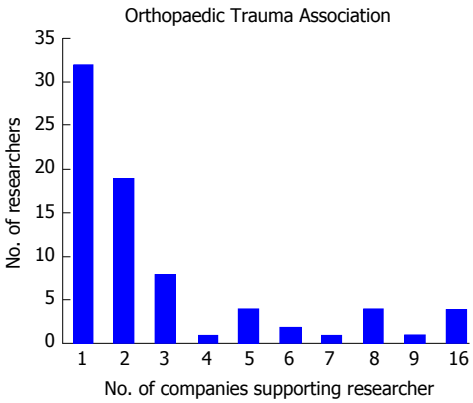

Figure 4 Number of researchers disclosing company/entity support at the Orthopaedic Trauma Association decreases as the number of disclosures increases.

searchers reporting sequentially increasing number of affiliations decreases (Figure 3). The mean number of companies/entities supporting researchers who reported disclosures was 3.09 with a range from 1 to 22 companies. Of those presenters who received support from companies, 78 (30.5%) researchers received support from only one company, 69 (27.0%) researchers received support from two companies, and 109 (42.6%) researchers received support from three or more companies. The number of physicians disclosing support from companies decreases at successively higher numbers of company support (Figure 4). Among presenters who provided specific types of financial disclosures, the most commonly cited form of disclosure was paid consultant (54.3%) followed by research support (46.1%) and paid speaker (42.6%). In descending order, the remaining disclosures include stock options (23.4%), royalties (19.5%), publisher (16.8%), other support (13.3%), unpaid consultant (12.1%), and employee (6.25%).

In total, 346 physicians presented at both the AAOS and OTA conferences in 2012. The number of co-presenters with discrepancies in financial disclosure was 112 (32.4%) with a mean of 2.47 and a range from 1 to 16 discrepancies. Among the co-presenters with disclosures, 55 (49.1%) had one discrepancy between the AAOS and OTA conferences, 21 (18.8%) of co-presenters had two discrepancies between the two conferences, and 36 (32.1%) of co-presenters had three or more discrepancies between the two conferences (Figure 5). Of the 112 co-presenters with discrepancies, 38 (33.9%) made zero disclosures at one conference but disclosed at least one financial relationship at the other conference while 74 (66.1%) of co-presenters with discrepancies disclosed at both conferences (Figure 6). The remaining 67.6% of physicians who presented at both conferences were found to have no discrepancies between their disclosures.

DISCUSSION

As funding for biomedical research has shifted significantly towards private industry[26], addressing COI has become an important topic for orthopaedic surgeons. Although previous studies have demonstrated disclosure inconsistencies by physicians presenting sports medicine and spine surgery at various orthopaedic conferences[18,19], no previous study has assessed the variability of COI disclosures by physicians presenting orthopaedic trauma research. The purpose of this study was to evaluate disclosures by physicians presenting at the 2012 AAOS and OTA annual meetings in order to quantify COI discrepancies. Overall, we found a high prevalence of disclosure discrepancies. Nevertheless, specific types of disclosures were similar between presenters at both the AAOS and OTA conferences; furthermore, the most common disclosure types were paid consulting, research support, and paid speaker. Finally, we found that the majority of physicians with discrepancies had more than one discrepancy, and a large portion of physicians with discrepancies disclosed nothing at one conference despite disclosing at least one COI at the other conference.

There was a high prevalence of disclosure discrepancies by physicians who presented at both the 2012 AAOS and OTA conferences with a total of about one third of all physicians with at least one discrepancy. This is consistent with previous reports in sports medicine and spine, which have also shown high discrepancy rates among researchers presenting in these fields. There are several possible explanations for this high number of discrepancies. First, it is possible that discrepancies between the two conferences can be explained simply by natural changes in industry affiliations that occurred between the two conferences; however the period of only a few months between conference abstract submission deadlines makes this explanation unlikely. A second possibility is that the discrepancies simply result from physician carelessness. Current penalties for inaccurate disclosure are fairly limited and leave researchers considerable discretion in what they decide to disclose[16,27]; lack of sufficient repercussion may decrease the effort some authors make in order to check or verify disclosure policies, leading to disclosure errors.

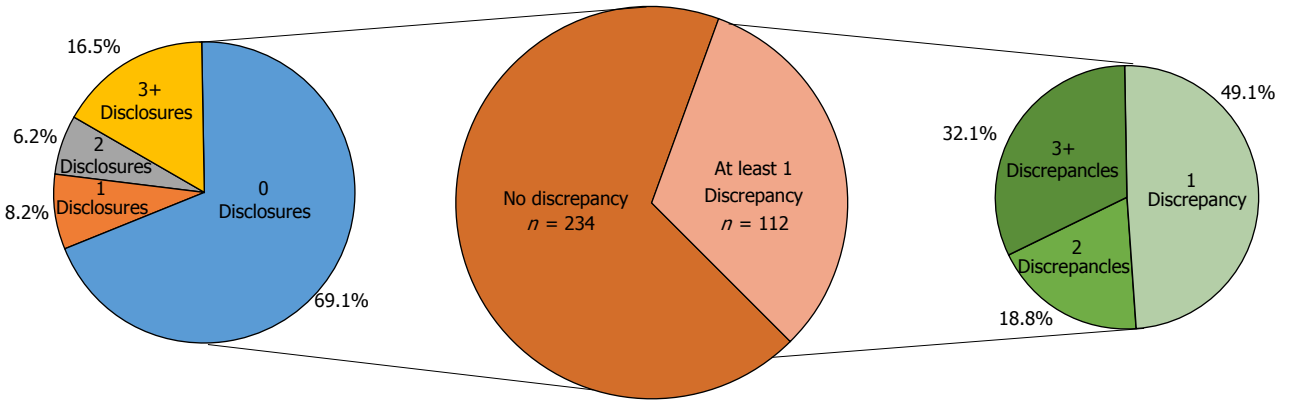

Figure 5 Number of disclosure discrepancies by physicians who disclosed at both the American Academy of Orthopaedic Surgery and Orthopaedic Trauma Association conferences.

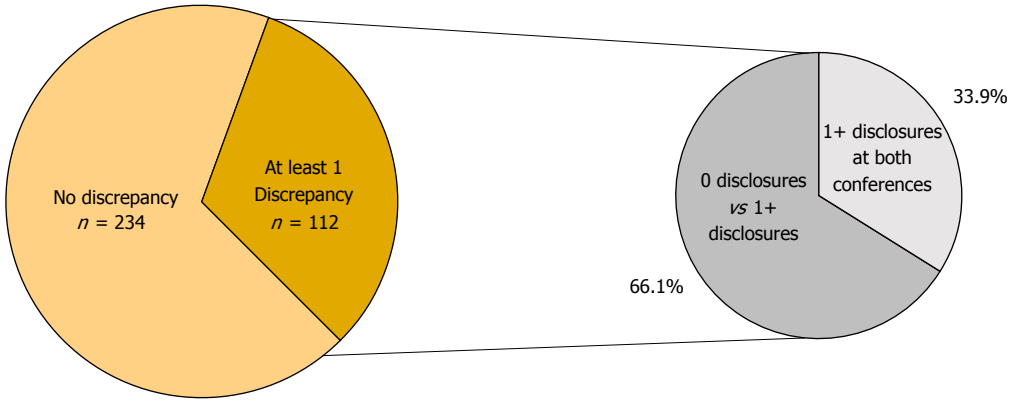

Figure 6 Disclosure patterns among researchers with disclosure discrepancies.

This carelessness might also explain the difference in total disclosures between the AAOS and OTA conferences: The AAOS is a larger conference, and hosts not only a higher number of attendees, but also features a larger number of orthopaedic topics including but not limited to trauma[28]. While it is possible that some physicians correctly assumed a global disclosure policy at the AAOS conference given the larger scope of the conference, when these same physicians presented at the OTA conference - a conference focused on a more niche topic - they may have erroneously assumed that they only needed to disclose project-specific industry relationships without checking for the true OTA global disclosure policy. This possibility is consistent with our data, which showed an increase in the proportion of physicians reporting disclosures at the AAOS conference compared to the OTA conference.

The three most common types of disclosures in descending order were paid consultant, research support, and paid speaker. These observations are consistent with previous studies within the fields of spine surgery, sports medicine, and pediatric orthopaedics, which have also been shown to have the same three most frequent financial relationships[29]. General trends in paid consultancies are also commonplace in total joint arthroplasty, with manufacturers often paying physicians to serve as experts[30]. These findings demonstrate that industry funding has become such a consistent factor in orthopaedic research that even the type of disclosures remains steady between orthopaedic trauma and other orthopaedic specialties. However the prevalence of industry funding within orthopaedic research is not necessarily detrimental. As we have already mentioned, industry funding in itself does not automatically decrease the credibility or validity of research. Secondly, the presence of industry funding in multiple orthopaedic specialties may actually be beneficial by providing an opportunity to compare rates of disclosure discrepancies between specialties and identify areas with lower discrepancies. This would ultimately be beneficial for orthopaedic trauma research by allowing researchers to adopt successful strategies to reduce COI discrepancies within this field.

Meaningful research requires more than proper technique and procedure, it also requires proper disclosure of conflicts of interest[31,32]. The inability of current disclosure guidelines to facilitate uniform and accurate physician disclosure regarding orthopaedic trauma research is demonstrated by the high variability in both the number and type of disclosure inconsistencies. Our data has shown that the majority of physicians with discrepancies in disclosure presented with more than one

discrepancy. Furthermore, over a third of physicians who reported at least one disclosure at one conference failed to report any COI at the other conference. Proper disclosure is crucial to inform the audience and allow readers to draw their own conclusions about the objectivity of the research[33]. At a time when the public is often cautious and even skeptical towards medical research, disclosure inconsistencies may negatively impact the integrity of research, and it is therefore important that orthopaedic surgeons hold themselves to a high standard of accuracy and decrease the inconsistencies in both the number and type of disclosures.

There were several limitations to our study. As previously mentioned, the AAOS and OTA conferences occurred during different months so there may have been changes in financial affiliations during that time. The disclosure deadline for the 2012 AAOS conference was June 2011 while the disclosure deadline for the 2012 OTA conference was February 2011. In these nine months, we predicted that there would only be minor changes, if any, in disclosures by anyone presenting at both conferences. Another limitation to our study was the fact that only two orthopaedic conferences were examined in this study. For this reason, the sampling of physician disclosures may not be representative of the total population of disclosures in orthopaedic trauma research, nor can the findings be generalized towards non-orthopaedic research. Nevertheless, we believe that our data does provide accurate insight into the realities of two of the most prominent venues for the presentation of orthopaedic trauma research in the world, and as such is relevant to the discussion of COI in orthopaedics.

In our study, we found substantial variability in disclosures from physicians presenting orthopaedic trauma research at the 2012 AAOS and OTA conferences. The origin of financial relationships between researchers and industry arise from multiple sources, and there is variability in both the number and type of discrepancies involved in trauma research. The large proportion of disclosure inconsistencies currently found in physicians presenting trauma research may be explained by factors such as physician carelessness, unclear disclosure instructions, or inadequate repercussions by the AAOS and OTA for failure to accurately disclose. Because the current system presents with a high number of disclosure discrepancies within orthopaedic trauma, we recommend adjusting current guidelines to be more clear and uniform as a first step in promoting accurate COI disclosure as well as research transparency and accountability.

COMMENTS

Background

Private industry has become an increasingly significant source of research funding. Financial relationships may create biases that compromise the integrity and objectivity of industry-sponsored medical research. To improve transparency, multiple orthopaedic organizations have developed specific disclosure policies. Unfortunately, current guidelines vary between organizations and are often not clearly explained to researchers. The purpose of this study was to quantify the variability of financial disclosures by authors presenting orthopaedic trauma research.

Research frontiers

Previous studies in sports medicine, spine surgery, and arthroplasty have shown that researchers presenting at separate national meetings within the same academic year have discrepancies in the financial disclosures they make.

Innovations and breakthroughs

This is the first study to our knowledge that has investigated: (1) the prevalence and characteristics of financial relationships; and (2) quantified discrepancies in conflict of interest disclosures by researchers presenting orthopaedic trauma research. The results of their study demonstrate that many authors reported financial disclosures at American Academy of Orthopaedic Surgeons and Orthopaedic Trauma Association, with a relatively high number of discrepancies.

Applications

Clearer instructions for authors regarding financial disclosures should be established in order to help make conflict of interest disclosures a more reliable and appropriate measure.

Terminology

A "conflict of interest" is defined as a situation in which a person or organization is involved in multiple personal or financial interests that may corrupt or otherwise influence the motivation and decision-making abilities of that individual.

Peer-review

The paper is an excellent paper with very important topic: Variability in conflict of interest disclosures by physicians presenting trauma research.

REFERENCES

1 **Boyd EA**, Bero LA. Assessing faculty financial relationships with industry: A case study. *JAMA* 2000; **284**: 2209-2214 [PMID: 11056592 DOI: 10.1016/s0002-9394(01)00842]

2 **Blumenthal D**, Causino N, Campbell E, Louis KS. Relationships between academic institutions and industry in the life sciences--an industry survey. *N Engl J Med* 1996; **334**: 368-373 [PMID: 8538709 DOI: 10.1056/NEJM199602083340606]

3 **Blumenthal D**, Campbell EG, Causino N, Louis KS. Participation of life-science faculty in research relationships with industry. *N Engl J Med* 1996; **335**: 1734-1739 [PMID: 8929266 DOI: 10.1056/NEJM199612053352305]

4 **Levine J**, Gussow JD, Hastings D, Eccher A. Authors' financial relationships with the food and beverage industry and their published positions on the fat substitute olestra. *Am J Public Health* 2003; **93**: 664-669 [PMID: 12660215 DOI: 10.2105/AJPH.93.4.664]

5 **Kubiak EN**, Park SS, Egol K, Zuckerman JD, Koval KJ. Increasingly conflicted: an analysis of conflicts of interest reported at the annual meetings of the Orthopaedic Trauma Association. *Bull Hosp Jt Dis* 2006; **63**: 83-87 [PMID: 16878823]

6 **Robertson C**, Rose S, Kesselheim AS. Effect of financial relationships on the behaviors of health care professionals: a review of the evidence. *J Law Med Ethics* 2012; **40**: 452-466 [PMID: 23061573 DOI: 10.1111/j.1748-720X.2012.00678.x]

7 **Perlis RH**, Perlis CS, Wu Y, Hwang C, Joseph M, Nierenberg AA. Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry. *Am J Psychiatry* 2005; **162**: 1957-1960 [PMID: 16199844 DOI: 10.1176/appi.ajp.162.10.1957]

8 **Tomaszewski C**. Conflicts of interest: bias or boon? *J Med Toxicol* 2006; **2**: 51-54 [PMID: 18072113 DOI: 10.1007/BF03161170]

9 **Djulbegovic B**, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, Kuderer NM, Lyman GH. The uncertainty principle and industry-sponsored research. *Lancet* 2000; **356**: 635-638 [PMID: 10968436 DOI: 10.1016/S0140-6736(00)02605-2]

10 **Kjaergard LL**, Als-Nielsen B. Association between competing

interests and authors' conclusions: epidemiological study of randomised clinical trials published in the BMJ. *BMJ* 2002; **325**: 249 [PMID: 12153921 DOI: 10.1136/bmj.325.7358.249]
11 **Bekelman JE**, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003; **289**: 454-465 [PMID: 12533125 DOI: 10.1001/jama.289.4.454]
12 **Lo B**, Field MJ. Institute of Medicine (US) Committee on Conflict of Interest in Medical Research E and P. Conflicts of Interest in Biomedical Research, 2009
13 **Cho MK,** Shohara R, Schissel A, Rennie D. Policies on faculty conflicts of interest at US universities. *JAMA* 2000; **284**: 2203-2208 [PMID: 11056591 DOI: 10.1001/jama.284.17.2203]
14 **Krimsky S,** Rothenberg LS. Conflict of interest policies in science and medical journals: editorial practices and author disclosures. *Sci Eng Ethics* 2001; **7**: 205-218 [PMID: 11349360 DOI: 10.1007/s11948-001-0041-7]
15 **Cooper RJ**, Gupta M, Wilkes MS, Hoffman JR. Conflict of Interest Disclosure Policies and Practices in Peer-reviewed Biomedical Journals. *J Gen Intern Med* 2006; **21**: 1248-1252 [PMID: 17105524 DOI: 10.1111/j.1525-1497.2006.00598.x]
16 **Department of Health and Human Services.** Responsibility of applicants for promoting objectivity in research for which public health service funding is sought and responsible prospective contractors. Final rule. *Fed Regist* 2011; **76**: 53256-53293 [PMID: 21894659]
17 **Rowan-Legg A**, Weijer C, Gao J, Fernandez C. A comparison of journal instructions regarding institutional review board approval and conflict-of-interest disclosure between 1995 and 2005. *J Med Ethics* 2009; **35**: 74-78 [PMID: 19103950 DOI: 10.1136/jme.2008.024299]
18 **Jegede KA**, Ju B, Miller CP, Whang P, Grauer JN. Quantifying the variability of financial disclosure information reported by authors presenting research at multiple sports medicine conferences. *Am J Orthop* (Belle Mead NJ) 2011; **40**: 583-587 [PMID: 22263213]
19 **Ju BL**, Miller CP, Whang PG, Grauer JN. Quantifying the variability of financial disclosure information reported by authors presenting at annual spine conferences. *Spine J* 2011; **11**: 1-8 [PMID: 20932807 DOI: 10.1016/j.spinee.2010.08.022]
20 **Okike K**, Kocher MS, Mehlman CT, Bhandari M. Conflict of interest in orthopaedic research. An association between findings and funding in scientific presentations. *J Bone Joint Surg Am* 2007; **89**: 608-613 [PMID: 17332110 DOI: 10.2106/JBJS.F.00994]
21 **American Academy of Orthopaedic Surgeons**. 2012 Annual Meeting Education Disclosures. Available from: URL: http://www.aaos.org/Education/anmeet/education/Disclosures.pdf
22 **HWB Foundation**. OTA 2012 Disclosure Listing-Alphabetical. Available from: URL: http://www.hwbf.org
23 **Thomas O**, Thabane L, Douketis J, Chu R, Westfall AO, Allison DB. Industry funding and the reporting quality of large long-term weight loss trials. *Int J Obes* (Lond) 2008; **32**: 1531-1536 [PMID: 18711388 DOI: 10.1038/ijo.2008.137]
24 **Bresalier RS**, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA; Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; **352**: 1092-1102[PMID: 15713943 DOI: 10.1056/NEJMoa050493]
25 **American Academy of Orthopaedic Surgeons**. Mandatory Disclosure Policy-AAOS. Available from: URL: http://www.aaos.org/about/policies/DisclosurePolicy.asp
26 **Bodenheimer T**. Uneasy alliance--clinical investigators and the pharmaceutical industry. *N Engl J Med* 2000; **342**: 1539-1544 [PMID: 10816196 DOI: 10.1056/NEJM200005183422024]
27 **Hanna J**, Simiele E, Lawson DC, Tyler D. Conflict of interest issues pertinent to Veterans Affairs Medical Centers. *J Vasc Surg* 2011; **54**: 50S-54S [PMID: 21872117 DOI: 10.1016/j.jvs. 2011.05.110]
28 **American Academy of Orthopaedic Surgeons**. Annual Meeting Programs-AAOS. Available from: URL: http://www.aaos.org/education/anmeet/programs/Programs.asp
29 **Matsen FA**, Jette JL, Neradilek MB. Demographics of disclosure of conflicts of interest at the 2011 annual meeting of the American Academy of Orthopaedic Surgeons. *J Bone Joint Surg Am* 2013; **95**: e29 [PMID: 23467877 DOI: 10.2106/JBJS.K.01514]
30 **Tanne JH**. US makers of joint replacements are fined for paying surgeons to use their devices. *BMJ* 2007; **335**: 1065 [PMID: 18033905 DOI: 10.1136/bmj.39405.383970.DB]
31 **Hirsch LJ**. Conflicts of interest, authorship, and disclosures in industry-related scientific publications: the tort bar and editorial oversight of medical journals. *Mayo Clin Proc* 2009; **84**: 811-821 [PMID: 19720779 DOI: 10.1016/S0025-6196(11)60491-6]
32 **Thompson DF.** Understanding financial conflicts of interest. *N Engl J Med* 1993; **329**: 573-576 [PMID: 8336759 DOI: 10.1056/NEJM199308193290812]
33 **Cohen JJ**. Trust us to make a difference: ensuring public confidence in the integrity of clinical research. *Acad Med* 2001; **76**: 209-214 [PMID: 11158850 DOI: 10.1097/00001888-200102000-00028]

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ORIGINAL ARTICLE

Retrospective Study

Associations among pain catastrophizing, muscle strength, and physical performance after total knee and hip arthroplasty

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Informed consent statement: All the participants provided written informed consent.

