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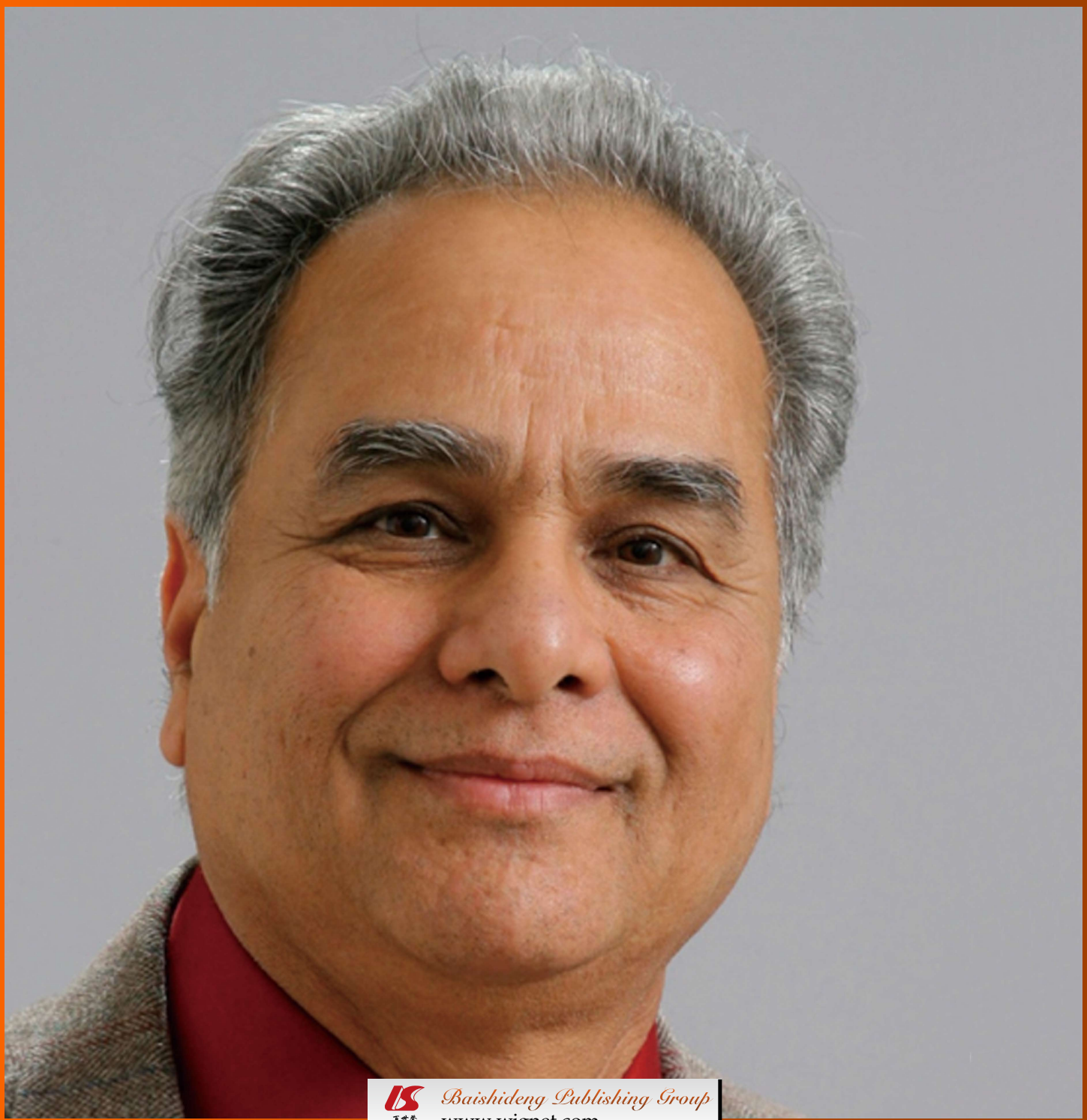

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EDITORIAL

Single row rotator cuff repair with modified technique

Sang-Hun Ko, Seung-Myeong Shin

Sang-Hun Ko, Seung-Myeong Shin, Department of Orthopedic Surgery, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan 682-714, South Korea
Author contributions: All the authors contributed to this article equally.
Correspondence to: Sang-Hun Ko, MD, Professor, Department of Orthopedic Surgery, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan 682-714, South Korea. sanghunko@yahoo.com
Telephone: +82-52-2507129 Fax: +82-52-235-2823
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Abstract

Rotator cuff tear is a common medical condition. We introduce various suture methods that can be used for arthroscopic rotator cuff repair, review the single row rotator cuff repair method with modified technique, and introduce the Ulsan-University (UU) stich. We compare the UU stitch with the modified Mason-Allen (MA) suture method. The UU stitch configuration is a simple alternative to the modified MA suture configuration for rotator cuff repair.

Key words: Shoulder; Rotator Cuff Repair; Mason-Allen Stitch; Ulsan-University Stitch

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INTRODUCTION

Rotator cuff tear is a common medical condition frequently diagnosed, in an increasingly active elderly population, due to the advancement of diagnostic technology such as magnetic resonance imaging[1,2]. Non-surgical treatment is generally used as the primary treatment of partial thickness rotator cuff tear and can improve symptoms. However, in the case of a full-thickness rotator cuff tear, surgical treatment can help improve the shoulder joint functions when non-surgical methods have failed[3,4]. Development of various surgical methods[5-8] such as open suture and mini-open suture[9,10] as well as arthroscopic suture[11] have been reported. A secure and stable suturing method is necessary for the repair of a broad rotator cuff tear[10]. By attaching the tendon to the greater tubercle of humerus the rotator cuff tissue is repaired and shoulder joint function improved. This method of surgical rotator cuff repair shifts from open suture to mini-open suture and arthroscopic suture[5,6]. There are several known advantages of arthroscopic suture[11,12]. However, this method has the limitation that it requires a long time for the surgeon to acquire enough skill and the tendon-suture connection is relatively weak. Therefore, arthroscopic suture can lead to more frequent re-tear than open suture. Use of arthroscopic rotator cuff repair has increased recently along with the development of more advanced surgical equipment and techniques as well as optical technology[13,14] and there are reports of good results. In this review, we introduce various suture methods that can be used for arthroscopic rotator cuff repair.

DETAIL REVIEW

Early re-tear of the arthroscopic suture may be caused by knot failure or suture anchor failure, but the most frequent cause is suture pull-out through the rotator cuff[4,15]. The initial weak connection and the distraction of the suture cause gap formation between tendon and bone tissue eventually resulting in imperfect tendon-bone healing. When re-tear of the sutured rotator cuff occurs, it inevitably leads to pain and functional weakening through time[13]. In the case of broad rotator cuff tears, in particular, a high rate of re-tear after the arthroscopic suture can be proven by objective evaluation[13,16]. The weakest area

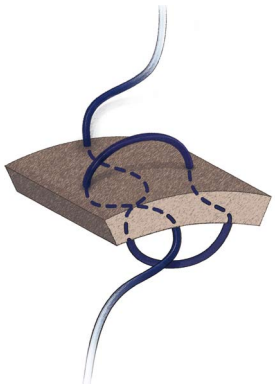

Figure 1 Modified Mason-Allen suture.

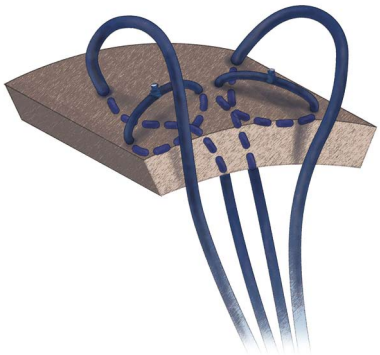

Figure 2 Massive Cuff stitch.

after rotator cuff repair is the contact surface between the rotator cuff tendon and the sutures. Since re-tear occurs in this area, the development of a suture method is needed to stitch up the tendon tissues with lasting strength.

Modified Mason-Allen suture

Compared with other suture methods for rotator cuff repair currently in use, the modified Mason-Allen (MA) (Figure 1) suture is considered a standard suture method that can securely stitch the tendon tissue[15,17-19]. The modified MA suture has been known to be biomechanically sturdier than simple suture and mattress suture as proven by *in vitro* studies[15]. Compared with Bunnel, Krackow and mattress suture methods, the modified MA suture was found to have a similar tendency to develop rotator cuff tissue necrosis as the simple suture[17,18]. However, the limitation of the modified MA suture is that it is difficult to perform using arthroscopy[17].

Massive cuff stitch

The previously reported Massive Cuff (MC)[11] (Figure 2) stitch can significantly increase the strength of single-row rotator cuff sutures and shows biomechanical strength comparable to that of the modified MA suture. This suture method uses two sutures, one forming a horizontal mattress connection loop, the other forming a simple vertical connection loop[17]. The simple vertical connection loop is routed through the inside of the horizontal mattress connection loop. This cross looping is similar to that of the modified MA suture. That is, the horizontal mattress connection loop acts as a check rein so that the re-tear of the sutured tendon does not cause the simple vertical connection loop to slide out through the tear gap. The advantage of the MC suture is that it can be performed easily using arthroscopy. This was reported by Scheibel and Habermeyer as another modified MA suture technique[18,20]. However, the MC suture has three knots in each stitch with one knot created in the horizontal mattress connection loop and two knots created in the two simple vertical connection loops. We believe that knot impingement is possibly higher when there are more knots in the sutured rotator cuff tissue. We propose a modified Mattress-Locking suture that can stitch without knots[11].