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Abstract

AIM

To investigate whether reductions in pain catastrophizing associated with physical performance in the early period after total knee arthroplasty (TKA) or total hip arthroplasty (THA).

METHODS

The study group of 46 participants underwent TKA or THA. The participants were evaluated within 7 d before the operation and at 14 d afterwards. Physical performance was measured by the Timed Up and Go (TUG) test, and 10-m gait time was measured at comfortable and maximum speeds. They rated their knee or hip pain using a visual analog scale (VAS) for daily life activities. Psychological characteristics were measured by the Pain Catastrophizing Scale (PCS). Physical characteristics were measured by isometric muscle strength of knee extensors and hip abductors on the operated side. The variables of percent changes between pre- and post-operation were calculated by dividing post-operation score by pre-operation score.

RESULTS

Postoperative VAS and PCS were better than pre-operative for both TKA and THA. Postoperative physical performance and muscle strength were poorer than

preoperative for both TKA and THA. The percent change in physical performance showed no correlation with preoperative variables. In TKA patients, the percent change of PCS showed correlation with percent change of TUG (P = 0.016), 10-m gait time at comfortable speeds (P = 0.003), and 10-m gait time at maximum speeds (P = 0.042). The percent change of muscle strength showed partial correlation with physical performances. The percent change of VAS showed no correlation with physical performances. On the other hand, in THA patients, the percent change of hip abductor strength showed correlation with percent change of TUG (P = 0.047), 10-m gait time at comfortable speeds (P = 0.001), and 10-m gait time at maximum speeds (P = 0.021). The percent change of knee extensor strength showed partial correlation with physical performances. The percent change of VAS and PCS showed no correlation with physical performances.

CONCLUSION

Changes in pain catastrophizing significantly associated with changes in physical performance in the early period after TKA. It contributes to future postoperative rehabilitation of arthroplasty.

Key words: Gait; Hip arthroplasty; Knee arthroplasty; Osteoarthritis; Pain; Pain management; Postoperative care

Core tip: This clinical trial investigated whether reductions in pain catastrophizing are associated with physical performance in the early period after total knee arthroplasty (TKA) or total hip arthroplasty (THA). We found that changes in pain catastrophizing were significantly associated with physical performance in the early period after TKA. These findings may contribute to future postoperative rehabilitation of the arthroplasties in lower limbs. Treatment based on cognitive-behavioral therapy might be useful in the early period, particularly after TKA.

Hayashi K, Kako M, Suzuki K, Hattori K, Fukuyasu S, Sato K, Kadono I, Sakai T, Hasegawa Y, Nishida Y. Associations among pain catastrophizing, muscle strength, and physical performance after total knee and hip arthroplasty. *World J Orthop* 2017; 8(4): 336-341 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i4/336.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i4.336

INTRODUCTION

Osteoarthritis leads to considerable morbidity in terms of pain, functional disability, lowered quality of life, and psychological problems[1]. Total knee arthroplasty (TKA) and total hip arthroplasty (THA) improve pain and physical performance in participants with end-stage arthritis[1]. The number of TKA and THA procedures performed is increasing worldwide[1]. Early postoperative recovery is important in particularly rehabilitation; however, uncertainty exists about effective rehabilitation methods for physical performance.

Pain treatment has targeted not only pain intensity, but also pain catastrophizing, which has been conceptualized as a negative cognitive-affective response to pain[2]. The patients with high pain catastrophizing suggest that cognitive-behavioral intervention should incorporate in treatment[2]. Recently systematic review concludes better outcome associates with grater reduction in pain catastrophizing during treatment in low back pain[3]. The review shows a mediating effect is found in all studies assessing the impact of a decrease in catastrophizing during treatment[3]. In addition, some studies have reported pain catastrophizing associated with physical performance than pain intensity, in low back pain[4,5]. On the other hand, the impact of reduction in pain catastrophizing on outcome has not investigated in patients with TKA or THA, although pain catastrophizing has investigated only at baseline[6-11]. In changes of pain related variables, the changes in postoperative pain intensity associate with changes in physical performance within 16 d after either TKA or THA[12]. It has not investigated whether pain intensity or pain catastrophizing have mediating effect of physical performance.

The purpose of the present study is to determine whether reductions in pain catastrophizing are associated with physical performance in the early period after TKA or THA.

MATERIALS AND METHODS

Participants

A total of 46 participants were enrolled. Twenty-three underwent initial TKA, and 23 underwent initial THA between September 2014 and April 2015 at Nagoya University Hospital (Table 1). Exclusion criteria were that the participant (1) was diagnosed with cognitive impairment; and (2) had pain in other body parts that was more severe than in the operative site. All participants underwent a baseline preoperative visit prior to their operation and received standardized in-participant treatment including usual rehabilitation, following either a primary total hip or total knee care pathway.

This cross sectional study was approved by the Ethics Committee of Nagoya University Hospital (No. 328). All the participants provided written informed consent.

Measures

Demographic data including age, sex, height, body weight, and body mass index were measured. The participants were evaluated within 7 d before the operation and at 14 d afterwards. Physical performance was measured

Table 1 Participant characteristics

	THA	TKA
Sex (male/female)	4/19	9/14
Age	61.17 ± 10.32	69.65 ± 8.52
Height (cm)	155.84 ± 8.34	153.01 ± 10.37
Body weight (kg)	58.66 ± 13.75	60.78 ± 12.87
Body mass index (kg/m^2)	24.05 ± 4.30	25.80 ± 4.25

Data for age, height, body weight, and body mass index are presented as mean ± SD. THA: Total hip arthroplasty; TKA: Total knee arthroplasty.

by the Timed Up and Go (TUG) test, and 10-m gait time was measured at comfortable and maximum speeds[13,14]. Participants were allowed to use a walking aid, based on walking ability. They rated their knee or hip pain using a visual analog scale (VAS) for daily life activities. Psychological characteristics were measured by the Pain Catastrophizing Scale (PCS)[15,16]. Physical characteristics were measured by isometric muscle strength of knee extensors and hip abductors on the operated side[17-22].

Physical performance: The 10-m gait test was used to measure the time it took the participant to walk 10 m at comfortable and maximum speeds. Timing at each of the two speeds was measured twice. Participants were timed using a stopwatch as they moved along a 10-m walkway. Participants stood directly behind the start line and were clocked from the moment the first foot crossed the start line until the lead foot crossed the finish line. Participants were instructed to continue at least 2 m past the finish line to eliminate the deceleration effects from stopping the gait. Gait speeds were then expressed as meters per second[13]. For the comfortable-gait speed trial, participants were instructed to walk at their normal comfortable speeds. For the maximum-speed trials, they were asked to walk as fast as they could safely do so without running. Each participant performed two valid trials, and the higher-speed trial was used for analysis.

The TUG test is a measure frequently used to assess function in older individuals[14]. Subjects were given verbal instructions to stand up from a chair, walk 3 m as quickly and as safely as possible, cross a line marked on the floor, turn around, walk back, and sit down. Each participant performed two valid trials, and the higher-speed trial was used for analysis.

Psychological measures: For the 13-item PCS, participants rate how frequently they have experienced various cognitions or emotions[15,16]. The PCS comprises three subscales: rumination (*e.g.,* "I keep thinking about how much it hurts"), magnification (*e.g.,* "I wonder whether something serious may happen"), and helplessness (*e.g.,* "There is nothing I can do to reduce the intensity of the pain")[15,16]. The total score range is 0-52[15,16]. Several findings support this scale's validity as a measure of PCS[15,16].

Isometric muscle strength: The isometric muscle strength of the hip abductors and knee extensors was measured using a hand-held gauge meter (μ-Tas F-100; Anima, Tokyo, Japan). The strength of the hip abductors was measured in the supine position with both lower limbs in neutral position. The transducer was placed at the lateral femoral condyles[17]. The strength-testing position of the knee extensors was confirmed using a goniometer at a hip angle of 90° and knee flexed to 60°. If necessary, the feet were supported by a small bench[18-22]. A strap was attached between the examination couch and a point on the participant's ankle, 5 cm above the lateral malleolus. The transducer was then placed at the front of the ankle under the strap to measure the extension strength. The participants were asked to push maximally against the force transducer for 5 s. Participants performed two contractions separated by a 60-s interval. The highest value was used for analysis. Muscle strength was expressed as the maximum voluntary torque with use of the external lever-arm length. The lever-arm length was the distance from the trochanter major to the center of the dynamometer for hip abductors and from the lateral femoral epicondyle to the center of the dynamometer for knee extensors.

Statistical analysis

All data are expressed as mean ± SD. The variables of percent changes between pre- and post-operation were quantified. It was calculated dividing post-operation score by pre-operation score[18]. Their resultant data were analyzed by paired *t*-test. The correlation of physical performance with psychological and physical variables was analyzed by the Pearson *r* rank test. The data were analyzed with SPSS software (version 20.0 for Microsoft Windows; SPSS, Chicago, IL, United States). A value of $P < 0.05$ was considered statistically significant.

RESULTS

Pre- and post-operative data are shown in Table 2. The mean ± SD of VAS in THA and TKA were at preoperative of 37.87 ± 24.20, and 41.91 ± 27.09, and postoperative at 14-d of 17.61 ± 20.29, and 25.22 ± 20.41. The mean ± SD of PCS in THA and TKA were at preoperative of 28.70 ± 9.28, and 28.26 ± 11.90, and postoperative at 14-d of 18.70 ± 11.19, and 20.26 ± 10.72. Postoperative VAS and PCS were better than preoperative for both TKA and THA. Postoperative physical performance and muscle strength were poorer than preoperative for both TKA and THA.

The correlations between physical performance and other variables are shown in Table 3. The percent change in physical performance showed no correlation with preoperative variables. In TKA patients, the percent change of PCS showed correlation with percent change of TUG ($P = 0.016$), 10-m gait time at comfortable speeds ($P = 0.003$), and 10-m gait time at maximum speeds ($P = 0.042$). The percent change of muscle strength showed

Table 2 Pre- and postoperative data according to site of replacement

	THA			TKA		
	Preoperative	Postoperative at 14-d	*P*-value	Preoperative	Postoperative at 14-d	*P*-value
TUG (s)	11.51 ± 3.82	13.67 ± 5.65	0.004[a]	12.22 ± 4.33	16.42 ± 9.09	0.004[a]
10 m gait speeds at comfortable (m/s)	0.97 ± 0.23	0.92 ± 0.20	0.187	0.99 ± 0.24	0.77 ± 0.23	0.000[a]
10 m gait speeds at maximum (m/s)	1.28 ± 0.34	1.11 ± 0.32	0.005[a]	1.19 ± 0.34	0.95 ± 0.32	0.000[a]
VAS	37.87 ± 24.20	17.61 ± 20.29	0.001[a]	41.91 ± 27.09	25.22 ± 20.41	0.004[a]
PCS	28.70 ± 9.28	18.70 ± 11.19	0.000[a]	28.26 ± 11.90	20.26 ± 10.72	0.003[a]
Muscle strength (kgf*m)						
Hip abductor strength (operated side)	2.62 ± 1.63	2.04 ± 1.36	0.026[a]	3.49 ± 2.06	2.10 ± 1.63	0.001[a]
Knee extensor strength (operated side)	4.78 ± 3.19	3.99 ± 1.59	0.240	4.46 ± 2.82	2.55 ± 2.13	0.001[a]

These data were analyzed with paired *t*-tests. Data for TUG, 10-m gait speeds, VAS, PCS, and muscle strength are presented as mean ± SD. [a]$P < 0.05$. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; TUG: Timed Up and Go; VAS: Visual analog scale; PCS: Pain Catastrophizing Scale.

Table 3 Correlation between percent changes from pre- to post-operative physical performance and other variables

	THA				TKA		
	ΔTUG (s)	Δ10 m gait speeds at comfortable (m/s)	Δ10 m gait speeds at maximum (m/s)		ΔTUG (s)	Δ10 m gait speeds at comfortable (m/s)	Δ10 m gait speeds at maximum (m/s)
Preoperative				Preoperative			
VAS	r = 0.184	0.083	-0.025	VAS	r = 0.237	-0.177	-0.287
	P = 0.402	0.707	0.908		P = 0.276	0.419	0.184
PCS	r = 0.270	0.021	-0.119	PCS	r = -0.184	0.122	0.169
	P = 0.213	0.923	0.588		P = 0.400	0.579	0.442
Hip abductor strength (operated side, kg f)	r = 0.063	-0.165	-0.161	Hip abductor strength (operated side, kg f)	r = -0.168	0.142	0.084
	P = 0.774	0.452	0.464		P = 0.444	0.517	0.703
Knee extensor strength (operated side, kg f)	r = 0.044	-0.235	-0.278	Knee extensor strength (operated side, kg f)	r = -0.077	0.070	-0.102
	P = 0.842	0.281	0.199		P = 0.726	0.751	0.643
Percent changes				Percent changes			
ΔVAS	r = 0.225	-0.093	-0.212	ΔVAS	r = 0.085	-0.265	-0.129
	P = 0.302	0.672	0.332		P = 0.699	0.221	0.558
ΔPCS	r = 0.117	-0.042	-0.047	ΔPCS	r = 0.495	-0.583	-0.427
	P = 0.594	0.849	0.831		P = 0.016[a]	0.003[a]	0.042[a]
ΔHip abductor strength (operated side, kg f)	r = -0.418	0.642	0.479	ΔHip abductor strength (operated side, kg f)	r = -0.333	0.373	0.546
	P = 0.047[a]	0.001[a]	0.021[a]		P = 0.121	0.079	0.007[a]
ΔKnee extensor strength (operated side, kg f)	r = -0.247	0.434	0.530	ΔKnee extensor strength (operated side, kg f)	r = -0.389	0.474	0.656
	P = 0.257	0.038[a]	0.009[a]		P = 0.066	0.022[a]	0.001[a]

These data were analyzed by the Pearson r rank test, with the r value as the correlation coefficient; [a]$P < 0.05$. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; TUG: Timed Up and Go; VAS: Visual analog scale; PCS: Pain catastrophizing scale.

partial correlation with percent change of physical performances. The percent change of VAS showed no correlation with percent change of physical performances. On the other hand, in THA patients, the percent change of hip abductor strength showed correlation with percent change of TUG (P = 0.047), 10-m gait time at comfortable speeds (P = 0.001), and 10-m gait time at maximum speeds (P = 0.021). The percent change of knee extensor strength showed partial correlation with percent change of physical performances. The percent change of VAS and PCS showed no correlation with percent change of physical performances.

DISCUSSION

The present study showed that changes in pain catastrophizing significantly associated with changes in physical performance in the early period after TKA, but not after THA. Changes in muscle strength significantly associated with changes in physical performance in the early period after TKA and THA. Quantification of early postoperative changes and their potential relationships to physical performance can reveal responsible mechanisms and contribute to future postoperative rehabilitation.

The importance of assessing pain catastrophizing has been highlighted in preoperative TKA or THA patients[6-11]. Pain catastrophizing associated with physical performance, more so than was pain intensity in low back pain[4,5]. In addition, better physical performance associated reduction in pain catastrophizing during treatment than scores at baseline in low back pain[3]. Some reports in low back pain showed pain catastrophizing at baseline was no

predictive for disability at follow-up[3]. This study, first, showed reductions in pain catastrophizing associated with physical performance in the early period after TKA. It is important in early postoperative treatment outcome, at least after TKA. For example, treatment that incorporates a cognitive-behavioral intervention can lead to reduction in pain catastrophizing concurrent with reduction in pain-related activity interference and disability among persons with persistent pain[2]. The intervention targeted a decrease in maladaptive behaviors, an increase in adaptive behaviors, identification, and correction of maladaptive thoughts and beliefs, and an increase in self-efficacy for pain management[23]. It was introduced to reduce pain and psychological distress and to improve physical and role function[23]. Medical staff should expand their evaluations beyond traditional demographics and medical status variables to include pain-related psychological constructs when addressing perioperative participants.

The present study showed that, in the early period after THA, changes in physical performances were not significantly associated with changes in pain catastrophizing. The VAS and PCS at postoperative at 14-d in THA was less than in TKA, consistent with previous study[24]. In general, pain-related disability might be resolved at an earlier stage than 14 d after THA. However, a recent systematic review concluded that there is no evidence for psychological factors as an influence on outcome after THA[8]. Further investigation is needed to assess longitudinal changes after THA.

Preoperative and postoperative muscle weakness is a major contributor to poor physical performance after TKA and THA[25-27]. The present study showed changes in physical performance were associated with changes in muscle strength.

There are several limitations in this study. We included only a small number of participants from a single medical center, so our observations must be interpreted with caution. The present study investigated only the early postoperative period; these findings should be considered preliminary for TKA and THA, although other studies have considered physical function in the early period after TKA and THA[12,18,24]. Scores on the preoperative PCS in the present study were higher than those reported in previous TKA studies[9-11]. This finding might be confined to the patients with high pain catastrophizing. A larger and long-term study to investigate further the association among changes in pain catastrophizing, muscle strength, and physical performance is required.

Changes in levels of pain catastrophizing were associated with changes in physical performance in the early period after TKA; and changes in muscle strength were associated with changes in physical performance in this period after both TKA and THA. These findings may contribute to future postoperative rehabilitation of lower-limb arthroplasties. Treatment based on cognitive-behavioral therapy might be useful in the early period, at least after TKA.

COMMENTS

Background

Pain treatment has targeted not only pain intensity, but also pain catastrophizing, which has been conceptualized as a negative cognitive-affective response to pain. The changes in postoperative pain intensity associate with changes in physical performance after total knee arthroplasty (TKA) or total hip arthroplasty (THA). On the other hand, the impact of changes in pain catastrophizing on outcome has not investigated in patients with TKA or THA.

Research frontiers

The purpose of the present study is to determine whether reductions in pain catastrophizing are associated with physical performance in the early period after TKA or THA.

Innovations and breakthroughs

This study, first, showed reductions in pain catastrophizing associated with physical performance in the early period after TKA.

Applications

The findings may contribute to future postoperative rehabilitation of lower-limb arthroplasties. Treatment based on cognitive-behavioral therapy might be useful in the early period, at least after TKA.

Peer-review

It is an interesting manuscript on investigating and comparing physical performance, pain ratings, pain catastrophizing, and muscle strength. This study is definitely worth publishing.

REFERENCES

1 **Healy WL**, Sharma S, Schwartz B, Iorio R. Athletic activity after total joint arthroplasty. *J Bone Joint Surg Am* 2008; **90**: 2245-2252 [PMID: 18829924 DOI: 10.2106/JBJS.H.00274]

2 **Quartana PJ**, Campbell CM, Edwards RR. Pain catastrophizing: a critical review. *Expert Rev Neurother* 2009; **9**: 745-758 [PMID: 19402782 DOI: 10.1586/ern.09.34]

3 **Wertli MM**, Burgstaller JM, Weiser S, Steurer J, Kofmehl R, Held U. Influence of catastrophizing on treatment outcome in patients with nonspecific low back pain: a systematic review. *Spine* (Phila Pa 1976) 2014; **39**: 263-273 [PMID: 24253796 DOI: 10.1097/BRS.0000000000000110]

4 **Swinkels-Meewisse IE**, Roelofs J, Oostendorp RA, Verbeek AL, Vlaeyen JW. Acute low back pain: pain-related fear and pain catastrophizing influence physical performance and perceived disability. *Pain* 2006; **120**: 36-43 [PMID: 16359797 DOI: 10.1016/j.pain.2005.10.005]

5 **Larivière C**, Bilodeau M, Forget R, Vadeboncoeur R, Mecheri H. Poor back muscle endurance is related to pain catastrophizing in patients with chronic low back pain. *Spine* (Phila Pa 1976) 2010; **35**: E1178-E1186 [PMID: 20881658 DOI: 10.1097/BRS.0b013e3181e53334]

6 **Burns LC**, Ritvo SE, Ferguson MK, Clarke H, Seltzer Z, Katz J. Pain catastrophizing as a risk factor for chronic pain after total knee arthroplasty: a systematic review. *J Pain Res* 2015; **8**: 21-32 [PMID: 25609995 DOI: 10.2147/JPR.S64730]

7 **Lewis GN**, Rice DA, McNair PJ, Kluger M. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. *Br J Anaesth* 2015; **114**: 551-561 [PMID: 25542191 DOI: 10.1093/bja/aeu441]

8 **Vissers MM**, Bussmann JB, Verhaar JA, Busschbach JJ, Bierma-Zeinstra SM, Reijman M. Psychological factors affecting the outcome of total hip and knee arthroplasty: a systematic review. *Semin Arthritis Rheum* 2012; **41**: 576-588 [PMID: 22035624 DOI: 10.1016/j.semarthrit.2011.07.003]

9 **Riddle DL**, Wade JB, Jiranek WA, Kong X. Preoperative pain catastrophizing predicts pain outcome after knee arthroplasty. *Clin*

Orthop Relat Res 2010; **468**: 798-806 [PMID: 19585177 DOI: 10.1007/s11999-009-0963-y]
10 **Forsythe ME**, Dunbar MJ, Hennigar AW, Sullivan MJ, Gross M. Prospective relation between catastrophizing and residual pain following knee arthroplasty: two-year follow-up. *Pain Res Manag* 2008; **13**: 335-341 [PMID: 18719716 DOI: 10.1155/2008/730951]
11 **Sullivan M**, Tanzer M, Reardon G, Amirault D, Dunbar M, Stanish W. The role of presurgical expectancies in predicting pain and function one year following total knee arthroplasty. *Pain* 2011; **152**: 2287-2293 [PMID: 21764515 DOI: 10.1016/j.pain.2011.06.014]
12 **Stratford PW**, Kennedy DM. Performance measures were necessary to obtain a complete picture of osteoarthritic patients. *J Clin Epidemiol* 2006; **59**: 160-167 [PMID: 16426951 DOI: 10.1016/j.jclinepi.2005.07.012]
13 **Watson MJ.** Refining the Ten-metre Walking Test for Use with Neurologically Impaired People. *Physiotherapy* 2002; **88**: 386-397 [DOI: 10.1016/S0031-9406(05)61264-3]
14 **Podsiadlo D**, Richardson S. The timed "Up & amp; Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991; **39**: 142-148 [PMID: 1991946 DOI: 10.1111/j.1532-5415.1991.tb01616.x]
15 **Sullivan MJL**, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. *Psychol Assess* 1995; **7**: 524-532 [DOI: 10.1037/1040-3590.7.4.524]
16 **Matsuoka H**, Sakano Y. Assessment of cognitive aspect of pain: development, reliability, and validation of Japanese version of Pain Catastrophizing Scale. *Jpn J Psychosom Med* 2007; **47**: 95-102
17 **Andrews AW**, Thomas MW, Bohannon RW. Normative values for isometric muscle force measurements obtained with hand-held dynamometers. *Phys Ther* 1996; **76**: 248-259 [PMID: 8602410]
18 **Holm B**, Kristensen MT, Husted H, Kehlet H, Bandholm T. Thigh and knee circumference, knee-extension strength, and functional performance after fast-track total hip arthroplasty. *PM R* 2011; **3**: 117-124; quiz 124 [PMID: 21333950 DOI: 10.1016/j.pmrj.2010.10.019]
19 **Winters JD**, Christiansen CL, Stevens-Lapsley JE. Preliminary investigation of rate of torque development deficits following total knee arthroplasty. *Knee* 2014; **21**: 382-386 [PMID: 24238649 DOI: 10.1016/j.knee.2013.10.003]
20 **Lienhard K**, Lauermann SP, Schneider D, Item-Glatthorn JF, Casartelli NC, Maffiuletti NA. Validity and reliability of isometric, isokinetic and isoinertial modalities for the assessment of quadriceps muscle strength in patients with total knee arthroplasty. *J Electromyogr Kinesiol* 2013; **23**: 1283-1288 [PMID: 24113423 DOI: 10.1016/j.jelekin.2013.09.004]
21 **Roy MA**, Doherty TJ. Reliability of hand-held dynamometry in assessment of knee extensor strength after hip fracture. *Am J Phys Med Rehabil* 2004; **83**: 813-818 [PMID: 15502733]
22 **Kwoh CK**, Petrick MA, Munin MC. Inter-rater reliability for function and strength measurements in the acute care hospital after elective hip and knee arthroplasty. *Arthritis Care Res* 1997; **10**: 128-134 [PMID: 9313401 DOI: 10.1002/art.1790100208]
23 **Buenaver LF**, Campbell CM, Haythornthwaite JA. Cognitive-Behavioral Therapy for Chronic Pain. In: Fishman SM, Ballantyne JC, Rathmell JP, editor. Bonica's Management of Pain, 4th ed. Philadelphia, PA: Lea and Febiger, 2009: 1220-1229
24 **Giaquinto S**, Ciotola E, Margutti F. Gait in the early days after total knee and hip arthroplasty: a comparison. *Disabil Rehabil* 2007; **29**: 731-736 [PMID: 17453995 DOI: 10.1080/09638280600926389]
25 **Mizner RL**, Petterson SC, Clements KE, Zeni JA, Irrgang JJ, Snyder-Mackler L. Measuring functional improvement after total knee arthroplasty requires both performance-based and patient-report assessments: a longitudinal analysis of outcomes. *J Arthroplasty* 2011; **26**: 728-737 [PMID: 20851566 DOI: 10.1016/j.arth.2010.06.004]
26 **Vaz MD**, Kramer JF, Rorabeck CH, Bourne RB. Isometric hip abductor strength following total hip replacement and its relationship to functional assessments. *J Orthop Sports Phys Ther* 1993; **18**: 526-531 [PMID: 8220410 DOI: 10.2519/jospt.1993.18.4.526]
27 **Bamaç B**, Çolak T, Özbek A, Çolak S, Cinel Y, Yenigün Ö. Isokinetic performance in elite volleyball and basketball players. *Kinesiology* 2008; **40**: 182-188

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ORIGINAL ARTICLE

Clinical Trials Study

RANK-ligand and osteoprotegerin as biomarkers in the differentiation between periprosthetic joint infection and aseptic prosthesis loosening

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Abstract

AIM

To assess serum levels of RANK-ligand (RANKL) and osteoprotegerin (OPG) as biomarkers for periprosthetic joint infection (PJI) and compare their accuracy with standard tests.

METHODS

One hundred and twenty patients presenting with a painful total knee or hip arthroplasty with indication for surgical revision were included in this prospective clinical trial. Based on standard diagnostics (joint aspirate, microbiological, and histological samples) and Musculoskeletal Infection Society consensus classification, patients were categorized into PJI, aseptic loosening, and control groups. Implant loosening was assessed

radiographically and intraoperatively. Preoperative serum samples were collected and analyzed for RANKL, OPG, calcium, phosphate, alkaline phosphatase (AP), and the bone-specific subform of AP (bAP). Statistical analysis was carried out, testing for significant differences between the three groups and between stable and loose implants.

RESULTS

All three groups were identical in regards to age, gender, and joint distribution. No statistically significant differences in the serum concentration of RANKL (P = 0.16) and OPG (P = 0.45) were found between aseptic loosening and PJI, with a trend towards lower RANKL concentrations and higher OPG concentrations in the PJI group. The RANKL/OPG ratio was significant for the comparison between PJI and non-PJI (P = 0.005). A ratio > 60 ruled out PJI in all cases (specificity: 100%, 95%CI: 89, 11% to 100.0%) but only 30% of non-PJI patients crossed this threshold. The positive predictive value remained poor at any cut-off. In the differentiation between stable and loose implants, none of the parameters measured (calcium, phosphate, AP, and bAP) showed a significant difference, and only AP and bAP measurements showed a tendency towards higher values in the loosened group (with P = 0.09 for AP and P = 0.19 for bAP).

CONCLUSION

Lower RANKL and higher OPG concentrations could be detected in PJI, without statistical significance.

Key words: Aseptic loosening; Diagnostic; RANK-ligand; Periprosthetic joint infection; Biomarker; Osteoprotegerin

Core tip: No statistically significant differences in the serum concentration of RANK-ligand (RANKL) and osteoprotegerin (OPG) were found between aseptic loosening and periprosthetic joint infection (PJI) with a certain trend of lower concentrations in the PJI group. Nevertheless, a RANKL/OPG ratio > 60 ruled out PJI in all cases. In the differentiation between a stable and loose implant the parameters measured showed no significant difference, which let to the conclusion that the sole use of these parameters for differentiating PJI and aseptic loosening cannot be recommended. RANK and OPG may have utility as a conformation test but are not an effective screening parameter for the discrimination of PJI and AL.

Friedrich MJ, Wimmer MD, Schmolders J, Strauss AC, Ploeger MM, Kohlhof H, Wirtz DC, Gravius S, Randau TM. RANK-ligand and osteoprotegerin as biomarkers in the differentiation between periprosthetic joint infection and aseptic prosthesis loosening. *World J Orthop* 2017; 8(4): 342-349 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i4/342.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i4.342

INTRODUCTION

Periprosthetic joint infection (PJI) after total joint replacement still remains one of the most serious complications and is a key challenge in orthopedic surgery. A precise and rapid diagnosis of implant failure is mandatory for treatment success. The differentiation between PJI and aseptic loosening can, in particular, be unyielding or controversial, and misdiagnosis can lead to serious and permanent impairment. As the treatment of PJI is completely different from the treatment of aseptic loosening, its correct and timely diagnosis is crucial for successful therapy and relies in part on the use of molecular markers. Nevertheless, establishing a definite diagnosis of PJI prior to surgical intervention is at times difficult. Numerous researchers have focused on the development of novel and more accurate molecular methods[1-5]. However, there is no diagnostic gold standard so far. Various definitions have been proposed and current recommendations are based on several prae-, intra-, and postoperative parameters[6,7].

Previous studies have suggested osteoprotegerin (OPG) and receptor activator of nuclear factor-κB ligand (RANK Ligand, RANKL) as markers of periprosthetic osteolysis[8,9]. RANKL and its receptor RANK and OPG play an important role in osteoclastogenesis as final effectors of bone resorption. RANKL, which expresses on the surface of osteoblast, stromal cells and activated T-lymphocytes, binds to RANK on osteoclastic precursors cells or mature osteoclasts, and thereby promotes osteoclastogenesis and bone resorption. OPG, which is expressed by osteoblasts and stromal cells, strongly inhibits bone resorption by binding to its ligand RANKL, and thereby preventing it from binding to its receptor, RANK. The RANKL/RANK/OPG system regulates the formation of multinucleated osteoclasts from their precursors as well as their activation and survival in normal bone remodeling[10,11]. Therefore, the balance between OPG and RANKL is essential to regulate bone remodeling, by controlling the activation state of RANK on osteoclasts[12].

In cases of aseptic loosening, it has been demonstrated that the accumulation of wear debris around the joint leads to an activation of mononuclear cells and T-lymphocytes, resulting in a multinuclear cell giant cell reaction. This causes an osteoclast activation and bone resorption[13]. Periprosthetic membranes retrieved from patients with aseptic loosening contain fibroblasts, macrophages, and T lymphocytes[14], as well as osteoclasts and multinucleated foreign body giant cells[15]. This periprosthetic tissue produces a variety of factors including tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6 and other peptides that stimulate osteoclasts through the induction of RANKL[16,17]. TNF in turn directly stimulates the production of RANKL by stromal cells, T-lymphocytes, and endothelial cells. Indirect stimulus of RANKL expression works the TNF-induced up regulation of prostaglandins, IL-1 or IL-17, resulting in an advanced expression of RANKL as well. The dominant form of this

response is due to innate reactivity to implant debris through danger associated molecular pattern signaling and inflammatory responses[18].

Correspondingly, in the pathogen-associated molecular patterns in PJI, bacterial toxins and parts of the pathogen's cell membrane seem to induce infiltration with mainly neutrophil granulocytes and macrophages. Though the trigger is a different one, the final result with bone loosening and prosthesis failure is the same. So far, there are no investigations concerning the exact role of interleukins and RANKL/OPG signaling in PJI-associated prosthesis failure. The role of the RANKL/RANK/OPG system has not yet been examined in the differentiation between PJI and aseptic prosthesis loosening. In this study, therefore, we defined the sensitivity, specificity, and accuracy of RANKL and OPG in patients with PJI *vs* aseptic loosening and compared these results to current standards of diagnostic testing. Total joint replacement without signs of PJI or aseptic loosening severed as the control group. Furthermore, we tested whether there is a difference between loosened and stable implants in the serum levels of these and other parameters.

Our hypothesis was that the measured serum levels of RANKL and OPG correlate positively: (1) with the presence of PJI; and (2) with implant loosening. Secondly, we investigated if the serum levels of calcium (Ca^{2+}), phosphate (PO_4), and alkaline phosphatase (AP) would be different in stable or loosened implants.

MATERIALS AND METHODS

This prospective study was approved by the local Institutional Review Board and Ethics committee with informed consent obtained in compliance with the declaration of Helsinki prior to being enrolled in the study. Between 2010 and 2011 we included 120 consecutive patients presenting with a painful total hip or total knee arthroplasty undergoing revision arthroplasty surgery for (1) PJI; (2) aseptic failure (AL); or (3) aseptic revision causes without PJI or aseptic loosening. Any patient scheduled to undergo revision surgery of a hip or knee arthroplasty were included. After signing of informed consent, all patients underwent standardized diagnostics as outlined in literature[19]. Preoperative serum samples were collected and joint aspiration was performed under strictly aseptic conditions for cell count, cell differentiation, and microbiological analysis.