Modified Mattress-Locking suture

The modified Mattress-Locking suture is a simplified method of arthroscopic suture for rotator cuff repair in which the simple vertical loop is connected to the horizontal mattress loop for easy arthroscopic manipulation. The follow-up observation over two years after the application of this method to the repair of mid-size full-thickness rotator tear revealed good results and we believe this modified Mattress-Locking suture can be used in rotator cuff repair with reduced failure rate[11]. The Ulsan-University (UU) suture is a further modification of this modified Mattress-Locking suture for more convenient use and it is similar to the tension-band suture.

Ulsan-University suture

Among those who did not show a positive response to conservative treatment, thus requiring surgery, there was a growing number of older patients at advanced stages of atrophic rotator cuff, fatty change and other conditions that may increase the risk of re-tear during surgery. To address this problem, various surgical techniques and suture methods were developed and introduced in order to improve post-operative rehabilitation and lower the frequency of re-tear. We employed the ∞-shaped UU suture, a method of locking the high-tension suture, to reduce the re-tear risk and improve suture strength.

Suture technique: UU suture is performed as follows: A banana-shaped suture needle (Banana Suture Lasso, Arthrex, Naple, FL) is inserted through the anterior entrance and is passed through the anterior section of the rotator cuff tear while lifting it with a retriever inserted through the anterior superior entrance. The banana-shaped needle is then passed through the posterior section of the rotator cuff tear while it is lifted with a retriever (Figure 3). A Polydioxanone suture is then inserted and is caught under the posterior spine of the scapula using a grasper positioned at the anterior superior entrance, having first removed the banana-shaped needle. A shuttle relay is created on the joint exterior and the suture is passed through the rotator cuff by hooking it through the shuttle-relay and pulling it between the rotator cuffs (Figure 4). One end of the suture is then pulled out through the anterior superior entrance. Likewise, a banana-shaped suture needle is inserted through the pos-

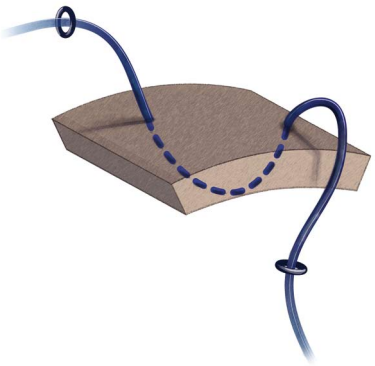

Figure 3 Ulsan-University stitch - Initial transverse suture loop.

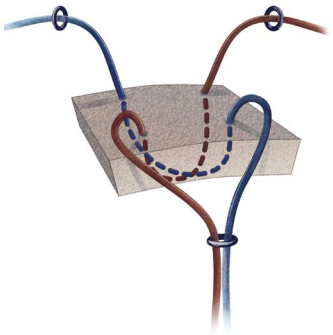

Figure 4 Ulsan-University stitch making two crossed transverse loops connected at the outside of the cannula.

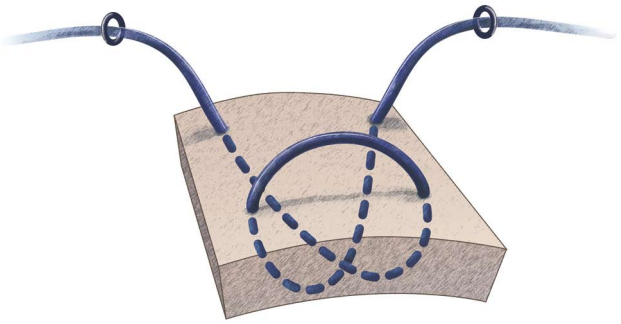

Figure 5 U-shaped medial horizontal loop. Circular horizontal mattress loop and vertical loop cross over.

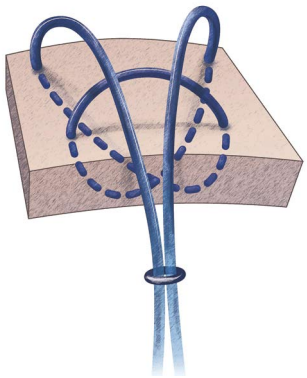

Figure 6 Like tension band suture. U-shaped loop at medial side and interference screw at lateral side.

terior entrance and passed through the rotator cuff and the Polydioxanone suture is pulled out using a grasper positioned at the anterior superior entrance. A U-shaped loop can be created in the interior of the rotator cuff by creating a shuttle relay on the suture which was pulled out to the joint exterior through the anterior superior entrance, hooking the suture previously pulled-out through the shuttle-relay and pulling it tight (Figure 5). Both ends of the suture are pulled out through the anterior superior entrance to complete preparation for the UU suture (Figure 6).

UU suture can be completed by connecting 4.5 mm interference screws (Push-lock screw, Arthrex, Naple, FL) to each end of the suture and screwing them through the cartilage of the articular fovea at the humeral head. When necessary, a stronger suture can be made by additionally creating a reverse mattress suture in the rotator cuff interior and connecting it to the interference screws in a similar way as in the UU suture.

After creating a medial row of sutures as described above, a lateral row could be created by hooking simple sutures through the anterior and posterior rotator cuff tear sections remaining without suture and fixing them with 4.5 mm interference screws.

Biomechanical and clinical results: Newly developed suture techniques must produce good clinical results, ensure the continuous integrity of the sutured muscle, and show similar or better performance than the existing suture techniques which are widely used and approved by biomechanical tests. Together with joint researchers, we tested the degree of fatigue and the biomechanical strength of the UU suture and performed a data analysis[20]. Compared with the modified MA suture method, which is generally known to be the strongest suture, our proposed UU suture did not show any significant differences when the strongest, currently available, suture material was used. The UU suture and the modified MA suture are considered to have similar biomechanical strength. The UU suture is a simplified version of the modified MA suture, which cannot be used in arthroscopic rotator cuff tear repair, but further modified to allow convenient use of arthroscopy. In the precedent study using a modified Mattress-Locking suture, we were able to achieve good results by applying it to the repair of mid-size full-thickness rotator cuff tear and we believe this modified Mattress-Locking suture can be used in rotator cuff repair with a reduced failure rate[11]. The UU suture could successfully be employed to repair relatively easy-to-suture narrow rotator cuff tears as well as mid-size full tears surrounded by wide spreading partial tears, to provide reinforcement of the surrounding thinned tendon and stitch the full tear section. The UU suture can also be used in the repair of large-size and broad rotator cuff full tears with advanced stages of degenerative fatty change - normally difficult to repair - to provide reinforcement to the weakened sections of tendon tissue and suture the full tear section. Recently, we used this

method in partially suturing non-suturable broad tears and could achieve good results. Broad rotator cuff tear is difficult to suture because it has a high degree of fatty change and is accompanied with atrophy and involution of muscles[21-23]. Even if complete suture is possible, re-tear can easily be caused by minor external force, making post-operative rehabilitation difficult[24]. Using the UU suture, we performed double-row suture on broad tears and could achieve good results compared with a simple suture. Using an arthroscopic suture on broad tears, we could achieve good results. When double-row suture using the UU suture method was compared with single-row suture using the simple suture method, no difference in clinical symptoms could be observed. However, when compared on the revision cuff repair, double-row suture showed superior results.

We performed arthroscopic repair of full-thickness rotator cuff tears using the UU suture and, from follow-up observations of over one year, achieved good results. Also, compared with the modified MA suture method, which is generally accepted as the strongest suture method, UU suture did not show significant differences when the strongest currently available suture material was used[21]. Based on these results, we believe that arthroscopic UU suture can reduce pain and improve joint function when used for the repairing of full-thickness rotator cuff tear.

DISCUSSION

The modified MA suture can provide strong stitching of tendon tissue but it is used in open suture and difficult to use in arthroscopic suture. MC suture[15] provides stronger stitches and has similar level of biomechanical strength as the modified MA suture, but since it consists of three knots, it may have higher risk of developing know impingement.

The modified Mattress-Locking suture method, without using knots, has been proposed[11]. This suture method uses a simple vertical loop and a horizontal mattress loop connected together. The UU suture was devised by further modifying the modified Mattress-Locking suture similarly to the high-tension suture.

Our biomechanical test revealed that there was no difference in resistance to cyclic loading between the UU suture and the modified MA suture. This indicates that the degree of relaxation of the UU suture is similar to that of the modified MA suture. Ultimate tensile load that causes tear also showed no difference between the two suture methods, which suggests that the same degree of postoperative activities will cause similar level of failure rates. We used the UU suture method for the repair of broad rotator cuff tears with much advanced fatty muscle replacement and for the revision cuff repair of re-tears. We used this method too for the augmentation of double-row sutures or the sutures performed with suture bridge technique and could achieve improvement of rotator cuff suture strength. We believe that the UU suture can be used for rotator cuff repair with improved biomechanical strength.