White blood cell count was determined from the blood samples, and serum samples were analyzed for C-reactive protein (CRP) (Dimension Vista, Siemens Medical Solutions Diagnostics GmbH, Eschborn, Germany), RANKL, and OPG (Sandwich ELISA, Fa. BioVendor GmbH, Heidelberg, Germany); Serum Ca^{2+}, serum PO_4, AP and the bone-specific subform of the AP (bAP) were also analyzed in serum (Immunolite, Siemens, Eschborn, Germany). Ratio of RANKL/OPG was calculated from the determined values.

Intraoperatively, tissue specimens were taken for microbiological and histological analysis[20], and the intraoperative aspect was recorded. Assessment of relevant implant instability is a routine for the experienced arthroplasty surgeon and part of many revision algorithms. If in the surgeon's view at least one implant component with bony contact could be removed with ease after debridement, the implant was considered "loosened"[19]. Also, radiographic signs of loosening were taken into account where implant migration or dislocation could clearly be seen preoperatively.

Depending on the results of the laboratory diagnostics, including serum CRP as well as cell count and differentiation of the aspirate, microbiologic assessment of aspirate and intraoperative cultures, as well as histopathology of the intraoperative samples, the diagnosis of PJI was considered proven following the criteria according to the Musculoskeletal Infection Society (MSIS) consensus paper by Parvizi *et al*[7], independent of the implant being loose or stable. Those who did not meet the criteria for a diagnosis of PJI and required a revision due to loosening were assigned as aseptic loosening (AL) group. Those without signs of PJI or loosening were assigned as controls (control group). For subanalysis of loosening, the PJI group was divided for those presenting with a macroscopically loosened implant *vs* those with stable implants. Demographic data (age, sex, body mass index, type of prosthesis [total hip arthroplasty (THA)/total knee arthroplasty (TKA)] were collected for comparative analysis.

Data were collected in Microsoft Excel (Microsoft Corporation, Richmond, United States), and statistical analysis was carried out using GraphPad Prism 5.04 (GraphPad Software, La Jolla, CA, United States), testing for statistical significance between the three groups with Kruskal-Wallis-ANOVA without assuming normal distribution and with Dunn's post-hoc test. To test for significance between PJI *vs* non-PJI or stable *vs* loose, Mann-Whitney *t*-tests were used, and Receiver-Operator-Characteristic (ROC) curves were calculated to assess the discriminatory strength on the basis of the area under the curve (AUC) and to determine optimal cut-off. Nonparametric Correlation (Spearman) was calculated between selected parameters. According to the "Standards for Reporting of Diagnostic Accuracy", probabilistic measures, such as sensitivity, specificity, likelihood ratios, and their confidence limits for individual values and combinations were calculated[21]. For calculating the geometric coefficient of variation (GCV), data was log-transformed and coefficient of variation calculated from the transformed data set.

RESULTS

One hundred and twenty patients were enrolled into our prospective cohort study. In all groups, there were no differences with regard to age, gender, or joint distribution. In the PJI group (26 THA, 54%) and in the aseptic loosening group (35 THA, 69%), more THA were recruited, while the control group included more TKA (13 TKA, 62%). The patient demographics and details are

Table 1 Patient demographics

Group	Total (*n*)	Mean age (± SD)	Sex (W:M)	Joint (hip:knee)
PJI	48	69.5 yr (± 12.1 yr)	27 female 21 male	22 TKA 26 THA
Aseptic loosening	51	68 yr (± 11.1 yr)	33 female 18 male	16 TKA 35 THA
Control	21	64.05 yr (± 11.9 yr)	13 female 8 male	13 TKA 8 THA
All	120	67.94 (± 11.7)	73 female 47 male	51 TKA 69 THA
P		0.2686	0.8611	0.1110

One hundred and twenty consecutive patients were enrolled in the study prospectively. Group assignment was done according to the criteria as mentioned above. There was no statistical difference in patient age, gender, or distribution of joints in the groups. More women than men were enrolled in total and in all groups. There was a lower number of total hip arthroplasties (THA) than total knee arthroplasties (TKA) only in the control group. PJI: Periprosthetic joint infection.

given in Table 1. In our collective, 31 out of 48 patients (64%) in the PJI group had consistent findings in two or more positive microbiology cultures, matching the "major" MSIS criterion for microbiology; another five patients had one positive culture, and the remaining 12 patients were "culture negative" PJIs.

Statistical analysis was completed to compare the means of laboratory values between the three groups. The results are summarized in Figure 1A and B. We found no significant differences in the mean values of PJI, AL, or the control group in the serum concentration of RANKL (P = 0.16) or OPG (P = 0.45) with a certain trend of lower RANKL concentrations and higher OPG concentrations in the PJI group. The "geometric" coefficients of variation were within a tolerable range. For RANKL, we calculated GCV as 10.65% (PJI), 18.6% (AL), and 15.85% (Control), for OPG we calculated GCV as 21.46% (OPG), 19.33% (AL) and 19.65% (Control). To assess discriminatory strength of these parameters, we pooled the AL and control group into a larger non-PJI group and calculated ROC with AUC, and a non-parametric *t*-test (Figure 1C-F). Neither RANKL nor OPG showed a significant difference (P = 0.26 for RANKL and P = 0.3 for OPG), and discriminatory strength was poor (AUC: 0.57 ± 0.05 for RANKL and 0.56 ± 0.06 for OPG). Since the aforementioned trend was still visible, we calculated sensitivity and specificity for different cut-offs and found the best, yet still poor likelihood ratio to detect a PJI for RANKL at < 188.9 pmol/L [sensitivity: 93.94%, 95% confidence interval (95%CI): 79,77% to 99.26%; specificity: 32.47%, 95%CI: 22.23% to 44.10%, likelihood ratio: 1.39], and for OPG at > 9.38 pmol/L (sensitivity: 28.13%, 95%CI: 13.75% to 46.75%; specificity: 89.33%, 95%CI: 80.06% to 95.28%, likelihood ratio: 2.64).

To determine if the parameters were independent of each other, we calculated the Spearman correlation, which showed an r of 0.01 (95%CI: 0.18 to 0.21, P = 0.88) stating that there was neither a positive nor a negative correlation between OPG and RANKL. We therefore calculated the RANKL/OPG ratio as an additional parameter, to make use of possible synergistic effects. Though this parameter also remained without statistical significance between all three groups (P = 0.1), the comparison between PJI and non-PJI (Figure 1G and H) was significant (with P = 0.005) and the discriminatory strength was much enhanced (AUC: 0.7 ± 0.05). A ratio > 60 ruled out PJI in all cases (specificity: 100%, 95%CI: 89.11% to 100.0%) but only 30% of non-PJI patients crossed this threshold (95%CI: 21.67% to 40.29%), while the positive predictive value remained poor at any cut-off.

Both groups, PJI and non-PJI included patients where parts of the prosthesis were loosened. We therefore assessed whether or not any of the parameters would correlate with the bony integration and a stable interface of the prosthesis. None of the parameters measured showed a significant difference in this analysis (Figure 2), and only the AP and bAP measurements showed a tendency towards higher values in the loosened group (with P = 0.09 for AP and P = 0.19 for bAP). No other trends were visible, and no further statistics were calculated.

DISCUSSION

The accurate diagnosis of PJI is difficult, as the clinical symptoms often resemble those of aseptic loosening, with nonspecific pain and swelling of the joint. Though both entities share a common final pathway, leading to osteolysis and implant failure, their exact pathomechanisms remain unclear. Analyzing the available evidence and existing published data on the definition of PJI, a workgroup convened by the MSIS presented a summary of recommendations concerning a new definition for PJI[7]. These recommendations are based on clinical findings, laboratory parameters, sterile joint aspiration for synovial leucocyte count, and microbiological analysis as well as tissue sampling for histopathology. Nevertheless, because of the inconsistent data, even the MSIS cannot provide general recommendations in interpretation of single aspects (*e.g.*, different cut-off values of CRP or leukocyte count in synovial tests). Consequently, there is a need for further research and development into new methods aimed at improving diagnostic accuracy and speed of detection.

Several studies have attempted to assess the clinical relevance of RANKL and OPG levels in a variety of human diseases characterized by local or systemic changes in bone remodeling[8,17,22,23]. The essential role of the OPG/RANK/RANKL pathway in regulating bone remodeling around orthopedic implants is well recognized, but the clinical usefulness of circulating OPG and RANKL levels in the differentiation between PJI and aseptic loosening is unknown.

Our hypothesis was therefore that the measured serum levels of RANKL and OPG correlate positively: (1) with the presence of PJI; and (2) with implant loosening. Secondly, we investigated if the serum levels of calcium, phosphate, and alkaline phosphatase would be different

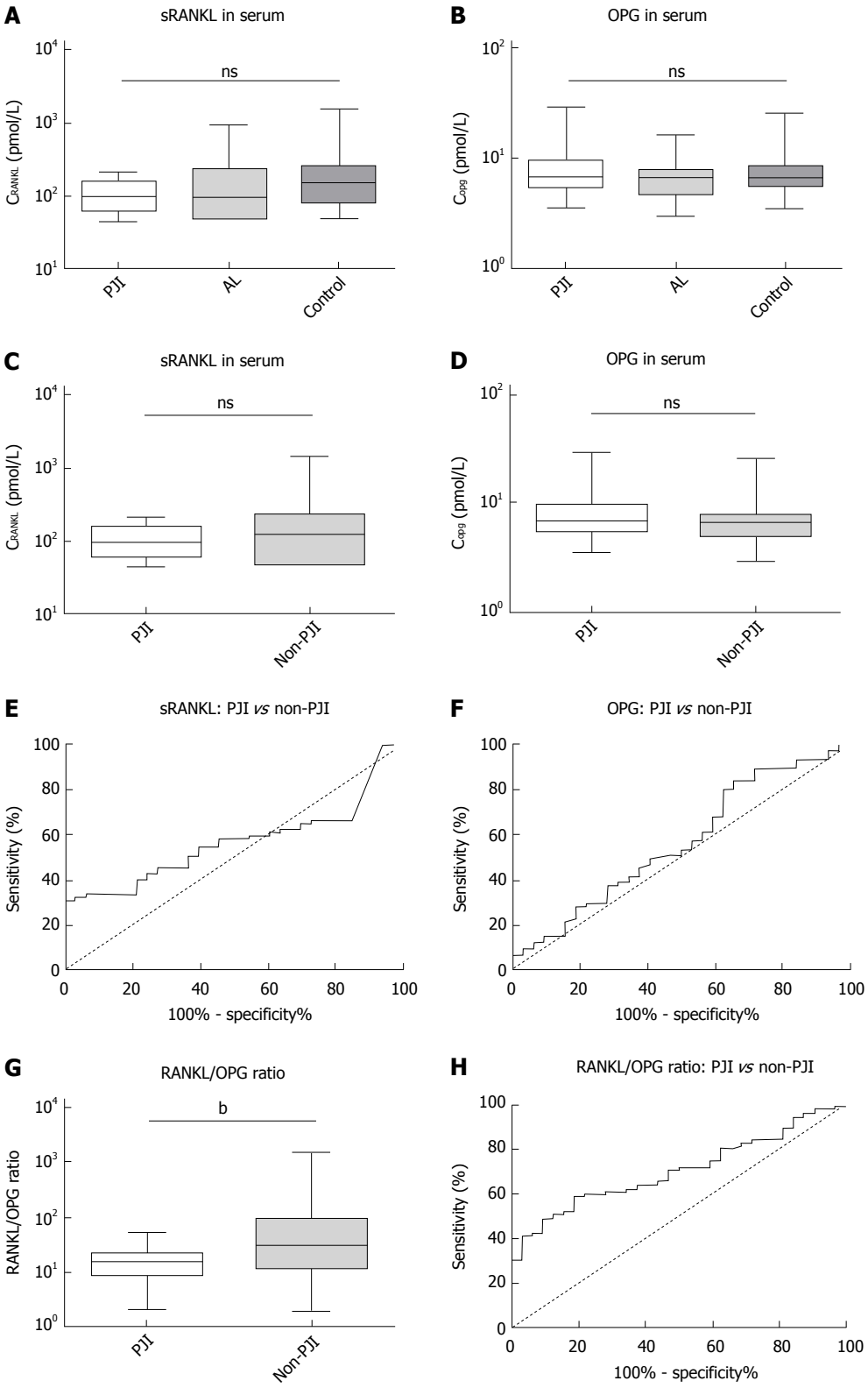

Figure 1 sRANKL and osteoprotegerin in serum, periprosthetic joint infection *vs* non-periprosthetic joint infection. Analysis of variance (Kruskal-Wallis-ANOVA) without assuming normal distribution with Dunn's *post-hoc* test. RANKL and OPG serum levels showed no significant (ns) differences in the mean values between periprosthetic joint infection (PJI) and aseptic loosening (AL) and between PJI and control (A and B). ANOVA for a pooled group of non-PJI (AL + control) *vs* PJI did not show a significant difference for either RANKL or OPG ($P = 0.26$ for RANKL and $P = 0.3$ for OPG) (C and D). The receiver-operating characteristic (ROC) curve of RANKL and OPG showed a poor discriminatory strength (AUC: 0.57 ± 0.05 for RANKL and 0.56 ± 0.06 for OPG) (E and F). ANOVA for the RANKL/OPG ratio showed a significant difference between PJI and non-PJI (G), and the discriminatory strength was enhanced with an AUC of 0.7 ± 0.05 (H); $^{b}P < 0.001$. RANKL: RANK-ligand; OPG: Osteoprotegerin.

in stable or loosened implants.

According to the results, we had to discard our above mentioned hypotheses, as we found no significant differences in the mean values of circulating RANKL and

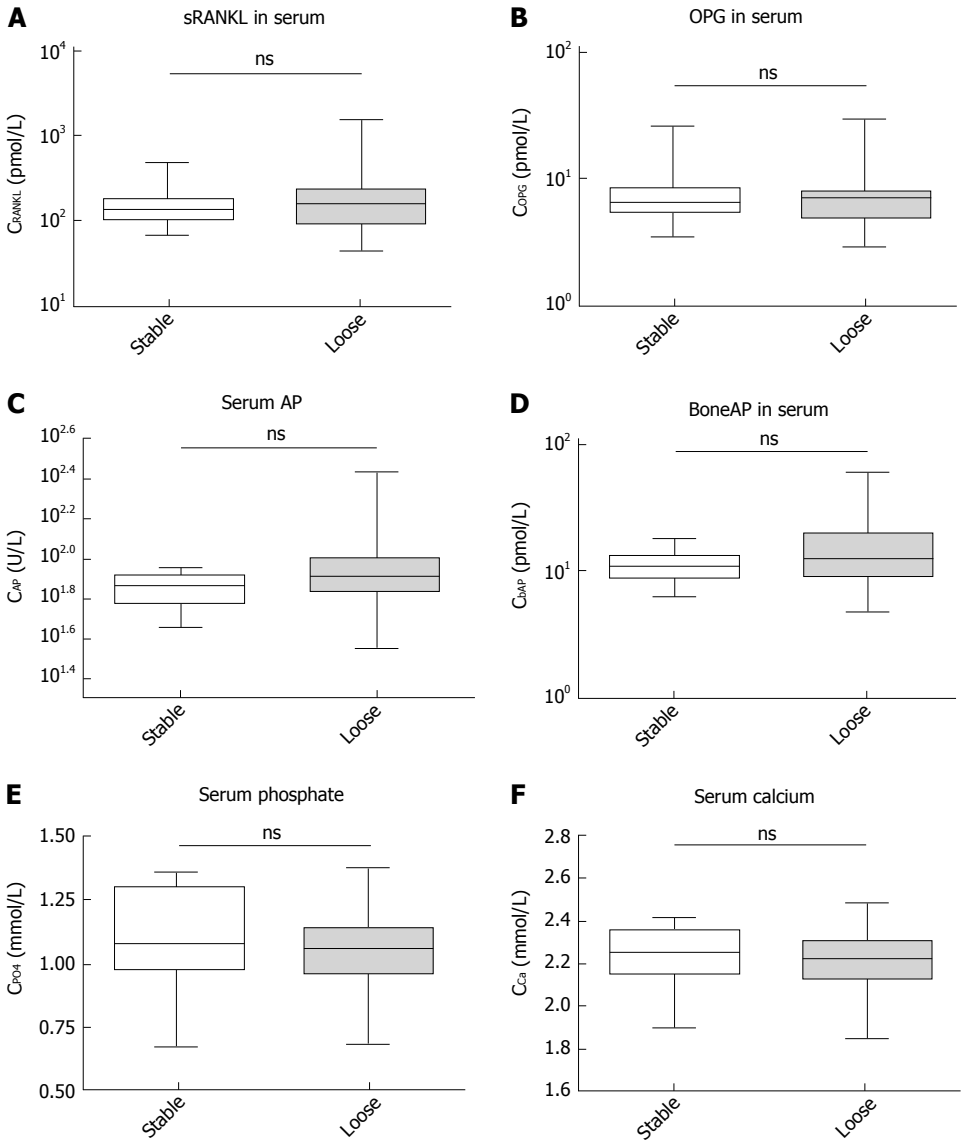

Figure 2 Serum parameters, loosened *vs* stable implants. Analysis of variance (Kruskal-Wallis-ANOVA) without assuming normal distribution with Dunn's *post-hoc* test. RANKL and OPG serum levels showed no significant (ns) differences in the mean values between a stable and loose implant (A and B), nor did the other parameters as alkaline phosphatase (AP), boneAP, and serum phosphate (C-F). RANKL: RANK-ligand; OPG: Osteoprotegerin.

OPG in PJI *vs* AL or control groups, but found a certain trend of lower RANKL concentrations and higher OPG concentrations in the PJI group.

Granchi *et al*[8] tried to evaluate whether serum levels of OPG and RANKL could be different in patients with aseptic loosening compared to patients with stable implants. While the serum levels of RANKL and the OPG-to-RANKL ratio showed no significant changes with the clinical condition or status of the implant, an increased serum level of OPG provides good diagnostic accuracy in detecting implant failure due to aseptic loosening with a sensitivity of 92%, a specificity of 75%, and a positive likelihood ratio of 7.1[8]. These findings are in accordance with the results of He *et al*[24] who analyzed multiple biomarkers for the detection of aseptic loosening in total hip arthroplasty. They found elevated plasma levels of OPG in failed THA and an increase of OPG plasma level from stable healthy patients to early aseptic loosening to late aseptic loosening, stating that OPG may reflect a protective mechanism of the skeleton to increased bone resorption thereby inhibiting osteoclast formation and bone resorbing activity in aseptic loosening. These findings are in contrast to our observations, as we could not see any significant differences of OPG and RANKL plasma levels in the subanalyses between stable and loose implants. Only the AP and bAP measurements showed a tendency towards higher values in the loosened group. On the other hand, we successfully evaluated and confirmed that the RANKL/OPG ratio as an additional parameter may help in the differentiation between aseptic loosening and PJI as a ratio > 60 ruled out PJI in all cases. These results suggest that osteolysis inside the periprosthetic interface of artificial joints is not associated with a significant systemic elevation of the RANKL/RANK/OPG system.

The current paradigm to explain aseptic loosening involves an inflammatory response to wear debris par-

ticles produced by prosthetic implants. These particles are phagocytosed by macrophages adjacent to the implant resulting in cell activation and the release of cytokines as well as in a localized inflammatory response. By examination of periprosthetic tissues of 59 patients undergoing hip replacement revision for aseptic loosening Veigl *et al*[25] could show that RANKL is present only in tissues with a large amount of wear debris and predominantly in cases involving loosened cemented implants. Gehrke *et al*[9] examined the presence and distribution of RANKL, RANK and OPG in the periprosthetic interface in cases of septic and aseptic loosening by immunohistochemistry and immunoblotting. They could show a different histopathologic pattern as well as a difference in grade of inflammatory infiltrate. The inflamed periprosthetic tissue produces a variety of factors including TNFα, IL-1, IL-6 and prostaglandin stimulating osteoclast to resorb bone through the induction of RANKL. However, none of these cytokines represents a final common pathway for the process of particle-induced osteoclast differentiation and maturation. While many of these biomarkers are established in the differentiation between aseptic loosening and PJI, to the best of our knowledge, the role of the RANKL/RANK/OPG system has not yet been examined.

We acknowledge that our study has limitations. It must be considered that group definition is difficult in revision arthroplasty. The MSIS has defined a "gold standard" in PJI diagnostics. But they also acknowledge that infection may be present even without major or minor criteria being fulfilled. We therefore cannot guarantee that patients with low-grade infections and low virulence would not be misclassified into the "aseptic loosening" or control group. Also, the sample size is low for a study investigating arthroplasties. The inhomogenity of the patients investigated is both a weakness and strength of the paper. We did not exclude patients with systemic or inflammatory diseases that may also interfere with the parameters investigated. Patients with PJI are complex and difficult to compare, but this represents day-to-day clinical experience. Eventually, new biomarkers and a further modification of the therapy algorithm may become necessary.

COMMENTS

Background

Periprosthetic joint infection (PJI) after total joint replacement still remains one of the most serious complications and is a key challenge in orthopedic surgery. A precise and rapid diagnosis of implant failure is mandatory for treatment success. Especially the differentiation between PJI and aseptic loosening can be unyielding or controversial and misdiagnosis can lead to serious and permanent impairment. As the treatment of PJI is completely different to the treatment of aseptic loosening the correct and timely diagnosis is crucial for successful therapy and relies in part on the use of molecular markers. Nevertheless, establishing a definite diagnosis of PJI prior to surgical intervention is at times difficult.

Research frontiers

Numerous researchers have focused on the development of novel and more accurate molecular methods. However, there is no diagnostic gold standard so far. Several studies have attempted to assess the clinical relevance of RANK-ligand (RANKL) and osteoprotegerin (OPG) levels in a variety of human diseases characterized by local or systemic changes in bone remodeling. The essential role of the OPG/RANK/RANKL pathway in regulating bone remodeling around orthopedic implants is well recognized, but the clinical usefulness of circulating OPG and RANKL levels in the differentiation between PJI and aseptic loosening is unknown.

Innovations and breakthroughs

No statistically significant differences in the serum concentration of RANKL and OPG were found between aseptic loosening and PJI, with a trend towards lower RANKL concentrations and higher OPG concentrations in the PJI group.

Applications

The sole use of these parameters for differentiating PJI and aseptic loosening cannot be recommended, but they may have utility as a conformation test.

Terminology

Receptor activator of nuclear factor-KB (RANK) ligand (RANKL), its receptor RANK and OPG play an important role in osteoclastogenesis as final effectors of bone resorption. RANKL, which expresses on the surface of osteoblast, stromal cells and activated T-lymphocytes, binds to RANK on osteoclastic precursors cells or mature osteoclasts, and thereby promotes osteoclastogenesis and bone resorption. While OPG, which is expressed by osteoblasts and stromal cells, strongly inhibits bone resorption by binding to its ligand RANKL and thereby preventing it from binding to its receptor, RANK. The RANKL/RANK/OPG system regulates the formation of multinucleated osteoclasts from their precursors as well as their activation and survival in normal bone remodeling. Therefore, the balance between OPG and RANKL is essential to regulate bone remodeling, by controlling the activation state of RANK on osteoclasts.

Peer-review

A good study with a well stated hypothesis and methodology.

REFERENCES

1 **Gollwitzer H**, Dombrowski Y, Prodinger PM, Peric M, Summer B, Hapfelmeier A, Saldamli B, Pankow F, von Eisenhart-Rothe R, Imhoff AB, Schauber J, Thomas P, Burgkart R, Banke IJ. Antimicrobial peptides and proinflammatory cytokines in periprosthetic joint infection. *J Bone Joint Surg Am* 2013; **95**: 644-651 [PMID: 23553300 DOI: 10.2106/JBJS.L.00205]

2 **Deirmengian C**, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Diagnosing periprosthetic joint infection: has the era of the biomarker arrived? *Clin Orthop Relat Res* 2014; **472**: 3254-3262 [PMID: 24590839 DOI: 10.1007/s11999-014-3543-8]

3 **Gravius S**, Randau TM, Casadonte R, Kriegsmann M, Friedrich MJ, Kriegsmann J. Investigation of neutrophilic peptides in periprosthetic tissue by matrix-assisted laser desorption ionisation time-of-flight imaging mass spectrometry. *Int Orthop* 2015; **39**: 559-567 [PMID: 25277763 DOI: 10.1007/s00264-014-2544-2]

4 **Friedrich MJ**, Randau TM, Wimmer MD, Reichert B, Kuberra D, Stoffel-Wagner B, Wirtz DC, Gravius S. Lipopolysaccharide-binding protein: a valuable biomarker in the differentiation between periprosthetic joint infection and aseptic loosening? *Int Orthop* 2014; **38**: 2201-2207 [PMID: 24827968 DOI: 10.1007/s00264-014-2351-9]

5 **Randau TM**, Friedrich MJ, Wimmer MD, Reichert B, Kuberra D, Stoffel-Wagner B, Limmer A, Wirtz DC, Gravius S. Interleukin-6 in serum and in synovial fluid enhances the differentiation between periprosthetic joint infection and aseptic loosening. *PLoS One* 2014; **9**: e89045 [PMID: 24586496 DOI: 10.1371/journal.pone.0089045]

6 **Zimmerli W**, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med* 2004; **351**: 1645-1654 [PMID: 15483283 DOI: 10.1056/NEJMra040181]

7 **Parvizi J**, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, Garvin KL, Mont MA, Wongworawat MD, Zalavras

CG. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. *Clin Orthop Relat Res* 2011; **469**: 2992-2994 [PMID: 21938532 DOI: 10.1007/s11999-011-2102-9]

8 **Granchi D**, Pellacani A, Spina M, Cenni E, Savarino LM, Baldini N, Giunti A. Serum levels of osteoprotegerin and receptor activator of nuclear factor-kappaB ligand as markers of periprosthetic osteolysis. *J Bone Joint Surg Am* 2006; **88**: 1501-1509 [PMID: 16818976 DOI: 10.2106/JBJS.E.01038]

9 **Gehrke T**, Sers C, Morawietz L, Fernahl G, Neidel J, Frommelt L, Krenn V. Receptor activator of nuclear factor kappaB ligand is expressed in resident and inflammatory cells in aseptic and septic prosthesis loosening. *Scand J Rheumatol* 2003; **32**: 287-294 [PMID: 14690142]

10 **Boyce BF**, Xing L. The RANKL/RANK/OPG pathway. *Curr Osteoporos Rep* 2007; **5**: 98-104 [PMID: 17925190]

11 **Boyce BF**, Xing L. Biology of RANK, RANKL, and osteoprotegerin. *Arthritis Res Ther* 2007; **9** Suppl 1: S1 [PMID: 17634140 DOI: 10.1186/ar2165]

12 **Boyle WJ**, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature* 2003; **423**: 337-342 [PMID: 12748652 DOI: 10.1038/nature01658]

13 **Charnley J**. Long-term results of low-friction arthroplasty. *Hip* 1982: 42-49 [PMID: 7166505]

14 **Goldring SR**, Schiller AL, Roelke M, Rourke CM, O'Neil DA, Harris WH. The synovial-like membrane at the bone-cement interface in loose total hip replacements and its proposed role in bone lysis. *J Bone Joint Surg Am* 1983; **65**: 575-584 [PMID: 6304106]

15 **Gravius S**, Mumme T, Delank KS, Eckardt A, Maus U, Andereya S, Hansen T. [Immunohistochemical analysis of periprosthetic osteolysis in aseptic loosening of hip arthroplasty]. *Z Orthop Unfall* 2007; **145**: 169-175 [PMID: 17492556 DOI: 10.1055/s-2007-965184]

16 **Chiba J**, Rubash HE, Kim KJ, Iwaki Y. The characterization of cytokines in the interface tissue obtained from failed cementless total hip arthroplasty with and without femoral osteolysis. *Clin Orthop Relat Res* 1994; (**300**): 304-312 [PMID: 7510596]

17 **Ritchlin CT**, Schwarz EM, O'Keefe RJ, Looney RJ. RANK, RANKL and OPG in inflammatory arthritis and periprosthetic osteolysis. *J Musculoskelet Neuronal Interact* 2004; **4**: 276-284 [PMID: 15615495]

18 **Landgraeber S**, Jäger M, Jacobs JJ, Hallab NJ. The pathology of orthopedic implant failure is mediated by innate immune system cytokines. *Mediators Inflamm* 2014; **2014**: 185150 [PMID: 24891761 DOI: 10.1155/2014/185150]

19 **Wimmer MD**, Randau TM, Petersdorf S, Pagenstert GI, Weißkopf M, Wirtz DC, Gravius S. Evaluation of an interdisciplinary therapy algorithm in patients with prosthetic joint infections. *Int Orthop* 2013; **37**: 2271-2278 [PMID: 23851647 DOI: 10.1007/s00264-013-1995-1]

20 **Krenn V**, Morawietz L, Kienapfel H, Ascherl R, Matziolis G, Hassenpflug J, Thomsen M, Thomas P, Huber M, Schuh C, Kendoff D, Baumhoer D, Krukemeyer MG, Perino G, Zustin J, Berger I, Rüther W, Poremba C, Gehrke T. [Revised consensus classification. Histopathological classification of diseases associated with joint endoprostheses]. *Z Rheumatol* 2013; **72**: 383-392 [PMID: 23446461 DOI: 10.1007/s00393-012-1099-0]

21 **Bossuyt PM**, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative. *Ann Intern Med* 2003; **138**: 40-44 [PMID: 12513043]

22 **Hofbauer LC**, Schoppet M. Serum measurement of osteoprotegerin--clinical relevance and potential applications. *Eur J Endocrinol* 2001; **145**: 681-683 [PMID: 11720890]

23 **Martin TJ**, Sims NA. RANKL/OPG; Critical role in bone physiology. *Rev Endocr Metab Disord* 2015; **16**: 131-139 [PMID: 25557611 DOI: 10.1007/s11154-014-9308-6]

24 **He T**, Wu W, Huang Y, Zhang X, Tang T, Dai K. Multiple biomarkers analysis for the early detection of prosthetic aseptic loosening of hip arthroplasty. *Int Orthop* 2013; **37**: 1025-1031 [PMID: 23467893 DOI: 10.1007/s00264-013-1837-1]

25 **Veigl D**, Niederlová J, Krystůfková O. Periprosthetic osteolysis and its association with RANKL expression. *Physiol Res* 2007; **56**: 455-462 [PMID: 16925460]

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ORIGINAL ARTICLE

Observational Study

T1ρ/T2 mapping and histopathology of degenerative cartilage in advanced knee osteoarthritis

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Abstract

AIM

To investigate whether normal thickness cartilage in osteoarthritic knees demonstrate depletion of proteoglycan or collagen content compared to healthy knees.

METHODS

Magnetic resonance (MR) images were acquired from 5 subjects scheduled for total knee arthroplasty (TKA) (mean age 70 years) and 20 young healthy control subjects without knee pain (mean age 28.9 years). MR images of T1ρ mapping, T2 mapping, and fat suppressed proton-density weighted sequences were obtained.

Following TKA each condyle was divided into 4 parts (distal medial, posterior medial, distal lateral, posterior lateral) for cartilage analysis. Twenty specimens (bone and cartilage blocks) were examined. For each joint, the degree and extent of cartilage destruction was determined using the Osteoarthritis Research Society International cartilage histopathology assessment system. In magnetic resonance imaging (MRI) analysis, 2 readers performed cartilage segmentation for T1ρ/T2 values and cartilage thickness measurement.

RESULTS

Eleven areas in MRI including normal or near normal cartilage thickness were selected. The corresponding histopathological sections demonstrated mild to moderate osteoarthritis (OA). There was no significant difference in cartilage thickness in MRI between control and advanced OA samples [medial distal condyle, P = 0.461; medial posterior condyle (MPC), P = 0.352; lateral distal condyle, P = 0.654; lateral posterior condyle, P = 0.550], suggesting arthritic specimens were morphologically similar to normal or early staged degenerative cartilage. Cartilage T2 and T1ρ values from the MPC were significantly higher among the patients with advanced OA (P = 0.043). For remaining condylar samples there was no statistical difference in T2 and T1ρ values between cases and controls but there was a trend towards higher values in advanced OA patients.

CONCLUSION

Though cartilage is morphologically normal or near normal, degenerative changes exist in advanced OA patients. These changes can be detected with T2 and T1ρ MRI techniques.

Key words: T1rho; Osteoarthritis; Magnetic resonance imaging; Cartilage; Knee

Core tip: Magnetic resonance images of eleven healthy knees and five knees with advanced osteoarthritis (OA) were studied using T1ρ and T2 mapping. Histopathologic samples were also taken from the five osteoarthritic knees following total knee arthroplasty. Our results indicate that even though cartilage is morphologically normal or near normal, cartilage degenerative changes exist in advanced OA patients. This suggests that normal thickness cartilage or mild cartilage thinning in the advanced OA knee demonstrates depletion of proteoglycan or collagen content compared with similar appearing cartilage in young healthy knees. These early changes can be detected with T2 and T1ρ MRI techniques.

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INTRODUCTION

Osteoarthritis (OA) is one of the fastest growing medical conditions worldwide, affecting at least 27 million people in the United States alone[1,2]. It is a major contributor to functional disability and loss of autonomy in older adults[3]. These factors represent a significant health and financial burden to the general population[2,4]. Knee and hip OA cause the greatest burden of disability, leading to the need for prosthetic joint replacements in the most severe cases[5]. Decreasing the need for such procedures, and costs to both the patient and society, motivates the need for research into disease prevention and early detection.

OA is characterized by the progressive loss of articular cartilage. However, significant damage to the collagen-proteoglycan matrix and elevation of cartilage water content are believed to precede the loss of cartilage and consequent symptoms of knee OA[6,7]. Magnetic resonance imaging (MRI) techniques are been developed over the past decade that allow for the detection of these early and subtle changes to the cartilage matrix[8-11]. Among these techniques, T1ρ has stood out as a high sensitivity option to detect early changes without the use of contrast agents[7].

Prior studies have already demonstrated increased cartilage T1ρ values, a surrogate of cartilage damage, in patients with knee OA[12-15]. Specifically, T1ρ and T2 values are known to be elevated in asymptomatic, healthy subjects with early stage OA compared to individuals without focal lesions[13]. While severe focal lesions are common indications for total knee replacement, patients may also be considered for joint sparing or cartilage preservation procedures. We aim to determine whether normal appearing cartilage by MRI in the non-symptomatic regions of advanced knee OA demonstrate depletion of proteoglycan and collagen content by T1ρ and T2 mapping and to correlate these measurements with degenerative changes of cartilage by histology. We hypothesize that normal thickness cartilage or mild cartilage thinning (early staged cartilage degeneration) in advanced knee OA will demonstrate depletion of proteoglycan or collagen content, compared with similar appearing cartilage in young healthy knees.

MATERIALS AND METHODS

Study population

Five advanced OA patients scheduled for total knee arthroplasty (TKA) were enrolled in this study. A board certified orthopaedic surgeon (RS) recruited them (Kellgren-Lawrence score of 3 or 4; mean age 70 years, range 62-90 years; 2 men and 3 women). Twenty knees from 20 healthy volunteers (mean age 28.9 years, range

19-38 years; 13 men and 7 women) without any history of knee symptoms or prior knee surgery were used as an imaging control group. The study protocol was approved by the institutional review board and all subjects provided written informed consent before any study-related procedures were performed.

MRI

All MR studies were performed on a 3.0-T unit (Achieva, Philips Healthcare, Netherland) utilizing an 8-channel knee receive-only radiofrequency coil. Three sagittal MR images were acquired including fat suppressed (FS) proton density-weighted imaging (PDWI) sequence, T2 mapping sequence, and T1ρ mapping sequence. All sagittal images were obtained without oblique angulation, parallel to the magnetic static field (B0). Parallel imaging was used on all imaging sequences utilizing Sensitivity Encoding for MRI. The acquisition parameters were as follows. FS PDWI: 2D turbo spin-echo; Repetition time (TR)/echo time (TE) = 4311/30 ms, number of excitation (NEX) = 2, and total acquisition time = 3 min 35 s. T2 mapping: 2D turbo spin-echo; TR/TE = 2700/13, 26, 39, 52, 65, 78, 91 ms, NEX = 1 and total acquisition time = 13 min 26 s. T1ρ: 3D FS PROSET (Principle of Selective Excitation Technique); TR/TE = 6.4/3.4 ms, flip angle = 10°, echo train length = 64, NEX = 1, spin-lock frequency = 575 Hertz, time of spin-lock (TSL), 20, 40, 60 and 80 ms, and acquisition time = 4 min 9 s × 4. All images were obtained with field of view = 140 × 140 mm, slice thickness/gap = 3/0 mm, image matrix = 512 × 512, number of slices = 31 and effective in-plane spatial resolution = 0.27 × 0.27 mm. Each femoral condyle was divided into 4 areas: The medial distal condyle (MDC), medial posterior condyle (MPC), lateral distal condyle (LDC), and lateral posterior condyle (LPC). Therefore, a total of 20 areas of MRI of the femoral condyle from 5 patients with advanced OA were reviewed.