In conclusion**,** The UU suture can provide a simple and excellent suture method that can be used for arthroscopic rotator cuff repair. We believe that this method can be used as an alternative to the modified Mason-Allen suture and that the arthroscopic UU suture is not only easy to perform in patients with full-thickness rotator cuff tear but also results in a similar level of symptomatic and functional improvement to other arthroscopic suture methods.

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TOPIC HIGHLIGHT

Quanjun Cui, MD, *Series Editor*

Current concepts in management of femoroacetabular impingement

Adam S Wilson, Quanjun Cui

Adam S Wilson, Quanjun Cui, Department of Orthopaedic Surgery, University of Virginia School of Medicine, Charlottesville, VA 22903, United States

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Correspondence to: Quanjun Cui, MD, Associate Professor, Department of Orthopaedic Surgery, University of Virginia School of Medicine, Charlottesville, VA 22903, United States. qc4q@hscmail.mcc.virginia.edu
Telephone: +1-434-2430236 Fax: +1-434-2430242

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Abstract

Femoroacetabular impingement (FAI) is an increasingly recognized condition, which is believed to contribute to degenerative changes of the hip. This correlation has led to a great deal of interested in diagnosis and treatment of FAI. FAI can be divided into two groups: cam and pincer type impingement. FAI can lead to chondral and labral pathologies, that if left untreated, can progress rapidly to osteoarthritis. The diagnosis of FAI involves a detailed history, physical exam, and radiographs of the pelvis. Surgical treatment is indicated in anatomic variants known to cause FAI. The primary goal of surgical treatment is to increase joint clearance and decrease destructive forces being transmitted through the joint. Treatment has been evolving rapidly over the past decade and includes three primary techniques: open surgical dislocation, mini-open, and arthroscopic surgery. Open surgical dislocation is a technique for dislocating the femoral head from the acetabulum with a low risk of avascular necrosis in order to reshape the neck or acetabular rim to improve joint clearance. Mini-open treatment is performed using the distal portion of an anterior approach to the hip to visualize and to correct acetabular and femoral head and neck junction deformities. This does not involve frank dislocation. Recently, arthroscopic treatment has gained popularity. This however does have a steep learning curve and is best done by an experienced surgeon. Short- to mid-term results have shown relatively equal success with all techniques in patients with no or only mild evidence of degenerative changes. Additionally, all techniques have demonstrated low rates of complications.

Key words: Femoroacetabular impingement; Pincer; Cam; Mini-open; Hip arthroscopy; Surgical dislocation; Osteochondroplasty

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INTRODUCTION

Femoroacetabular impingement (FAI) is an anatomical condition that has recently been gaining recognition as potentially leading to future degenerative changes within the hip. FAI has recently been demonstrated to have an extremely high correlation for development of osteoarthritis. Some authors have suggested that FAI is likely the

leading cause in what has previously been labeled "idiopathic" osteoarthritis of the hip[1-9].

FAI can be divided between two subgroups based on anatomic deformities: cam impingement or pincer impingement[2]. In cam impingement the anatomy of the proximal femur is abnormal, such as a nonspherical femoral head or decreased head-neck offset[2,6]. Pincer impingement is present when there is abnormal anatomy of the acetabulum such as acetabular rim overgrowth, acetabular retroversion, or coxa profunda[2]. Both of these conditions lead to abnormal, repetitive abutment of the acetabulum and the femoral neck[10,11].

Cam impingement leads to forceful contact of the abnormal femoral head and neck with the opposing joint surface during activity. This force is most noticeable during motions that place the hip in extremes of flexion[4]. The most frequent lesions both of labral tears and chondral injuries noted with cam impingement are located in the anterosuperior aspect of the joint[3,12,13].

In pincer impingement the abnormality is with the acetabulum. The predominant injury pattern seen in pincer impingement involves the labrum most often at the anterior aspect of the joint, the area of acetabular overcoverage[14,15]. The injury and inflammation to the labrum frequently leads to osteophyte formation, effectively worsening FAI by creating increased acetabular overcoverage[1-3]. This leads to contact with the femoral neck at even earlier points in the range of motion of the hip. The leveraging created by this contact between the femoral neck and acetabular rim can sometimes lead to articular cartilage injuries opposite the site of impingement. Frequently these injuries are smaller than those seen in cam impingement and less symptomatic[15].

The results of these anatomical variations leading to impingement are many. Those that contribute to osteoarthritis include: injury to the articular cartilage and labral tears. These injuries can then lead to progressive degeneration of the joint, ultimately resulting in pain and decreased motion through the hip joint. The insult to the joint caused by abutment of the femoral head or neck with the acetabular rim leads to decreased clearance for the joint, which in turn leads to worsening injury and a repetitive cycle that leads to degeneration of the joint[1-3,8,9]. The joint clearance is directly related the femoral head-neck offset as well as degree of acetabular coverage[4]. The forces that result from FAI can create very significant articular cartilage and labral injuries. This effect has been increasingly recognized over the past decade leading to increased research and development of novel techniques to treat both the cause of impingement as well as the resulting injuries in an attempt to slow the degenerative process[1,2,7,8,10].

DIAGNOSIS

History

Diagnosis of FAI is critical in order to treat it early and prevent further injury to the chondral surface or labrum. Patients frequently present complaining of hip pain that is worsened with physical activity. Often the pain is exacerbated by activities that require the hip to assume a flexed position. These patients may also complain of difficulty with prolonged sitting due to pain and discomfort[8,10,16].

Physical examination

Physical exam often demonstrates lack of full flexion of the hip and decreased internal rotation with the hip in the flexed position. Pain can usually be reproduced by the impingement test, which is performed by attempting to place the hip in flexion, adduction, and internal rotation[13,16].

Imaging

A standard anteroposterior radiograph of the pelvis should be obtained to assess the version of the acetabulum and the shape of the femoral head and neck. Additionally, a cross-table lateral of the affected hip should be obtained with the hip in 15 degrees of internal rotation. This view allows for better analysis of the sphericity of the femoral head as well as the femoral head-neck offset. MRI (specifically MR arthrography) can be used to evaluate for the presence of any articular surface or labral injuries[14,16].

Conservative management

All patients with symptomatic FAI should undergo a trial of nonoperative treatment prior to consideration of surgical treatment. Unfortunately, conservative measures are often unsuccessful or unrealistic with many patients as they are frequently younger, active patients. Conservative treatment generally entails restrictions of activities and motions that place the hip the offending, most often flexed, position. Nonsteroidal anti-inflammatory drugs may be used for inflammation and pain control, but ultimately have no effect on the disease process. Frequently, patients with FAI wish to return to their previous activity levels and therefore may be indicated for surgical treatment[8-10,14].

INDICATIONS

Indications for surgical management of FAI begin with the failure of conservative treatment measures. Additionally, the surgical patient should have signs and symptoms of FAI along with a radiographically definable anatomic variant known to result in impingement[14,17-20].

CONTRAINDICATIONS

Contraindications for surgical treatment of FAI include advanced age, moderate (or worse) osteoarthritis of the hip, and morbid obesity. In these situations the surgeon should more likely perform total hip arthroplasty if surgical intervention is warranted. This discussion should take place with the patient[14,17-20].

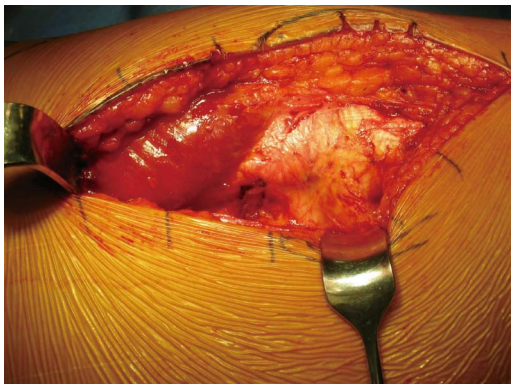

Figure 1 Straight lateral approach is shown for Ganz surgical dislocation. It is extremely important to well visualize the posterior border of the greater trochanter prior to proceeding for the trochanteric flip osteotomy.

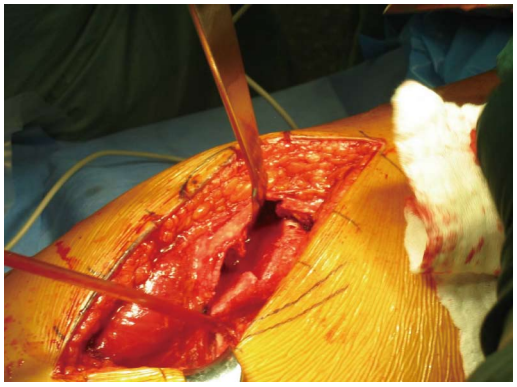

Figure 2 Trochanteric flip osteotomy begins at the posterior border of the greater trochanter and is carried anterior exiting superficial to the piriformis fossa and distal to the vastus ridge.

SURGICAL TECHNIQUES

The primary focus of surgical treatment of FAI should be to improve joint clearance, ultimately reducing destructive forces across the joint surfaces[17-20]. Appropriate preoperative planning should be done so that the most beneficial approach is used and the area of impingement is correctly identified and addressed. Multiple techniques for addressing FAI have been developed and each of their advantages and disadvantages have been the subject of much debate over the past decade.