TKA

TKA was conducted as scheduled on each operative candidate. Surgically resected condyles were recovered intraoperatively and divided into 4 parts (MDC, MPC, LDC, LPC). A total of 20 specimens (bone and cartilage blocks) were histopathologically examined.

Pathology

The MDP, MPC, LDC and LDP of the distal femur removed at surgery were fixed in 10% neutral buffered formalin for at least 72 h, decalcified using dilute hydrochloric acid (Rapid Bone Decalcifier, American Master Tech Inc., Lodi CA) for two days, and post fixed in formalin for at least 2 more days. Sagittal sections across the entire mid portion of each of the condyles underwent routine paraffin embedding and staining with hematoxylin and eosin. In this way, the same region was sampled for each of the specimens, and maximum extent of the lesion could be assessed in the mid sagittal plane of each of the condyles. Additional paraffin sections were stained with Masson's trichrome and Alcian blue. For each joint, the degree and extent of cartilage destruction was determined using the Osteoarthritis Research Society International cartilage histopathology assessment system[16] by a pathologist with experience in bone and soft tissue pathology. For this system, the degree of cartilage destruction (OA grade) and the extent of destruction (OA stage) are multiplied to determine the OA score. The surgical edges were not assessed to avoid possible over-interpretation of surgical artifacts.

Imaging analysis

Images were transferred in Digital Imaging and Communications in Medicine format to a personal computer (Windows 7), which was used to perform all post-processing and analyses. T2 and T1ρ analyses were performed using in-house developed and implemented software in MatLab (MathWorks, Natick, MA) (Figure 1). Manual cartilage extraction of the femoral condyle in healthy volunteers (n = 20) and advanced OA patients (n = 5) was performed on both T2 and T1ρ images by a board-certified orthopaedic surgeon with 14 years of experience and a board-certified radiologist with 13 years of experience, independently. Images with TE = 26 in T2 and TSL = 20 in T1ρ were chosen for segmentation due to high signal-to-noise ratio compared to the other images, based on prior studies[17,18]. T2 and T1ρ values were measured in a range of -10 to 20 degrees for the distal condyle and 70 to 100 degrees for the posterior condyle (Figure 2). The angle 0 is defined along B0. We calculated average T2 and T1ρ values of two observers at each femoral condyle, and average thickness of the cartilage as pixel numbers in the segmented area at each condyle.

Statistical analysis

Differences in T2/T1ρ values and thickness of the cartilage between normal cartilage and advanced degenerative cartilage do not conform to normal distributions. These differences were assessed using a nonparametric Mann-Whitney U test. Statistical review of the study was performed by a researcher with training in biomedical statistics. SPSS Statistics version 22 (IBM, Armonk, New York) was used for calculations. In all cases, a P value of 0.05 or less was deemed statistically significant.

RESULTS

A total of 20 areas on MRI of the femoral condyles from 5 advanced OA patients were reviewed. Eleven areas including normal or near normal cartilage thickness (2 MDCs, 2 MPCs, 4 LDCs, 3 LPCs) were selected. The average OA grade, stage, and, scores of corresponding specimens (bone blocks and cartilage) were 3.82 (range: 3-4.5), 3.45 (range: 2-4), and 13.1 (range: 7-16), respectively, compatible with mild to moderate OA (Table 1). Examples of FS PDWI, hematoxylin and eosin stain, Alcian blue stain,

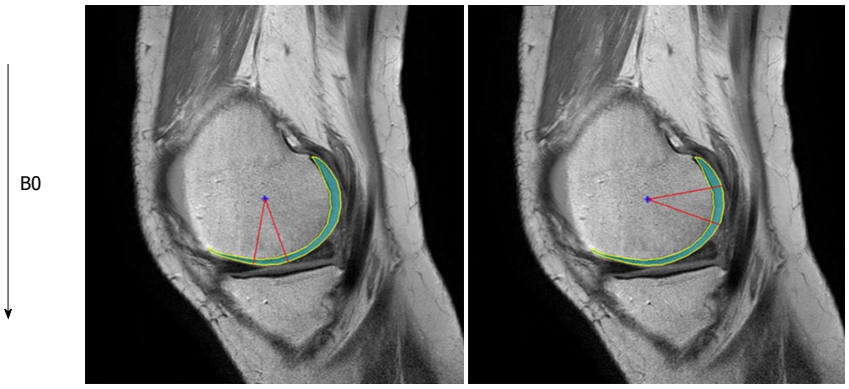

Figure 1 T2 and T1ρ relaxation time measurement. T2 and T1ρ relaxation times were measured in a range of -10 to 20 degrees for the distal condyle and 70 to 100 degrees for the posterior condyle. The angle 0 is defined along B0.

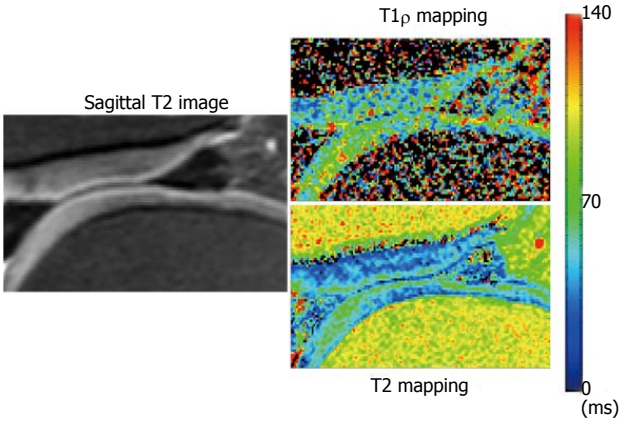

Figure 2 Example of sagittal fat suppressed proton density-weighted imaging, T1ρ mapping and T2 mapping.

and Masson's trichrome stain are demonstrated in Figure 3.

Table 2 shows the T2/T1ρ values and thickness of the cartilage in normal volunteers and advanced osteoarthritis patients. Although the difference of each cartilage thickness between normal volunteers and advanced OA patients was not observed, T2/ T1ρ values were significantly higher at the MPC in advanced OA patients compared to normal volunteers ($P < 0.05$). T2/T1ρ values also tended to be higher in advanced OA patients compared to normal volunteers at the MDC, LDC and LPC without significant difference.

DISCUSSION

Knee OA is a multifactorial disease with a significant population burden[1]. Novel strategies in the management of knee OA are based on early detection and minimally invasive procedures[11,19]. Certain patients with focal advanced knee OA may benefit from joint preservation strategies if remaining articular cartilage is healthy. In our study we aimed to assess whether normal appearing cartilage in advanced knee OA patients demonstrate depletion of proteoglycan and collagen content by T2/ T1ρ analysis, markers of early OA. We have demonstrated that although non-osteoarthritic portions of the femoral condyle in patients with advanced knee OA have similar morphologic characteristics compared to controls in routine MRI, there are significant changes on T2/T1ρ mapping that can measure differences on the biomolecular level.

Many *in vivo* studies have demonstrated an association between increased T2/T1ρ values and various stages of OA about the knee[12-15]. T1ρ values have been seen to increase with age, but are also higher in middle-aged populations with isolated patellofemoral and tibiofemoral compartment knee OA[13,14,20]. T1ρ relaxation times in particular may be elevated by as much as 30%-40% in patients with early knee OA[14]. Furthermore, Stahl *et al*[13] demonstrated that patients with asymptomatic knee OA have increased T2/T1ρ values in some compartments compared to healthy controls. These data are consistent with our findings that T2/T1ρ values are consistently higher in multiple compartments in patients with advanced OA compared to asymptomatic controls. By isolating pathologic samples with mild or near normal pathologic changes of articular cartilage we have demonstrated a subset of patients with mild arthritic changes. Li *et al*[12] have already shown significantly elevated T1ρ relaxation times in subcompartments of knee OA subjects where no prior morphologic changes were observed. This type of study demonstrates the utility of quantitative MRI sequences in detecting early biochemical changes within the articular cartilage matrix, but is limited to radiographic assessments alone. We have isolated not only radiographically similar, but pathologically similar cartilage samples to be used in this type of analysis.

This study agrees with multiple other publications that demonstrate the use of T2/T1ρ relaxation times for the early detection of knee OA[13,21,22]. The unique contribution is the comparison of normal or near normal imaging samples between cases and controls. Thuillier *et al*[23] examined patients with patellar-femoral pain but without radiographic evidence of knee OA and found significantly elevated T1ρ values in the lateral patellar cartilage compared to controls. Several other studies have also showed that focal cartilage defects identified on arthroscopy are correlated with elevated

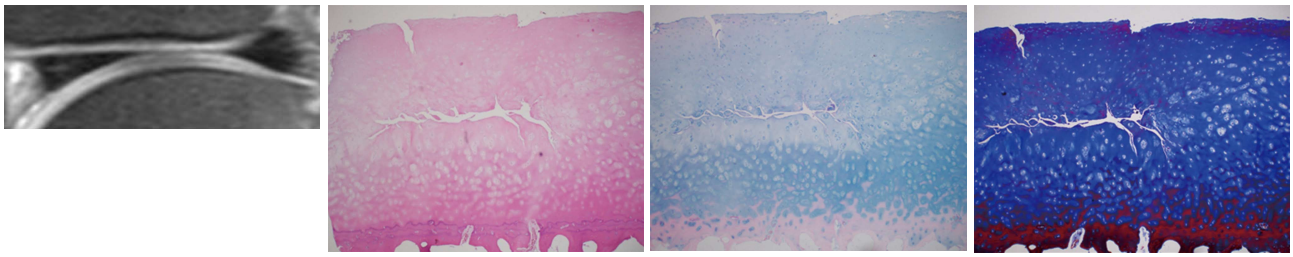

Figure 3 Example of normal thickness magnetic resonance imaging with corresponding hematoxylin and eosin, Alcian blue, and Masson trichrome stains. OA grade/stage/score in this case is 4/3/12, compatible with early OA. MRI: Magnetic resonance imaging; HE: Hematoxylin and eosin; OA: Osteoarthritis.

Table 1 Results of pathologic analysis of bone block and cartilage specimens

No.	Location	Grade	Stage	Score	Pathology comments
1	MDC	4	4	16	Superficial erosion, prominent vertical fissures and depletion of more than the upper 2/3 of proteoglycans by alcian blue staining
2	MPC	4	3	12	Focal erosion, a few small vertical clefts, depletion of the upper 1/2 to 2/3 of proteoglycans by alcian blue staining
3	LDC	3	4	12	Superficial fibrillation, small vertical clefts, minimal superficial depletion of proteoglycans by alcian blue staining
4	LDC	4.5	3	13.5	Deep erosion extending almost to bone and almost complete depletion of proteoglycans by alcian blue staining
5	MDC	4	3	12	Superficial erosion, prominent vertical and horizontal fissures and depletion of more than the upper 2/3 of proteoglycans by alcian blue staining
6	LPC	3.5	2	7	Focal superficial erosion almost complete depletion of proteoglycans by alcian blue staining
7	MPC	4	4	16	Erosion, focally deep and superficial depletion of proteoglycans by alcian blue staining over most of the surface, with complete depletion at region of deep erosion
8	LDC	3.5	4	14	Focal erosion and vertical fissures extending to mid zone with complete depletion of proteoglycans by alcian blue staining at site of fissures
9	LPC	3	4	12	Focal vertical fissures extending to mid zone with minimal depletion of proteoglycans by alcian blue staining
10	LDC	4.5	3	13.5	Focal deep erosion and superficial depletion of proteoglycans by alcian blue staining
Mean		3.82	3.45	13.09	

MDC: Medial distal condyle; MPC: Medial posterior condyle; LDC: Lateral distal condyle; LPC: Lateral posterior condyle.

MRI relaxation times[22,24,25]. We have similarly shown that morphologically normal articular cartilage, though adjoining osteoarthritic compartments of the knee, exhibit early changes in cartilage degeneration. These early changes include articular cartilage hydration, loss of proteoglycan content, thinning and loosening of collagen fibrils. While statistically significant changes were not observed in all compartments for this small sample size, the trends are readily apparent in all groups and notably significant in the MPC.

The utility of these sequences in joint preservation or replacement remains to be seen. T2 and T1ρ mapping have increasingly been applied with high fidelity to track outcomes after articular cartilage repair[26]. Studies have shown significant improvements in T1ρ relaxation times following microfracture and mosaicplasty, but values do not appear to ever return to baseline[26-28]. The question stands as to whether focal articular cartilage defects about the knee are amenable to preservation therapies if surrounding articular cartilage exhibits degenerative changes. No doubt there is a spectrum and diversity of cartilage injuries, and only a subset are arthritic in nature, but our data suggest that patients should be closely examined for early articular changes prior to such therapies. T2 and T1ρ mapping may have an important role in identifying which patients may benefit from preservation strategies and which are better candidates for joint replacement. Furthermore, these strategies may be used to develop personalized, systematic recommendations for patients with articular cartilage injuries.

This study is not without limitations. Only five patients undergoing TKA were recruited for the OA arm of the study. Although T2 and T1ρ were significantly higher in the posteromedial condylar segments, this study was underpowered to demonstrate statistically significant differences in the remaining condyles. We believe that a larger sample size would bolster our conclusions. Of note, there was a marked difference in age between the OA group and controls (70 years *vs* 28.9 years). Differences in T2 and T1ρ mapping may be confounded by physiologic changes with age alone, as previously mentioned. Although the concept of morphologically normal but biochemically impaired cartilage is valid, this observation may weaken the validity of our argument

Table 2 Comparison of T2/T1ρ values and cartilage thickness between the control cohort and advanced osteoarthritis patient

		Control (n = 20)	AOA (n = 5)	P[1]
MDC	T2-value[2]	52.23	64.9	0.524
	T1ρ-value	52.5	52.98	0.642
	T2-cartilage thickness[3]	6.13	5.38	0.461
	T1ρ-cartilage thickness	5.7	6.8	0.97
MPC	T2-value	46.83	59.3	0.016
	T1ρ-value	57.15	73.5	0.043
	T2-cartilage thickness	8.6	10.05	0.352
	T1ρ-cartilage thickness	8.7	8.93	0.938
LDC	T2-value	48.93	53.7	0.067
	T1ρ-value	55.85	62.55	0.371
	T2-cartilage thickness	6.58	6.4	0.654
	T1ρ-cartilage thickness	6.2	5.75	0.587
LPC	T2-value	44.2	50.8	0.218
	T1ρ-value	48.53	68.5	0.055
	T2-cartilage thickness	8.93	7.95	0.55
	T1ρ-cartilage thickness	8.5	9.15	0.601

[1]Mann-Whitney *U* test; [2]T2 and T1ρ values, measured in milliseconds; [3]Thickness, measured in pixels. AOA: Advanced osteoarthritis; MDC: Medial distal condyle; MPC: Medial posterior condyle; LDC: Lateral distal condyle; LPC: Lateral posterior condyle.

regarding joint preservation options. Furthermore, this is a cross-sectional design with no long-term follow-up as all OA patients underwent TKA. They also were not recruited according to degree or radiographic severity of disease and there is no long-term follow-up regarding symptom development in control subjects. However, there are lessons to be learned from this work that may help in the development of personalized treatments for OA and cartilage injuries.

In conclusion, our findings lend additional support to the use of T2 and T1ρ mapping in the diagnosis and management of OA of the knee. We have uniquely shown that even though cartilage is morphologically normal or near normal, cartilage degenerative changes exist in advanced OA patients. These early changes can be detected with T2 and T1ρ MRI techniques and consideration should be given to the use of these sequences in the early detection of OA.

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COMMENTS

Background

Characterized by the progressive loss of articular cartilage, osteoarthritis (OA) is one of the largest and fastest growing medical conditions worldwide. Significant damage to the collagen-proteoglycan matrix is believed to precede the loss of cartilage and consequent symptoms of knee OA. Among imaging techniques, magnetic resonance T1ρ has stood out as a high sensitivity option to detect these early changes in otherwise young, healthy joints.

Research frontiers

Prior studies have demonstrated increased cartilage T1ρ values, a surrogate of cartilage damage, in patients with knee OA. Specifically, T1ρ and T2 values are known to be elevated in asymptomatic, healthy subjects with early stage OA compared to individuals without focal lesions. The basic science foundation for the use of these techniques is now understood, but translating them into clinical practice is an area of current interest.

Innovations and breakthroughs

In recent years, novel strategies have been explored for the early detection of OA. Magnetic resonance T1ρ and T2 mapping has emerged as an excellent candidate for this endeavor. The authors have uniquely shown that even though cartilage is morphologically normal or near normal, cartilage degenerative changes exist in advanced OA patients. These early changes can be detected with T2 and T1ρ magnetic resonance imaging techniques and consideration should be given to the use of these sequences in the early detection of OA.

Applications

The authors' findings lend support to the use of T2 and T1ρ mapping in the diagnosis and management of OA of the knee. The results of this study suggest that asymptomatic individuals under consideration for knee joint preservation strategies may benefit from pre-procedure T2 and T1ρ analysis. Future studies should build upon their results to determine specific T2 and T1ρ parameters whereby joint preservation strategies are likely to fail.

Terminology

Standard T2 and lesser-known T1ρ magnetic resonance pulse sequences can be used as surrogates of cartilage damage in patients with knee OA. Specifically, T1ρ and T2 values are known to be elevated in asymptomatic, healthy subjects with early stage OA compared to individuals without focal lesions.

Peer-review

It is a well-written paper.