Open surgical dislocation

An open surgical technique is the most established technique for FAI. Ganz *et al*[17] described a safe technique for open surgical dislocation in 2001. This technique involves surgical dislocation utilizing a trochanteric flip osteotomy. This technique provides relatively safe access to the hip joint with low risk of injury to the vascular supply of the femoral head. Many authors feel that this technique provides the surgeon with the most versatile approach to the hip, allowing sufficient access for osteochondroplasty of the acetabular rim or the femoral head-neck junction as well as labral repair[17-19,21-24].

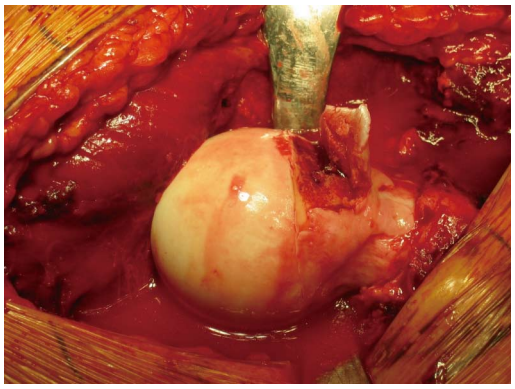

Figure 3 Impingement at the femoral head neck junction is corrected using a curved osteotome to shave slivers of the area of concern.

For an open surgical dislocation the patient should be placed in the lateral decubitus position such that the surgeon can use either a straight lateral approach or a posterolateral approach depending on surgeon preference[17,18,23]. Whichever approach is chosen it is extremely important to well visualize the greater trochanter prior to proceeding further with the operation (Figure 1). The posterior border of the greater trochanter must be well visualized, as it is the starting point for the trochanteric flip osteotomy with the medial circumflex artery in close proximity[21,22]. This portion of the operation is where the blood supply to the femoral head is at the greatest risk[21]. The trochanteric osteotomy is performed with the leg in internal rotation and care should be taken to leave the external rotators uninjured. The osteotomy begins at the posterior border of the greater trochanter and is carried anterior exiting superficial to the piriformis fossa and distal to the vastus ridge (Figure 2)[17,18,22,23]. Following osteotomy, muscle should be carefully dissected from the capsule. A Z-shaped capsulotomy is performed starting at the posterior acetabular rim then along the anterolateral femoral neck to the anteromedial femoral neck[17]. During this step, extreme care must be taken to avoid injury to any of the vasculature[17,22].

Once capsulotomy has been performed the hip should be assessed. The located hip should be taken through a full range of passive motion to most precisely locate the area of impingement. This step should always be performed prior to dislocation of the femoral head so that the surgeon may better visualize the area where osteochondroplasty must be performed in order to alleviate the impingement[17,23].

Moving the limb into flexion and external rotation then dislocates the femoral head. To completely dislocate the femoral head, the round ligament must be transected. This may need to be done if the lesions causing impingement are believed to be along the posterior femoral head or neck or the posterior acetabular rim[17,18].

At this point, impingement caused by femoral head-neck junction can be corrected by performing osteochondroplasty (Figure 3). Along with identification of the site

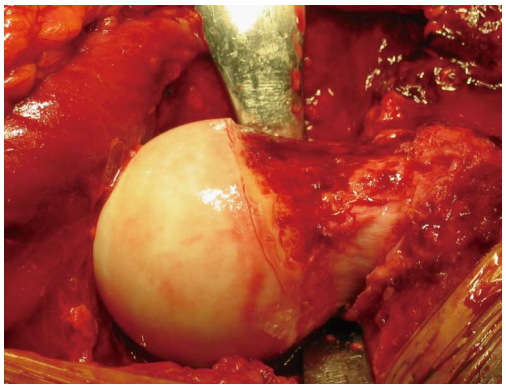

Figure 4 Osteochondroplasty is continued until the femoral head neck junction has been restored to the appropriate anatomical shape to relieve the impingement.

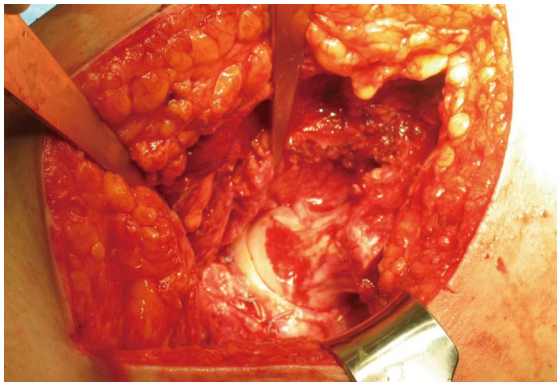

Figure 5 After adequate osteochondroplasty of the femoral head and neck junction and the acetabulum, the labrum is reattached using suture anchors, the femoral head is re-located. The hip should once again be taken through a full range of motion paying special attention to those positions that were noted to cause impingement prior to dislocation. If adequate resection of the offending lesions has been performed the hip should be able to be taken through a full range of motion with no further impingement.

of impingement during range of motion of the hip, the area involved in FAI often has a distinct inflammatory appearance due to repetitive contact with the acetabulum. The femoral neck should be corrected to a normal contour using a curved osteotome to shave off slivers of the area of concern in a stepwise fashion taking care to avoid femoral neck vasculature (Figure 4)[1,17,18,23].

Next the acetabular rim and labrum should be inspected. If the anterior acetabular rim is contributing to FAI, it should be resected. To perform resection osteoplasty of the acetabular rim, the labrum must be mobilized or resected. If the labrum appears significantly diseased, it should be resected, otherwise attempts to mobilize and preserve the labrum should be attempted in order to preserve normal function of the hip joint. Once again, osteochondroplasty should be done with a curved osteotome. The resection should be done in a stepwise fashion until the area of impingement is removed and the underlying articular cartilage appears healthy. At this time the healthy labrum can be reattached to the new acetabular rim (Figure 5)[3,17,18,25].

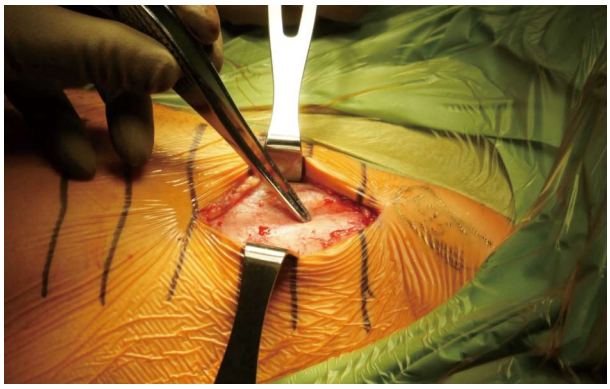

Figure 6 Mini-open technique using "Heuter Approach", also called the "Short Smith-Pete" because it follows the interval of the Smith-Petersen distal to the anterior superior iliac spine, is used for access to the capsule and femoral neck. The forceps point to the internervous plane between the femoral nerve (Sartorius) and the superior gluteal nerve (tensor fascia lata).

Once the femoral head and neck and the acetabulum have been addressed the dislocated femoral head may be reduced. Following reduction, the hip should once again be taken through a full range of motion paying special attention to those positions that were noted to cause impingement prior to dislocation. If adequate resection of the offending lesions has been performed the hip should be able to be taken through a full range of motion with no further impingement[17,18,23,25,26]. If the osteochondroplasty is deemed acceptable the capsule should be closed loosely. The trochanteric osteotomy may then be reduced and fixed with cortical screws. The remainder of the wound should be closed in a layered fashion appropriate for the chosen approach[17,18].

Mini-open approach

The mini-open technique for treatment of FAI is generally done as a combination of open and arthroscopic procedures. Currently only a few studies examining the use of a mini-open technique are reported in the literature[25-29].

For the mini-open technique the patient is positioned supine on an operating room table with traction available[25]. The hip is not formally dislocated in the mini-open approach. Lesions within the joint are inspected using an arthroscope[25,27]. Shaving of chondral lesion or labral lesions are done during this arthroscopic investigation[27].

A partial anterior approach, the "Heuter Approach", also called the "Short Smith-Pete" because it follows the interval of the Smith-Petersen distal to the anterior superior iliac spine, is used for access to the capsule and femoral neck (Figure 6). This can be accomplished with an incision ranging from 2 to 12 cm depending on the size of the patient This is done through the internervous plane between the femoral nerve (Sartorius, iliopsoas, and rectus femoris) and the superior gluteal nerve (gluteus minimus and medius and tensor fascia lata) (Figure 7)[27-29]. The capsulotomy is then performed using the same avas-

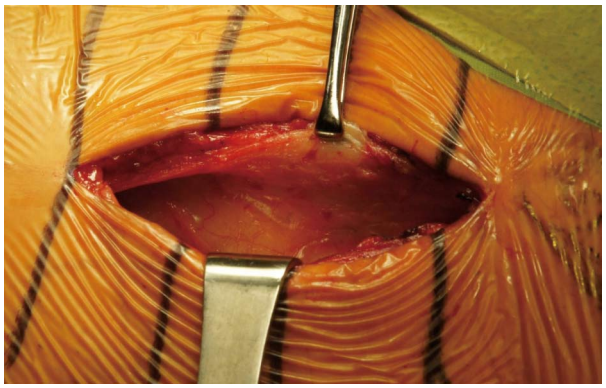

Figure 7 Using "Heuter Approach", also called the "Short Smith-Pete", the superficial internervous plane between the femoral nerve (Sartorius) and the superior gluteal nerve (tensor fascia lata) is developed.

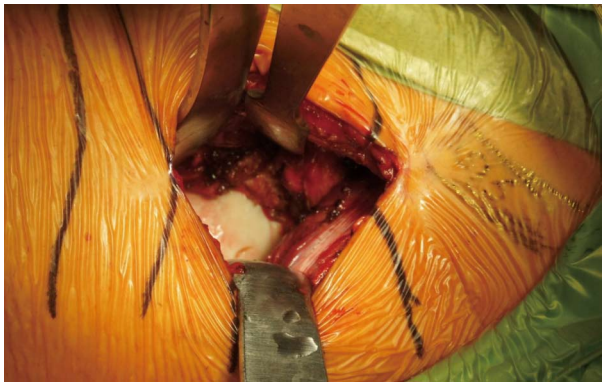

Figure 8 Anterior capsulotomy is performed. Labrum and femoral head and neck junction is adequately exposed. The distinct inflammatory appearance with red color of the cartilage is visualized.

cular location as that of the open surgical dislocation. This technique again allows easy identification of the lesion at the femoral head-neck junction (Figure 8). A high speed burr or an arthroscopic burr can be used for contouring of the femoral neck[27].

As with open dislocation, once all work has been completed the hip is fully ranged to assure complete resolution of the impingement. Following confirmation the capsule may be loosely closed and the remainder of the closure done in a layered fashion[27-29].

Arthroscopic surgery

Some surgeons assert that FAI cannot be adequately treated using arthroscopy due to the limited view of the femoral neck and acetabulum. They also feel that lesions cannot be adequately accessed with the femoral head remaining located within the acetabulum. However, advocates of hip arthroscopy claim that due to the consistent location of most FAI lesions a 360-degree view of the femoral head, neck, and acetabulum is not necessary. Techniques believed to be useful for treatment of FAI using arthroscopy have been described in the literature[27,30-34].

The patient should be placed either in the lateral

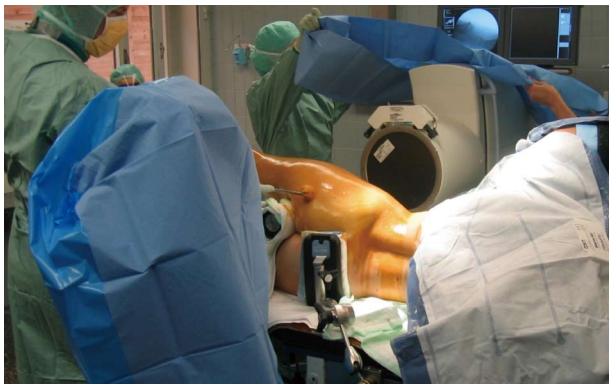

Figure 9 For arthroscopic debridement of femoroacetabular impingement, the patient is placed in a lateral position. The operative leg is placed in a traction device and fluoroscopy is used to identify the areas of impingement and placement of instruments.

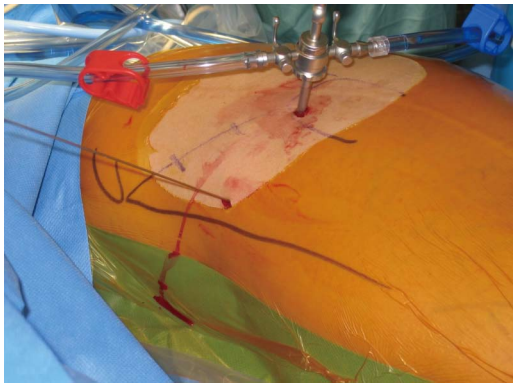

Figure 10 Arthroscopic portal placement: the anterolateral portal is placed about 1 cm proximal and 1 cm anterior to the tip of the greater trochanter. The anterior portal is placed directly distal to the anterosuperior iliac spine and medial to the anterolateral portal.

position or supine based on surgeon's preference. The operative leg should be placed in a traction device and fluoroscopy should be used to identify the areas of impingement (Figure 9). Fluoroscopy can also be used while placing the portals, which include anterior, anterolateral, and posterolateral portals[27,33,34].

The anterolateral portal is placed about 1 cm proximal and 1 cm anterior to the tip of the greater trochanter using fluoroscopy with the hip distracted. A 30-degree arthroscope is placed in the portal and the anterior portal is placed under direct visualization (Figure 10)[15,27,31]. The hip joint is then inspected and probed for articular cartilage damage as well as labral injuries. Both labral and chondral lesions can be debrided until stable tissue is reached[15,30,32,34]. Additionally, osteophytes can be removed with a burr. Some surgeons also advocate the use of microfracture techniques in areas where notable articular cartilage damage is seen[30,31].

Following the assessment of the articular surface, the arthroscope is placed in the anterolateral portal outside of the joint capsule. The capsule is dissected using instruments through the anterior portal. Once the capsule is

well visualized an anterior capsulotomy is performed with minimal resection of the capsule. This allows for exposure of the femoral head-neck junction and manipulation of the instruments. Osteochondroplasty is then performed using a burr. Contour of the femoral neck should be checked using fluoroscopy throughout this portion of the procedure[27,30-32,34].

After all steps are completed the traction is removed from the leg and the hip is ranged while still being directly visualized using the arthroscope to check for any residual impingement[30,31,34].

POST-OPERATIVE CARE

Open surgical dislocation

Postoperatively the patient should be restricted to toe-touch weight bearing on the operative extremity for six to eight weeks. The patient should ambulate using crutches or a walker for assistance during this time to prevent falls. Physical therapy may be started immediately using passive range of motion for the first and second weeks postoperatively. At ten to fourteen days active motion may begin, however flexion should be limited 70 degrees for the first six to eight weeks. Early range of motion will help prevent the formation of adhesions[17-24].

Mini-open

Laude *et al*[28] report keeping patients with protected weight-bearing and use of crutches for five days. After 5 d the patients are allowed full weight bearing without crutches. At this time they are also encouraged to begin low impact active exercise, such as cycling. Patients are kept from high impact or contact sports for a total of six months postoperatively[25-29].

Arthroscopy

Patients should be made toe-touch weight-bearing and ambulate with aids for 2 to 4 wk. At that time low impact active motion may be resumed. At three months postoperatively the patient no longer has any activity restrictions[15,27,30-32].

OUTCOMES

A recent review by Matsuda *et al*[25] found an overall result of surgical intervention for FAI with good to excellent results to be 65% to 95%. This was accompanied by an overall rate of complications of 0% to 20%.

Open surgical dislocation

Over the past decade numerous studies have helped define clear indications for surgical treatment of FAI. Thus far, surgical dislocation has demonstrated great success with most studies showing 65% to 95% of patients with good to excellent results in midterm follow-up[12,19,25,35]. Many studies have shown at least midterm benefit of halting or slowing of degenerative changes noted on follow-up radiographs of patients with Grade 0 or Grade 1 degenerative changes following surgical dislocation and removal of lesions, which had created FAI. Patients which Grade 2 or higher degeneration have shown less predictable results, although young patients with Grade 2 degenerative changes may be acceptable candidates for a trial of surgical dislocation[12].

Potential complications include trochanteric nonunion, heterotopic ossification, sciatic nerve palsy, osteonecrosis of the femoral head, femoral neck fracture. Osteonecrosis of the femoral head is rare with open surgical dislocation as the technique is designed to minimize risk to the blood supply to the femoral head. Additionally, risk of femoral neck fracture is minimized by limiting the depth of osteochondroplasty at the femoral head-neck junction to not greater than 30% of the diameter of the femoral neck[25,26].

Studies of open surgical dislocations have shown a rate of conversion to total hip arthroplasty of 0% to 30%, however the most recent studies with defined surgical indications show a lower rate of 0% to 5%[25].

Mini-open

A review of studies looking at mini-open treatment of FAI shows a reported success rate of 71% to 92%. Some researchers demonstrated an improvement in both the Harris hip score and UCLA activity score following mini-open treatment of FAI. Conversion to total hip arthroplasty was 0% to 11% and complications were seen in 0% to 17%. The literature suggests that there is a relatively high incidence of iatrogenic lateral femoral cutaneous nerve injury with the mini-open technique. There is limited data looking at mini-open treatment of FAI[25,27,29].

Arthroscopy

Some surgeons advocate hip arthroscopy when the lesion is localized and easily accessed with an arthroscope, especially those felt to be isolated labral tears. However many authors assert that labral tears do not occur without trauma or the presence of FAI. One study showed that less than 50% of patients treated with isolated arthroscopic labral debridement. Hip arthroscopy has also been noted to be associated with neuropraxia of many of the nerves near the hip joint due to the traction necessary for adequate visualization[5,25,27,32].

Other surgeons believed that adequate treatment of FAI might be achieved by arthroscopy. They advocate this technique as the claim patients are able to return to normal activities more quickly than with open surgical dislocation. Advocates also point toward series that demonstrate 75%-95% good to excellent outcomes at midterm follow-up for FAI treated arthroscopically. Series also show a conversion to total hip arthroplasty of 0% to 9%[25,32].

CONCLUSION

With the recently increased recognition of FAI and its possible contribution to early degenerative changes of

the hip, the past decade has seen much study and advancement of various techniques to treat the pathologic anatomy of FAI. The techniques include open surgical dislocation, a mini-open technique with or without arthroscopy, and purely arthroscopic treatment.