REFERENCES

1 **Lawrence RC**, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008; **58**: 26-35 [PMID: 18163497 DOI: 10.1002/art.23176]

2 **Helmick CG**, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, Liang MH, Kremers HM, Mayes MD, Merkel PA, Pillemer SR, Reveille JD, Stone JH. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum* 2008; **58**: 15-25 [PMID: 18163481 DOI: 10.1002/art.23177]

3 **Felson DT**, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P, Levy D. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 1995; **38**: 1500-1505 [PMID: 7575700]

4 **Murphy L**, Schwartz TA, Helmick CG, Renner JB, Tudor G, Koch G, Dragomir A, Kalsbeek WD, Luta G, Jordan JM. Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum* 2008; **59**: 1207-1213 [PMID: 18759314 DOI: 10.1002/art.24021]

5 **Litwic A**, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. *Br Med Bull* 2013; **105**: 185-199 [PMID: 23337796 DOI: 10.1093/bmb/lds038]

6 **Mankin HJ**, Brandt KD. Pathogenesis of arthritis. Philadelphia W.B. Saunders, 1993

7 **Wáng YX**, Zhang Q, Li X, Chen W, Ahuja A, Yuan J. T1ρ magnetic resonance: basic physics principles and applications in knee and intervertebral disc imaging. *Quant Imaging Med Surg* 2015; **5**: 858-885 [PMID: 26807369 DOI: 10.3978/j.issn.2223-429

2.2015.12.06]
8 **Potter HG**, Black BR, Chong le R. New techniques in articular cartilage imaging. *Clin Sports Med* 2009; **28**: 77-94 [PMID: 19064167 DOI: 10.1016/j.csm.2008.08.004]
9 **Radcliff KE**, Sidhu GD, Kepler CK, Gruskay J, Anderson DG, Hilibrand A, Albert TJ, Vaccaro AR. Complications of Flat Bed Rest After Incidental Durotomy. *Clin Spine Surg* 2016; **29**: 281-284 [PMID: 23197257 DOI: 10.1097/BSD.0b013e31827d7ad8]
10 **Matzat SJ**, van Tiel J, Gold GE, Oei EH. Quantitative MRI techniques of cartilage composition. *Quant Imaging Med Surg* 2013; **3**: 162-174 [PMID: 23833729 DOI: 10.3978/j.issn.2223-4292.2013.06.04]
11 **Link TM**, Stahl R, Woertler K. Cartilage imaging: motivation, techniques, current and future significance. *Eur Radiol* 2007; **17**: 1135-1146 [PMID: 17093967 DOI: 10.1007/s00330-006-0453-5]
12 **Li X**, Han ET, Ma CB, Link TM, Newitt DC, Majumdar S. In vivo 3T spiral imaging based multi-slice T(1rho) mapping of knee cartilage in osteoarthritis. *Magn Reson Med* 2005; **54**: 929-936 [PMID: 16155867 DOI: 10.1002/mrm.20609]
13 **Stahl R**, Luke A, Li X, Carballido-Gamio J, Ma CB, Majumdar S, Link TM. T1rho, T2 and focal knee cartilage abnormalities in physically active and sedentary healthy subjects versus early OA patients--a 3.0-Tesla MRI study. *Eur Radiol* 2009; **19**: 132-143 [PMID: 18709373 DOI: 10.1007/s00330-008-1107-6]
14 **Regatte RR**, Akella SV, Wheaton AJ, Lech G, Borthakur A, Kneeland JB, Reddy R. 3D-T1rho-relaxation mapping of articular cartilage: in vivo assessment of early degenerative changes in symptomatic osteoarthritic subjects. *Acad Radiol* 2004; **11**: 741-749 [PMID: 15217591 DOI: 10.1016/j.acra.2004.03.051]
15 **Wang L**, Chang G, Xu J, Vieira RL, Krasnokutsky S, Abramson S, Regatte RR. T1rho MRI of menisci and cartilage in patients with osteoarthritis at 3T. *Eur J Radiol* 2012; **81**: 2329-2336 [PMID: 21908122 DOI: 10.1016/j.ejrad.2011.07.017]
16 **Pritzker KP**, Gay S, Jimenez SA, Ostergaard K, Pelletier JP, Revell PA, Salter D, van den Berg WB. Osteoarthritis cartilage histopathology: grading and staging. *Osteoarthritis Cartilage* 2006; **14**: 13-29 [PMID: 16242352 DOI: 10.1016/j.joca.2005.07.014]
17 **Kaneko Y**, Nozaki T, Yu H, Chang A, Kaneshiro K, Schwarzkopf R, Hara T, Yoshioka H. Normal T2 map profile of the entire femoral cartilage using an angle/layer-dependent approach. *J Magn Reson Imaging* 2015; **42**: 1507-1516 [PMID: 25917977 DOI: 10.1002/jmri.24936]
18 **Nozaki T**, Kaneko Y, Yu HJ, Kaneshiro K, Schwarzkopf R, Hara T, Yoshioka H. T1rho mapping of entire femoral cartilage using depth- and angle-dependent analysis. *Eur Radiol* 2016; **26**: 1952-1962 [PMID: 26396106 DOI: 10.1007/s00330-015-3988-5]
19 **Cole BJ**, Pascual-Garrido C, Grumet RC. Surgical management of articular cartilage defects in the knee. *Instr Course Lect* 2010; **59**: 181-204 [PMID: 20415379]
20 **Kumar D**, Souza RB, Subburaj K, MacLeod TD, Singh J, Calixto NE, Nardo L, Link TM, Li X, Lane NE, Majumdar S. Are There Sex Differences in Knee Cartilage Composition and Walking Mechanics in Healthy and Osteoarthritis Populations? *Clin Orthop Relat Res* 2015; **473**: 2548-2558 [PMID: 25716211 DOI: 10.1007/s11999-015-4212-2]
21 **Li X**, Benjamin Ma C, Link TM, Castillo DD, Blumenkrantz G, Lozano J, Carballido-Gamio J, Ries M, Majumdar S. In vivo T(1rho) and T(2) mapping of articular cartilage in osteoarthritis of the knee using 3 T MRI. *Osteoarthritis Cartilage* 2007; **15**: 789-797 [PMID: 17307365 DOI: 10.1016/j.joca.2007.01.011]
22 **Nishioka H**, Hirose J, Nakamura E, Okamoto N, Karasugi T, Taniwaki T, Okada T, Yamashita Y, Mizuta H. Detecting ICRS grade 1 cartilage lesions in anterior cruciate ligament injury using T1ρ and T2 mapping. *Eur J Radiol* 2013; **82**: 1499-1505 [PMID: 23743050 DOI: 10.1016/j.ejrad.2013.04.038]
23 **Thuillier DU**, Souza RB, Wu S, Luke A, Li X, Feeley BT. T1ρ imaging demonstrates early changes in the lateral patella in patients with patellofemoral pain and maltracking. *Am J Sports Med* 2013; **41**: 1813-1818 [PMID: 23845401 DOI: 10.1177/0363546513495167]
24 **Lozano J**, Li X, Link TM, Safran M, Majumdar S, Ma CB. Detection of posttraumatic cartilage injury using quantitative T1rho magnetic resonance imaging. A report of two cases with arthroscopic findings. *J Bone Joint Surg Am* 2006; **88**: 1349-1352 [PMID: 16757771 DOI: 10.2106/JBJS.E.01051]
25 **Witschey WR**, Borthakur A, Fenty M, Kneeland BJ, Lonner JH, McArdle EL, Sochor M, Reddy R. T1rho MRI quantification of arthroscopically confirmed cartilage degeneration. *Magn Reson Med* 2010; **63**: 1376-1382 [PMID: 20432308 DOI: 10.1002/mrm.22272]
26 **Jungmann PM**, Baum T, Bauer JS, Karampinos DC, Erdle B, Link TM, Li X, Trattnig S, Rummeny EJ, Woertler K, Welsch GH. Cartilage repair surgery: outcome evaluation by using noninvasive cartilage biomarkers based on quantitative MRI techniques? *Biomed Res Int* 2014; **2014**: 840170 [PMID: 24877139 DOI: 10.1155/2014/840170]
27 **Holtzman DJ**, Theologis AA, Carballido-Gamio J, Majumdar S, Li X, Benjamin C. T(1ρ) and T(2) quantitative magnetic resonance imaging analysis of cartilage regeneration following microfracture and mosaicplasty cartilage resurfacing procedures. *J Magn Reson Imaging* 2010; **32**: 914-923 [PMID: 20882622 DOI: 10.1002/jmri.22300]
28 **Theologis AA**, Schairer WW, Carballido-Gamio J, Majumdar S, Li X, Ma CB. Longitudinal analysis of T1ρ and T2 quantitative MRI of knee cartilage laminar organization following microfracture surgery. *Knee* 2012; **19**: 652-657 [PMID: 22018879 DOI: 10.1016/j.knee.2011.09.004]

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SYSTEMATIC REVIEWS

Total hip arthroplasty in patients with Paget's disease of bone: A systematic review

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Abstract

AIM

To investigate the clinical and functional outcomes following total hip arthroplasty (THA) in patients with Paget's disease.

METHODS

We carried out a systematic review of the literature to determine the functional outcome, complications and revision rates of THA in patients with Paget's disease. Eight studies involving 358 hips were reviewed. The mean age was 70.4 years and follow-up was 8.3 years. There were 247 cemented THAs (69%), 105 uncemented THAs (29%) and 6 hybrid THAs (2%).

RESULTS

All studies reported significant improvement in hip function following THA. There were 19 cases of aseptic loosening (5%) at a mean of 8.6 years. Three cases occurred in the uncemented cohort (3%) at a mean of 15.3 years and 16 cases developed in the cemented group (6%) at a mean of 7.5 years (P = 0.2052). There were 27 revisions in the 358 cases (8%) occurring at a mean of 7 years. Six revisions occurred in the uncemented cohort (6%) at a mean of 8.6 years and 21 in the cemented cohort (9%) at a mean of 6.5 years (P = 0.5117).

CONCLUSION

The findings support the use of THA in patients with Paget's disease hip arthropathy. The post-operative functional outcome is largely similar to other patients; however, the revision rate is higher with aseptic loosening being the most common reason for revision. Uncemented

implants appear to be associated with a lower failure rate, however, there were no modern stem designs fixed using current generation cementing techniques used in the reported studies, and as such, caution is advised when drawing any conclusions.

Key words: Total hip arthroplasty; Paget's disease; Revision; Loosening; Heterotopic ossification

Core tip: Patients with Paget's disease commonly develop structural bone deformities in the proximal femur, making total hip arthroplasty (THA) technically demanding. In addition, achieving adequate fixation of hip implants in the hypervascular and often sclerotic bone may prove challenging. This review has shown that, despite its challenging nature, THA can be very successful in terms of improving symptoms and restoring hip function in this unique group of patients. The failure rate, however, appears to be slightly higher than in other patients undergoing a primary total hip replacement. The most common reason for revision surgery is aseptic loosening, and using modern uncemented implants appear to reduce the risk of this occurring.

Hanna SA, Dawson-Bowling S, Millington S, Bhumbra R, Achan P. Total hip arthroplasty in patients with Paget's disease of bone: A systematic review. *World J Orthop* 2017; 8(4): 357-363 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i4/357.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i4.357

INTRODUCTION

Paget's disease of bone (PDB) is a chronic deforming metabolic disorder characterised by increased osteoclastic bone resorption and subsequent erratic compensatory formation of new woven bone of an abnormal microstructure[1]. British surgeon Sir James Paget first described PDB in 1877 as a chronic inflammation of bone and termed it "osteitis deformans"[2]. The resultant bone is mechanically weaker, larger, less compact, more vascular, and more susceptible to fracture than normal adult lamellar bone[1]. Although the exact aetiology of PDB remains unknown, both genetic and environmental factors have been suggested[3]. PDB is more common in Europe, North America and Australasia than in Asia and Africa. It is thought to result from a slow viral infection occurring in individuals with a genetic predisposition[4]. PBD evolves through three distinct phases: An initial osteolytic phase, a mixed phase with lytic and blastic features, and a final osteoblastic or sclerotic phase[5]. Its prevalence has been shown to increase with age and the most commonly involved sites include the pelvis, femur, spine, skull and tibia[5]. The pelvis and proximal femur are involved in 20%-80% of patients resulting in disabling hip disease[6]. A number of structural bony deformities such as coxa vara, anterolateral femoral bowing and acetabular protrusio are commonly seen in patients with advanced PDB hip arthropathy[3]. When secondary degenerative changes occur in the hip, symptoms may be initially treated with activity and life-style modifications, anti-inflammatory and anti-pagetic medications, functional bracing and physical therapy. If these measures fail, total hip arthroplasty (THA) is indicated to manage significant pain, joint stiffness and deformity. If THA is considered, preoperative treatment with bisphosphonates or calcitonin is thought to reduce the incidence of intraoperative bleeding, heterotrophic ossification and loosening, although no randomised controlled trials exist to support their use[7]. The increased bone turnover and remodelling is associated with elevated levels of serum alkaline phosphatase (ALP), which is used to assess the activity of the PDB and the effectiveness of medical treatment by bisphosphonates[8].

THA in the context of PDB can be a technically challenging procedure because of a number of reasons. The broad spectrum of deformities developing in the hip, including acetabular protrusio, coxa vara and femoral bowing, may hamper dislocation of the hip necessitating a neck cut *in-situ*. A trochanteric osteotomy may also be required for adequate exposure. A marked deformity of the proximal femur may require a corrective osteotomy to enable adequate femoral component alignment and fixation. The presence of dense sclerotic bone may make reaming and bone preparation extremely difficult. Bone hypervascularity may impair visualisation, require higher than usual fluid and blood replacement, and compromise cement implant fixation. Inability to achieve a dry bone bed for cement interdigitation/micro-interlock may compromise long-term implant fixation[3], which probably explains why the published results of cemented THA in PDB patients appear to be generally poorer than results in other patients[7]. Concerns also exist when using uncemented hip implants in patients with PDB, as the increased bone turnover is believed to predispose to failure of osseointegration and early aseptic loosening in some cases[9].

It is estimated that approximately 3% to 4% of the population over age 50 in the United States are affected by PDB[10]. Although the majority of these patients will not require surgical intervention, those who do, however, represent a unique subset of patients and orthopaedic pathology. When taking into account the exponential increase in the number of THAs performed annually, it can be extrapolated that arthroplasty surgeons will be faced with caring for an increasing number of patients with PDB in the future. It is, therefore, important to recognise the unique problems and challenges inherent to performing THA in patents with PDB. To this end, we therefore performed a systematic review of the literature to determine the method of fixation, failure rates, complication rates and functional outcome of THA in patients with PDB of the hip.

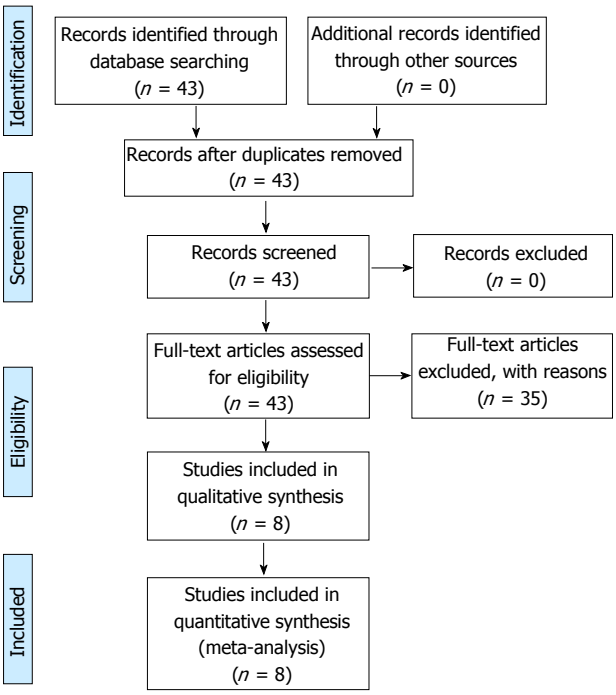

Figure 1 PRISMA flowchart illustrating the search strategy and number of records screened and included.

MATERIALS AND METHODS

Search strategy

MEDLINE and EMBASE were searched on 1/7/2016 to identify relevant studies in the English literature describing the results of THA in patients with PDB between 1980 and July 2016 in line with the PRISMA statement. Keywords used for the searches were "total hip arthroplasty" or "total hip replacement" and "Paget's disease". The bibliographies of all included studies and pertinent reviews were checked carefully for identifying additional studies. We did not contact the corresponding authors to obtain extra data.

Eligibility criteria

Inclusion criteria included all papers, which described the results of THA in patients with PDB published in the English language. Isolated case reports/series with 5 or less patients were excluded. The included articles met the PICO criteria for systematic reviews (Population, Intervention, Comparison and Outcomes).

Data extraction

One reviewer (Sammy A Hanna) extracted data through a standardized data collection form, and then another reviewer (Sebastian Dawson-Bowling) checked the data for accuracy. Any inconsistent results were handled by discussion. Data of the number of patients, follow-up period, type of implant, type of fixation, complications, re-operations, revision rate and functional outcome were extracted and entered in a spreadsheet. Figure 1 represents a PRISMA flowchart illustrating the search strategy and number of records screened and included.

Statistical analysis

Fisher's exact test was used to compare the incidence of aseptic loosening and revision THA between the uncemented and cemented groups. A P value of < 0.05 was considered statistically significant.

RESULTS

Search results

A total of 43 relevant article titles were identified. After reviewing the full text, a total of 8 studies[7,11-17] satisfied the eligibility criteria and the search strategy illustrated in Figure 1. The excluded 35 articles did not meet the PICO criteria. The included 8 studies were small to medium size retrospective case series (n = 19-98). The range of follow-up was 2 to 12.3 years.

Quality assessment

All studies were small to medium size retrospective case series (n = 19-98) describing the outcome of THA in patients with PDB of the hip. The range of follow-up in the studies was 2 to 12.3 years.

Cohort characteristics

The studies included 358 THAs performed in patients with a mean age of 70.4 years who were followed-up for a mean of 8.3 years (0.7 to 20). There were 247 cemented THAs (69%), 105 uncemented THAs (29%) and 6 hybrid THAs (2%). The demographics of the patients in the studies are summarised in Table 1.

Outcome analysis

Functional outcome: All studies reported significant improvement in hip function and patient satisfaction following THA. The Harris Hip Score improved by a mean of 40 points post-operatively (27 to 57) in 5 studies[12,13,15-17]. The Hospital for Special Surgery Scale improved from 18 to 30 post-operatively in one study[11].