Current literature with midterm follow-up shows similar success rates with all techniques. Additionally, all approaches have demonstrated similar conversions to total hip arthroplasty as well as similar rates of major complications. Open surgical dislocation showed a slightly higher rate of complications and reoperation, largely due to a 20% nonunion rate of the trochanteric flip osteotomy. Much more literature exists with respect to the arthroscopic approach to FAI. One important factor to note is surgeons with extensive experience with hip arthroscopy have performed all reported series of arthroscopic treatment of FAI. Hip arthroscopy is known to have a very steep learning curve. Therefore, the reliability of this technique likely depends heavily on the experience of the surgeon. The least studied technique is the mini-open technique.

The three techniques described in the literature of the past decade all have shown great success at treating FAI with significant improvement in symptoms. Midterm follow-up shows evidence supporting the slowing of degenerative changes in patients with minimal degeneration preoperatively. As the management of FAI continues to develop it is extremely important that a surgeon is comfortable with the technique chosen when surgical intervention is indicated.

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REVIEW

Osteoclast fusion and regulation by RANKL-dependent and independent factors

Lianping Xing, Yan Xiu, Brendan F Boyce

Lianping Xing, Yan Xiu, Brendan F Boyce, Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY 14642, United States
Author contributions: Xing L and Boyce BF involve in experimental design, data analysis and interpretation, drafting the manuscript and final approval of the version to be published; Xiu Y involves in experimental design, acquisition of data and data analysis, revising the manuscript, and final approval of the version to be published.

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Correspondence to: Lianping Xing, PhD, Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, 601 Elmwood Avenue, Box 626, Rochester, NY 14642, United States. lianping_xing@urmc.rochester.edu
Telephone: +1-585-273-4090 Fax: +1-585-756-4468
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Abstract

Osteoclasts are the bone resorbing cells essential for bone remodeling. Osteoclasts are formed from hematopoietic progenitors in the monocyte/macrophage lineage. Osteoclastogenesis is composed of several steps including progenitor survival, differentiation to mononuclear pre-osteoclasts, fusion to multi-nuclear mature osteoclasts, and activation to bone resorbing osteoclasts. The regulation of osteoclastogenesis has been extensively studied, in which the receptor activator of NF-κB ligand (RANKL)-mediated signaling pathway and downstream transcription factors play essential roles. However, less is known about osteoclast fusion, which is a property of mature osteoclasts and is required for osteoclasts to resorb bone. Several proteins that affect cell fusion have been identified. Among them, dritic cell-specific transmembrane protein (DC-STAMP) is directly associated to osteoclast fusion *in vivo*. Cytokines and factors influence osteoclast fusion through regulation of DC-STAMP. Here we review the recently discovered new factors that regulate osteoclast fusion with specific focus on DC-STAMP. A better understanding of the mechanistic basis of osteoclast fusion will lead to the development of a new therapeutic strategy for bone disorders due to elevated osteoclast bone resorption. Cell-cell fusion is essential for a variety of cellular biological processes. In mammals, there is a limited number of cell types that fuse to form multinucleated cells, such as the fusion of myoblasts for the formation of skeletal muscle and the fusion of cells of the monocyte/macrophage lineage for the formation of multinucleated osteoclasts and giant cells. In most cases, cell-cell fusion is beneficial for cells by enhancing function. Myoblast fusion increases myofiber size and diameter and thereby increases contractile strength. Multinucleated osteoclasts have far more bone resorbing activity than their mono-nuclear counterparts. Multinucleated giant cells are much more efficient in the removal of implanted materials and bacteria due to chronic infection than macrophages. Therefore, they are also called foreign-body giant cells. Cell fusion is a complicated process involving cell migration, chemotaxis, cell-cell recognition and attachment, as well as changes into a fusion-competent status. All of these steps are regulated by multiple factors. In this review, we will discuss osteoclast fusion and regulation.

Key words: Osteoclasts; Fusion; Dritic cell-specific transmembrane protein; Receptor activator of NF-κB ligand; Bone resorption.

Peer reviewers: Xiang-Hang Luo, Professor, Institute of Endocrinology and Metabolism, the Second Xiangya Hospital of Central South University, No. 139, Middle Renmin Road, Changsha 410011, Hunan Province, China; Chih-Shung Wong, MD, PhD, Professor and Director, Department of Anesthesiology, Cathay General Hospital, No. 280, Renai Road, Section 4, Taipei, Taiwan, China

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INTRODUCTION

Osteoclasts are the only multinucleated cells in the body that resorb bone, a process essential for postnatal bone remodeling. Humans and mice with deficient osteoclast generation or function form skeleton during embryonic bone development, but develop severe osteopetrosis in later stages of life. In osteopetrosis, the bone marrow cavity is filled with un-resorbed bone matrix[1,2]. Osteopetrosis is often accompanied by early death due to bone marrow failure-associated with immune deficiency and a high risk of infection[3,4]. Thus, osteoclasts are not required for embryonic bone development and modeling, but they are essential for postnatal bone remodeling. Osteoclasts are hematopoietic cells originating from embryonic mesoderm along with bone and cartilage. They are formed from bone marrow myeloid progenitor cells[5]. Under the influence of macrophage colony-stimulating factor (M-CSF), these progenitor cells survive and proliferate to expand themselves[6]. Receptor activator for NF-κB ligand (RANKL, also named TNSF11 or osteoprotegerin ligand) triggers the differentiation of M-CSF-dependent progenitor cells to osteoclast precursors and then to mature osteoclasts, which are stained positive for Tartrate-resistant acid phosphatase (TRAP, also named acid phosphatase 5)[7,8]. Osteoclast precursors are TRAP+ mono-nucleated pre-osteoclasts (pre-OCs), which fuse to form multinucleated mature TRAP+ osteoclasts. TRAP+ pre-OCs do not resorb bone in *in vitro* cultures and mice with defective pre-OC fusion develop osteopetrosis[9,10]. Thus, pre-OC fusion is a critical cellular event for osteoclast function, and understanding its regulation will have an important impact on the development of a new therapy to control bone loss via targeting osteoclast cell fusion.

OSTEOCLAST FUSION

Under physiological conditions, both TRAP+ mono-nucleated pre-OCs and TRAP+ multinucleated osteoclasts are found only on the bone surface, indicating that pre-OC formation from TRAP- myeloid progenitor cells and subsequent fusion must occur on the bone surface. Since TRAP- myeloid progenitor cells are present in multiple organs and tissues while TRAP+ pre-OCs and osteoclasts only are present on the bone surface within the bone marrow, to initiate cell fusion, progenitor cells must be recruited, migrated and attached to the bone surface and differentiate to pre-OCs. Thus in a broad sense, factors that affect recruitment, migration and attachment of progenitor cells should also be considered factors that regulate cell fusion. However, although the events that are involved in pre-OC fusion are continuous events *in vivo*, they can be divided into a series of steps experimentally in cell cultures. Myeloid progenitor cells isolated from multiple tissues, such as peripheral blood[11], spleen[12], liver[13] and even lymph nodes (our unpublished observation), can all give rise to TRAP+ mono-nucleated pre-OCs in the presence of M-CSF and RANKL, which fuse spontaneously within 1-3 d to form multinucleated osteoclasts on plastic culturing plates. Thus, the fusion of pre-OCs, at least *in vitro*, is an independent process, apart from recruitment, migration and adhesion. In this review we will specifically discuss factors that control the fusion process of pre-OCs. We will not include factors that regulate progenitor recruitment, migration and adhesion, although these are prerequisite to fusion *in vivo*[14,15]. Because mouse genetic studies indicate that depletion of Dendritic cell-specific transmembrane protein (DC-STAMP, TM7SF4)[9,10] in mice affects only the cell-cell fusion process, we will discuss the recent findings of DC-STAMP and its regulation in detail.

FACTORS THAT REGULATE OSTEOCLAST FUSION

Information on factors that regulate osteoclast fusion comes from two lines of study. One is from *in vitro* experiments in which samples from different stages (d) of osteoclast differentiation are used for the expression levels of factor that are known to regulate macrophage fusion; and the loss or gain of function experiments to determine the effect of manipulating these factors on pre-OC fusion. Another is from *in vivo* experiments in which bone phenotype and TRAP+ osteoclast morphology (mono-nucleated *vs* multi-nucleated) are examined in genetically modified mice to determine if a specific gene is responsible for or only responsible for pre-OC fusion.

Several factors are important for macrophage fusion including CD44, CD47, macrophage fusion receptor, CD9, DC-STAMP[16,17]. To investigate the expression pattern of these factors during osteoclast differentiation, we treated primary bone marrow mono-nuclear cells, of which 30% of them expressed pan myeloid marker CD11b, with M-CSF for 2 d to enrich myeloid progenitor cells. At this stage more than 90% of the cells expressed CD11b and all of them were TRAP negative[18] (Figure 1). We then treated these myeloid progenitor cells with RANKL for 3 or 4 d and examined the expression levels of known fusion genes, and compared their status of osteoclast fusion and differentiation (Figure 1). M-CSF-induced myeloid progenitor cells expressed high levels of CD44, CD47, and triggering receptor expressed on myeloid cells-2 (TREM2) at day 0 before RANKL treatment and gave rise to multinucleated osteoclasts at day 3 after they were cultured with RANKL. Osteoclast formation was accompanied by significant up-regulation of a set of fusion genes including CD9, macrophage fusion receptor (MFR), ATP6V0d2 and DA-STAMP. Compared to the

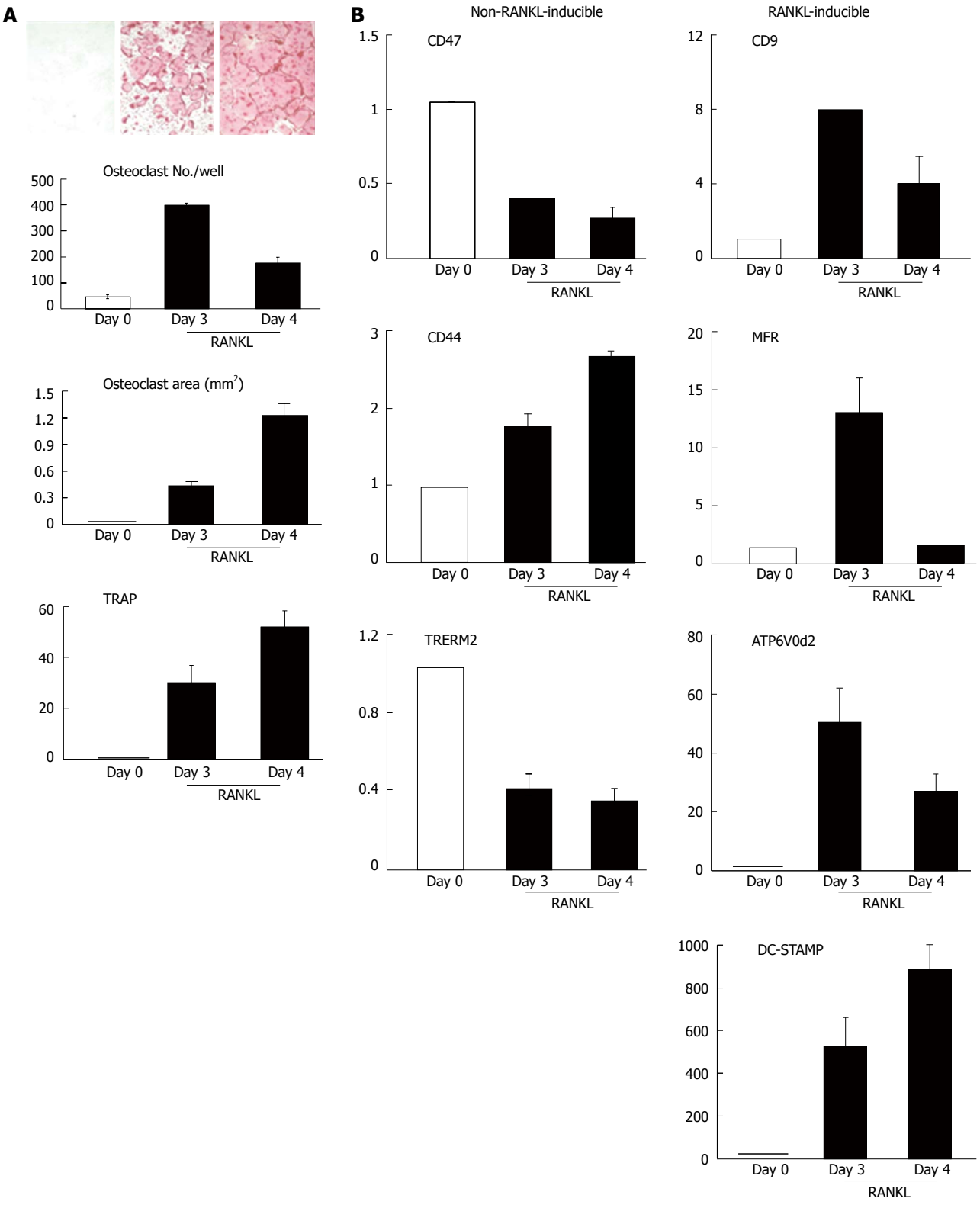

Figure 1 Receptor activator of NF-κB ligand increases the expression of a set of fusion genes in osteoclasts derived from WT bone marrow cells. Bone marrow mono-nuclear cells were cultured with macrophage colony-stimulating factor for 2 d and were then treated with Receptor activator of NF-κB ligand (RANKL) for additional 3 or 4 d. Cells were harvested at day 0 (before RANKL), day 3 and day 4 after RANKL treatment. A: Tartrate-resistant acid phosphatase (TRAP) staining, osteoclast number and area, and TRAP mRNA expression; B: The expression levels of fusion genes by quantitative polymerase chain reaction. The values are the fold increase *vs* the value on Day 0 as 1. MFR: Macrophage fusion receptor; DC-STAMP: Dritic cell-specific transmembrane protein

day 0 samples, the expression of ATP6V0d2 and DA-STAMP was induced by 50- and 500-fold, respectively. These data (Figure 1) are consistent with other reports regarding the changes of expression of these genes during

pre-OC fusion in Raw264.7 cells, a mouse macrophage/osteoclast precursor cell line[19], and divide fusion factors into 2 groups: factors (CD44, CD47, TREM2) that are not regulated by RANKL or those (CD9, ATP6V0d2 and DC-STAMP) that are regulated by RANKL. The factors whose regulation is induced by RANKL express at a higher level in M-CSF-dependent myeloid progenitor cells and the changes of their expression levels are less than 3-fold during the period from the TRAP-cells at day 0 to the TRAP+ multinucleated osteoclasts at day 3. In contrast, the factors that highly respond to RANKL are induced more than 8-folds by RANKL in the same samples (Figure 1).

FACTORS THAT ARE NOT REGULATED BY RANKL

CD47

CD47 is an integrin-associated protein that binds to its receptor, MFR (also called signal regulatory protein alpha)[20]. MFR is the first molecule identified to be critical for macrophage fusion[21,22]. In macrophages, CD47 and MFR interaction mediates cell-cell recognition at the stage before cell-cell fusion rather than during the fusing process itself. This is also the case in osteoclast fusion (Figure 1). The involvement of CD47 in bone remodeling and bone cell regulation was first studied *in vitro* using neutralizing antibodies to CD47 or MFR to block the CD47/MFR pathway. These neutralizing antibodies strongly reduced the formation of TRAP+ multinucleated osteoclasts in cultures of murine bone marrow cells in the presence of RANKL and M-CSF[23]. The role of CD47 in bone was further studied in mice that had global depletion of CD47. The numbers of osteoclasts were reduced when *Cd47*-/- spleen or bone marrow cells were cultured *in vitro*. The mechanism of reduced osteoclast numbers was due to a lack of SHPS-1 phosphorylation, SHP-1 phosphatase recruitment, and subsequent dephosphorylation of non-muscle cell myosin IIA. However, despite reduced osteoclast formation *in vitro*, *Cd47*-/- mice developed low bone mass phenotypes with a significant decrease in osteoblastogenesis in bone marrow stromal cells, which overrides the defect in osteoclast formation and fusion. Because CD47 is an integrin-associated protein, it has functions other than just regulating fusion[24]. The role of CD47 on osteoclast fusion in bone remodeling *in vivo* needs to be studied in mice with specific depletion of CD47 deletion in osteoclast precursors and in mice with pathological bone disorders.

CD44

CD44, a receptor for hyaluronic acid, is a type I transmembrane glycoprotein that connects a variety of extracellular matrix proteins to the cell surface. It binds to chondroitin sulfates and osteoponin to inhibit macrophage fusion. CD44 is highly expressed in macrophages prior to fusion[25]. As cell fuse, the intracellular domain of CD44 is cleaved and translocated to the nucleus, where it activates the NF-κB pathway and stimulates fusion[26]. CD44 is involved in actin cytoskeletal organization in osteoclasts by linking to podosome cores[27]. The role of CD44 in osteoclast generation and fusion *in vivo* was examined in *Cd44*-/- mice. *Cd44*-/- mice had normal basal bone volume. Osteoclast size and numbers on the bone surfaces of *Cd44*-/- mice were similar to that of WT mice, indicating that CD44 expression is not essential for pre-OC fusion under physiological conditions[28]. To investigate if CD44 plays a role in pathological bone disorders, *Cd44*-/- mice were crossed with TNF-Tg, a mouse model of inflammatory arthritis due to over-expression of the human TNF transgene[29]. Compared to TNF-Tg mice, TNF-Tg/*Cd44*-/- mice developed much more severe joint inflammation and bone erosion and systemic bone loss. Increased osteoclast number, size and resorptive capacity were observed in TNF-Tg/*Cd44*-/- mice, but bone formation and osteoblast differentiation in these mice were normal. *Cd44*-/- osteoclasts had elevated activation of the p38 mitogen-activated protein kinase in response to TNF, indicating that CD44 is a critical inhibitor of TNF-driven joint destruction and inflammatory bone loss[30].