Aseptic loosening: Overall, there were 19 cases of aseptic loosening in 358 cases (5%) at a mean of 8.6 years (1.5 to 20). Three cases occurred in the uncemented cohort (3%) at a mean of 15.3 years (14 to 17) and 16 cases developed in the cemented group (6%) at a mean of 7.5 years (1.5 to 20) - (P = 0.2052). There was only one case of failure of osseointegration/early subsidence of the femoral stem in the uncemented patients (1%) occurring at 7 mo.

Revisions rate: There were 27 failures requiring revision surgery in the 358 cases (8%) occurring at a mean of 7 years (0.6 to 20). Six revisions occurred in the uncemented cohort (6%) at a mean of 8.6 years (0.6 to 17) and 21 in the cemented cohort (9%) at a mean of 6.5 years (1.5 to 20) - (P = 0.5117). The reasons for failure were aseptic loosening (70%, n = 19), septic loosening (11%, n = 3), periprosthetic fracture (11%, n = 3),

Table 1 Demographics of the patients included in the studies and summary of the results

Study and country	No. of hips	Age (yr)	Follow-up (yr)	Type of fixation	Approach	Complications (implant related)	Heterotopic ossification (%)	Revision rate (%)	Functional outcome (pre and post op)
Merkow *et al*[11] 1984, United States	21	68.6 (57-80)	5.2 (2-11.4)	Cemented	Direct lateral (7) Antero-lateral (14)	Aseptic loosening (2)	52%	10%	HSS scale: 18 to 30
McDonald *et al*[12] 1987, United States	91	69.9 (49-85)	7.2 (0.7-15)	Cemented	Direct lateral (64) Antero-lateral (27)	Aseptic loosening (12) Deep infection (2) Instability (2) Foot drop (1) Nonunion of GT osteotomy (7)	37%	15%	HHS: 39 to 83
Ludkowski *et al*[13] 1990, United States	37	71.5 (60-81)	7.8 (1-18.4)	Cemented	Direct lateral	Superficial infection (3)	65%	0%	HHS: 48.1 to 83.2
Sochart *et al*[14] 2000, United Kingdom	98	67.4 (51-79)	10.4 (5.3-20)	Cemented	Direct lateral	Stem fracture (1) Deep infection (1) Instability (1) Aseptic loosening (2) Nonunion of GT osteotomy (1) Foot drop (1)	29%	5%	
Kirsh *et al*[15] 2001, Australia	20	72 (62-82)	5.7 (4-8)	Uncemented (17) Hybrid (3)	Antero-lateral (13) Posterior (7)	Instability (1)	50%	0%	HHS: 31 to 88
Parvizi *et al*[16] 2002, United States	19	71.3 (54-85)	7 (2-15)	Uncemented	Posterior	Instability (1)	32%	0%	HHS: 59.8 to 86.7
Wegrzyn *et al*[17] 2010, France	39	74.2 (55-89)	6.6 (2-12)	Uncemented (36) Hybrid (3)	Antero-lateral (36) Posterior (3)	Intra-operative posterior column acetabular fracture (1) Periprosthetic fractures (2)	56%	0%	HHS: 54 to 89
Imbuldeniya *et al*[7] 2014, Australia	33	75 (63-85)	12.3 (10.3-17)	Uncemented	Posterior	Aseptic loosening/ poly wear (4) Periprosthetic fracture (2)	45%	18%	

HSS: Hospital for special surgery; HHS: Harris hip score.

Table 2 Comparison of the complication rates between the cemented and uncemented groups *n* (%)

Complication	Cemented THR (*n* = 247)	Uncemented THR (*n* = 105)
Aseptic loosening	16 (6)	3 (3)
Septic loosening	3 (1)	0 (0)
Periprosthetic fracture	0 (0)	4 (4)
Intra-operative fracture	0 (0)	1 (1)

THR: Total hip replacement.

femoral stem fracture (4%, *n* = 1) and instability (4%, *n* = 1). Table 2 summarises the different complication rates between the cemented and uncemented groups.

DISCUSSION

THA appears to be a generally successful procedure in patients with PDB. The reported post-operative improvement in functional outcome and patient satisfaction is significant in all studies in this review, and is largely comparable to the outcome of THA in other patients[17]. The overall revision rate was 8% at 7 years with aseptic loosening being the main reason for revision (70%). The revision rate was lower in the uncemented patients (6%) at 8.6 years compared with (9%) in the cemented group at 6.5 years and the incidence of aseptic loosening was higher when cemented implants were used (6%), compared with uncemented porous coated implants (3%). Both differences were not statistically significant (P = 0.5117 and 0.2052 respectively). Aseptic loosening also occurred much earlier in the cemented patients (7.5 years *vs* 15.3 years). These failure rates are slightly higher than those in other patients undergoing THA[18]. According to the Australian National Joint Registry, a revision rate of > 7.5% at 10 years is considered higher than anticipated[19]. It is important to note that the vast majority of cemented THAs in this review included modifications of the Charnely stem coupled with a conventional ultra high molecular weight polyethylene liner and fixed with first/second generation cementing techniques. This may have contributed to the relatively high failure rates[20]. Cementless implants may have a theoretical advantage over cemented ones in the context of PDB. Cement penetration and interdigitation may

be limited in Pagetic bone, which is typically sclerotic and more prone to bleeding. In contrast, many authors believe that the altered bone morphology and increased turnover may hamper osseointegration of uncemented implants[7]. Interestingly, there was only one case in the uncemented cohort (1%) where failure of bone ingrowth/osseointegration had occurred. This required revision at 7 mo post index surgery.

The overall reported incidence of heterotopic bone (HO) formation was 46% (29% to 65%). It is unclear how the surgical approach to the hip affects this. It is also unclear as to how best to prevent it in terms of dose and timing of radiation and/or chemoprophylaxis[21,22].

Taking into account the exponential increase in the number of THAs performed annually, it can be extrapolated that arthroplasty surgeons will be faced with caring for an increasing number of patients with PDB in the future. It is, therefore, important to understand the implications of PDB on the medical management of patients, intra-operative technical considerations and the outcomes and complications associated with surgery. When planning to perform THA in a PDB patient, a systematic approach is paramount to ensure optimal outcome. The following pre, intra and post-operative considerations need to be adequately addressed.

Pre-operative considerations /requirements

Differentiating mechanical joint pain from Pagetic bone pain is important. Diagnostic injections are a useful tool to confirm the intra-articular origin of the hip pain and to rule our concurrent pathology.

Good quality imaging studies including long leg views ± computed tomography (CT) scans to assess bone morphology and extra-articular deformities. This is important to plan surgery, including the need for any extra intra-operative steps such as corrective osteotomy and to choose the appropriate implants.

Review by a cardiologist is recommended to assess cardiac function and the presence of high-output cardiac failure. This will likely have anaesthetic implications and may require optimisation prior to performing the surgery.

Preoperative treatment with bisphosphonates or calcitonin reduces intraoperative bleeding by decreasing disease activity. Anti-pagetic medications should be started at least 6 wk prior to elective surgery. Disease activity can be monitored using ALP serum levels[23].

Pre-operative optimisation of Haemoglobin levels is important to compensate for blood loss intra-operatively. Pre-operative autologous blood donation may also be considered.

Intra-operative considerations /requirements

Effective blood salvage strategies should be employed including expeditious surgery and the administration of tranexamic acid.

Surgery should be performed through an extensile approach when necessary with liberal soft tissue releases in patients with severe contractures.

Preparation of the femoral side must be performed with caution because standard rasps and reamers may not be effective when used in extremely sclerotic bone. A high-speed burr may be useful to aid in bone preparation. As discussed previously, sclerotic bone may compromise the interdigitation of cement, and uncemented implants may be preferred under these circumstances.

If an uncemented shell is used, it is important to achieve good peripheral rim fit and the use of acetabular screws are recommended to enhance fixation[24].

Concurrent osteotomy to achieve satisfactory femoral component alignment can be difficult. It is advisable to perform the osteotomy in the metaphysis when possible. A previous study has shown that osteotomy performed in a metaphyseal location had a better outcome than those performed through diaphysis[25]. However, the complex nature of the deformity in some of these patients may necessitate diaphyseal, and in some occasions multi-planar osteotomies to achieve a satisfactory correction.

Post-operative considerations /requirements

Bisphosphonate treatment should continue if the disease activity high (ALP levels).

It is advisable to administer prophylaxis against HO with preventive measures such as radiation and/or prophylactic drug regimens[21]. The efficacy of indomethacin in preventing HO is well documented[26]. The most common treatment is to give 25 mg three times a day for five to six weeks. Several studies have shown the efficacy of radiation therapy in reducing the incidence of HO following lower limb arthroplasty. The most appropriate dose regimen appears to be 7 to 8 Gy given as a single fraction either < 4 h pre-operatively or < 72 h post-operatively[26].

The main limitation of this review is that it included studies dating back to 1980, with three of the eight papers included being published in 1990 or earlier. Only two articles were published in the last 10 years. This potentially has an impact the results as dated implants and techniques have poorer survivorship. However, although Paget's disease is fairly common (3%-4% of the United States population above the age of 50 are affected)[10], very limited new information has been published on the topic. With the exponential annual increase of THAs, most arthroplasty surgeons will care for patients with Paget's disease at some point, which makes this review relevant to clinical practice, especially by highlighting the potential challenges and expected outcomes of THA in this unique group of patients.

Conclusion

The findings of this review support the use of THA to alleviate debilitating hip pain and functional limitation in PDB patients with hip arthropathy. Post-operative patient satisfaction and functional improvement is similar to other patients, however, the revision rate is higher with

aseptic loosening being the most common reason for revision. Uncemented implants appear to be associated with a lower failure rate. However, there are no studies reporting on the use of modern stem designs fixed using current generation cementing techniques in PDB patients, so caution is advised when drawing any conclusions.

COMMENTS

Background

Paget's disease is a fairly common disorder, which affects approximately 3% to 4% of the United States population over the age of 50. Although the majority of these patients will not require surgical intervention, those who do, however, represent a unique subset of patients and orthopaedic pathology. Hip involvement is common and performing total hip arthroplasty (THA) in this group of patients is technically demanding. There are three main issues the surgeon needs to address during the procedure: How to deal with the structural deformities present in the hip, how to achieve adequate implant fixation in the hypervascular and sclerotic bone, and how to manage blood loss intra-operatively. This review attempts to answer these questions based on current evidence.

Research frontiers

The optimal method of fixation of hip implants in patients with Paget's disease is frequently debated amongst hip surgeons with no clear consensus. The role of Bisphosphonate therapy peri and post-operatively in reducing blood loss is also a controversial issue.

Innovations and breakthroughs

The review supports the use of THA in patients with Paget's disease. The functional benefit after the procedure is similar to other patients undergoing a primary THA. However, the authors found a slightly higher revision rate in tis group of patients, with aseptic loosening being the most common reason for revision. Although uncemented implants appear to be associated with a lower failure rate, however, they did not find any studies evaluating the role of modern polished tapered cemented stem designs in patients with Paget's disease. Caution is therefore advised when drawing any conclusions.

Applications

The results highlight the need for a structured, planned and multidisciplinary approach when managing patients with Paget's disease of bone undergoing THA in order to optimise outcome and reduce the risk of complications.

Peer-review

This is a systematic review on THA in patients with Paget's disease of bone. The introduction is well written and convincing. This systematic review seems to be highly original and no systematic review currently exists on this topic; thus, this manuscript is timely.

REFERENCES

1 **Rebel A**, Basle M, Pouplard A, Malkani K, Filmon R, Lepatezour A. Bone tissue in Paget's disease of bone. Ultrastructure and Immunocytology. *Arthritis Rheum* 1980; **23**: 1104-1114 [PMID: 7000080 DOI: 10.1002/art.1780231006]

2 **Paget J**. On a Form of Chronic Inflammation of Bones (Osteitis Deformans). *Med Chir Trans* 1877; **60**: 37-64.9 [PMID: 20896492 DOI: 10.1177/095952877706000105]

3 **Lewallen DG**. Hip arthroplasty in patients with Paget's disease. *Clin Orthop Relat Res* 1999; (**369**): 243-250 [PMID: 10611879]

4 **Rebel A**, Basle M, Pouplard A, Malkani K, Filmon R, Lepatezour A. Towards a viral etiology for Paget's disease of bone. *Metab Bone Dis Relat Res* 1981; **3**: 235-238 [PMID: 6762481 DOI: 10.1016/0221-8747(81)90038-2]

5 **Lander PH**, Hadjipavlou AG. A dynamic classification of Paget's disease. *J Bone Joint Surg Br* 1986; **68**: 431-438 [PMID: 2942548]

6 **Guyer PB**, Chamberlain AT, Ackery DM, Rolfe EB. The anatomic distribution of osteitis deformans. *Clin Orthop Relat Res* 1981; **156**: 141-144 [PMID: 7226642 DOI: 10.1097/00003086-198105000-00016]

7 **Imbuldeniya AM**, Tai SM, Aboelmagd T, Walter WL, Walter WK, Zicat BA. Cementless hip arthroplasty in Paget's disease at long-term follow-up (average of 12.3 years). *J Arthroplasty* 2014; **29**: 1063-1066 [PMID: 24268583 DOI: 10.1016/j.arth.2013.10.015]

8 **Delmas PD**, Meunier PJ. The management of Paget's disease of bone. *N Engl J Med* 1997; **336**: 558-566 [PMID: 9023094 DOI: 10.1056/NEJM199702203360807]

9 **Lusty PJ**, Walter WL, Walter WK, Zicat B. Cementless hip arthroplasty in Paget's disease at medium-term follow-up (average of 6.7 years). *J Arthroplasty* 2007; **22**: 692-696 [PMID: 17689777 DOI: 10.1016/j.arth.2006.09.010]

10 **American Academy of Orthopaedic Surgeons**. Paget's Disease of Bone. Available from: URL: http://orthoinfo.aaos.org/topic.cfm?topic=a00076

11 **Merkow RL**, Pellicci PM, Hely DP, Salvati EA. Total hip replacement for Paget's disease of the hip. *J Bone Joint Surg Am* 1984; **66**: 752-758 [PMID: 6725323 DOI: 10.2106/00004623-198466050-00015]

12 **McDonald DJ**, Sim FH. Total hip arthroplasty in Paget's disease. A follow-up note. *J Bone Joint Surg Am* 1987; **69**: 766-772 [PMID: 3597478 DOI: 10.2106/00004623-198769050-00020]

13 **Ludkowski P**, Wilson-MacDonald J. Total arthroplasty in Paget's disease of the hip. A clinical review and review of the literature. *Clin Orthop Relat Res* 1990; (**255**): 160-167 [PMID: 2189627]

14 **Sochart DH**, Porter ML. Charnley low-friction arthroplasty for Paget's disease of the hip. *J Arthroplasty* 2000; **15**: 210-219 [PMID: 10708088 DOI: 10.1016/S0883-5403(00)90286-9]

15 **Kirsh G**, Kligman M, Roffman M. Hydroxyapatite-coated total hip replacement in Paget's disease: 20 patients followed for 4-8 years. *Acta Orthop Scand* 2001; **72**: 127-132 [PMID: 11372942 DOI: 10.1080/000164701317323363]

16 **Parvizi J**, Schall DM, Lewallen DG, Sim FH. Outcome of uncemented hip arthroplasty components in patients with Paget's disease. *Clin Orthop Relat Res* 2002; (**403**): 127-134 [PMID: 12360018 DOI: 10.1097/00003086-200210000-00020]

17 **Wegrzyn J**, Pibarot V, Chapurlat R, Carret JP, Béjui-Hugues J, Guyen O. Cementless total hip arthroplasty in Paget's disease of bone: a retrospective review. *Int Orthop* 2010; **34**: 1103-1109 [PMID: 19669762 DOI: 10.1007/s00264-009-0853-7]

18 **Mariconda M**, Galasso O, Costa GG, Recano P, Cerbasi S. Quality of life and functionality after total hip arthroplasty: a long-term follow-up study. *BMC Musculoskelet Disord* 2011; **12**: 222 [PMID: 21978244 DOI: 10.1186/1471-2474-12-222]

19 **Australian Orthopaedic Association National Joint Replacement Registry**. Annual Report. Adelaide: AOA, 2011

20 **Bjørgul K**, Novicoff WM, Andersen ST, Brevig K, Thu F, Wiig M, Ahlund O. The Charnley stem: clinical, radiological and survival data after 11-14 years. *Orthop Traumatol Surg Res* 2010; **96**: 97-103 [PMID: 20417906 DOI: 10.1016/j.rcot.2010.02.009]

21 **Ferguson DJ**, Itonaga I, Maki M, McNally E, Gundle R, Athanasou NA. Heterotopic bone formation following hip arthroplasty in Paget's disease. *Bone* 2004; **34**: 1078-1083 [PMID: 15260016 DOI: 10.1016/j.bone.2004.01.027]

22 **Iorio R**, Healy WL. Heterotopic ossification after hip and knee arthroplasty: risk factors, prevention, and treatment. *J Am Acad Orthop Surg* 2002; **10**: 409-416 [PMID: 12470043 DOI: 10.5435/00124635-200211000-00005]

23 **Drake MT**, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc* 2008; **83**: 1032-1045 [PMID: 18775204 DOI: 10.4065/83.9.1032]

24 **Parvizi J**, Klein GR, Sim FH. Surgical management of Paget's disease of bone. *J Bone Miner Res* 2006; **21** Suppl 2: P75-P82 [PMID: 17229013 DOI: 10.1359/jbmr.06s214]

25 **Parvizi J**, Frankle MA, Tiegs RD, Sim FH. Corrective osteotomy for deformity in Paget disease. *J Bone Joint Surg Am* 2003; **85-A**:

697-702 [PMID: 12672847 DOI: 10.2106/00004623-200304000-00017]
26 **Board TN**, Karva A, Board RE, Gambhir AK, Porter ML. The prophylaxis and treatment of heterotopic ossification following lower limb arthroplasty. *J Bone Joint Surg Br* 2007; **89**: 434-440 [PMID: 17463108 DOI: 10.1302/0301-620X.89B4.18845]

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