TREM2

TREM2 is the main DNAX activating protein 12 (DAP12)-associated receptor in osteoclasts. In the bone, TREM-2 induces fusion of pre-OCs into multinucleated cells; thus, osteoclast development is blocked in the absence of TREM-2, resulting in inefficient bone resorption[31,32]. *In vitro* loss of function experiments demonstrated that known-down of DAP12 or TREM2 impairs osteoclast development and fusion[33]. DAP12/TREM-2 is also involved in the formation of foreign body giant cells and is induced by IL-4. IL-4 is a cytokine produced by T helper cells and plays a critical role in macrophage fusion[34]. Macrophages express an uncharacterized TREM-2 ligand[35]. It has been hypothesized that DAP12- and TREM-mediated macrophage fusion is mediated by the interaction between TREM-2 ligand-expressing macrophages and TREM-expressing macrophages. DAP12/TREM2 signaling can therefore be considered as an endogenous macrophage trigger leading to increased gene transcription and expression of factors required for efficient fusion. It can be separated from the exogenous IL-4 stimulus because both IL-4-induced and basal macrophage fusion levels are reduced in the absence of DAP12 signaling[31,32].

FACTORS THAT ARE REGULATED BY RANKL

CD9

CD9 is a member of the tetraspanin superfamily proteins, which are implicated in a variety of cell processes including fusion. Members of tetraspanin superfamily proteins that mediate cell fusion include CD9, CD63, CD81. Blockage of CD9 and CD81 with neutralizing antibodies enhances macrophage fusion to multinucleated giant cells[36]. CD9 is expressed in a specific membrane lipid

raft of Raw267.4 cells, which is enhanced by RANKL treatment. Blockage of CD9 by a neutralizing antibody or RNA interference reduces osteoclast formation while over-expression of CD9 promotes cell fusion in the absence of RANKL[19]. CD9 protein expression is increased in activated osteoclasts on bone surfaces in mice with ovariectomy- or arthritis-induced bone loss, suggesting that CD9 plays important roles in bone destruction[37].

ATP6v0d2

Among numerous fusion regulators, gene knockout studies revealed that the expression of DC-STAMP (Dendritic cell-specific transmembrane protein, TM7SF4)[9,10] and ATP6V0d2 (ATPase, H+ transporting, lysosomal 38 kDa, V0 subunit d2) are required for osteoclast fusion under basal conditions. ATP6V0d2 is a component of the ATPase pump. However, osteoclasts from *ATP6V0d2*-/- mice do not have defective v-ATPase activity and differentiation, rather the fusion of pre-OCs to mature osteoclasts is blocked[38]. Apart from defective fusion, bone formation is significantly increased in *ATP6V0d2*-/- mice. Since osteoblasts do not express ATP6V0d2 and bone marrow stromal cells from *ATP6V0d2*-/- mice differentiate to osteoblasts *in vitro* normally, it is speculated that increased bone formation in *ATP6V0d2*-/- mice works through an indirect mechanism. The expression levels of DC-STAMP and MFR is un-changed in *ATP6V0d2*-/- cells. ADAM8 and ADAM12 expression levels are markedly reduced. Over-expression of ADAM8 or ADAM12 rescues pre-OC fusion defect of *ATP6V0d2*-/- cells[38].

A disintegrin and metalloprotease 8 (ADAM8) expresses in osteoclast precursors and stimulates osteoclast formation[39]. Recently, Dr. David Roodman's lab generated TRAP-ADAM8 transgenic mice which specifically over-expressed ADAM8 in TRAP-expressing pre-OCs and osteoclasts, and global *ADAM8*-/- mice. TRAP-ADAM8 transgenic mice developed a low bone mass phenotype with increased osteoclast numbers. *In vitro* studies demonstrated that cells from TRAP-ADAM8 transgenic mice had increased RANKL-mediated signaling pathways including NF-κB, Erk and Akt. Apart from increased osteoclast differentiation and bone resorption, pre-OCs had increased fusion capacity. Interestingly, basal levels of DC-STAMP expression were significantly increased in TRAP-ADAM8 cells, which was further enhanced by RANKL. In contrast, the expression of other fusion proteins such as CD44, CD47 and ATP6v0d2 were only slightly increased in the later time of cultures. Increased DC-STAMP was considered due to increased RANKL-mediated signaling such as c-Fos, NFATc1 and NF-κB, all of them up-regulate DC-STAMP expression[40]. However, it is not clear why ATP6v0d2 expression was not changed since it is also regulated by RANKL-NFATc1 pathway and over-expression of ADAM8 in ATP6v0d2-/- cells rescues the fusion defect.

DC-STAMP

DC-STAMP is a seven-pass transmembrane protein which is encoded by the gene named Tm7sf4[41]. In 2006, Dr. Toshio Suda's lab used a DNA subtraction screen between osteoclasts and mononuclear macrophages and identified that DC-STAMP was highly expressed in osteoclasts but not in macrophages. They generated *DC-STAMP*-/- mice and demonstrated that mice developed osteopetrosis due to a defect in osteoclast fusion. Cells from *DC-STAMP*-/- mice were still able to respond RANKL-induced expression of osteoclast functional genes such as TRAP and *cathepsin K*. In contrast to *ATP6V0d2*-/- mice, osteoblast-mediated bone formation was normal in *DC-STAMP*-/- mice. Currently, *DC-STAMP*-/- mice is the only mouse model where the increased bone mass is solely due to a defect of pre-OC fusion. The foreign body giant cell reaction in *DC-STAMP*-/- mice was also defected, confirming the known role of DC-STAMP in macrophage cell fusion[9]. Cells from *DC-STAMP*-/- mice can still resorb the bone tissues with significantly reduced capacity, indicating that cell fusion is not essential for bone resorption but significantly affects its efficiency. These data suggest that cell fusion is an important step in osteoclast differentiation, and osteoclast size determines resorptive capacity and functions of osteoclasts.

REGULATION OF DC-STAMP BY FACTORS IN THE RANKL PATHWAY

RANK and RANKL are key regulatory molecules for osteoclast formation and activation[13,42-44]. RANKL is expressed on the surface of osteoblastic cells in the marrow cavity and by osteocytes embedded within bone[45,46] and it interacts with its receptor RANK located on the surface of osteoclasts and osteoclast precursors. RANKL/RANK interaction leads to recruitment of TNF receptor-associated factors (TRAFs), adaptor proteins to which enzymes, including MAP kinases and Src tyrosine kinase, bind and are activated to mediate downstream signaling. TRAF-mediated signaling leads to activation of NF-κB, c-Fos, and NFATc1 (nuclear factor of activated T cells cytoplasmic 1)[13,42-44], transcription factors that are essential for osteoclast differentiation. These transcription factors also regulate osteoclast fusion, mainly via DC-STAMP.

NFATc1

NFATc1 is a RANKL downstream gene[47]. Dr. Miyamoto's lab (2007) demonstrated that the DC-STAMP promoter contains AP-1 and NFATc1 binding sites, which are required for RANKL-induced DC-STAMP expression. c-Fos and NFATc1 are indispensable for DC-STAMP expression and cell-cell fusion in osteoclasts, but both factors are dispensable for giant cell formation by macrophages, suggesting that DC-STAMP transcription is regulated in a cell type-specific manner[48]. Over-expression of NFATc1 in WT bone marrow-derived macrophages does not affect the expression levels of CD9, CD44, and MFR, but significantly increases Atp6v0d2 and DC-STAMP expression, indicating that among fu-

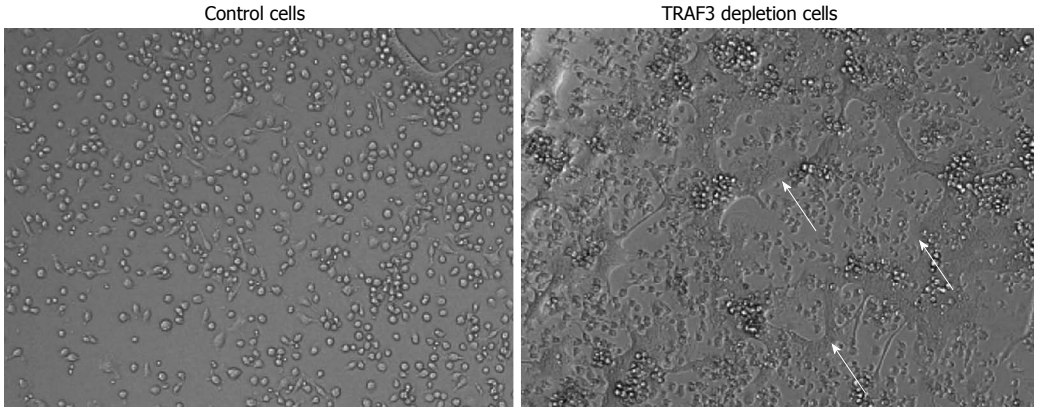

Figure 2 Increased osteoclast fusion in cells from TRAF3f/f; CSK-Cre mice. Bone marrow mono-nuclear cells from control mice (TRAF3f/f) and TRAF3f/f; CSK-Cre mice were cultured with M-CSF for 2 d and then treated with RANKL for additional 2 d. Photos show multi-nuclear mature osteoclasts (arrows) in cells from TRAF3f/f; CSK-Cre mice. TNF: Tumor necrosis factor; TRAF: TNF receptor-associated factors; M-CSF: Macrophage colony-stimulating factor.

sion regulators, Atp6v0d2 and DC-STAMP are RANKL target genes. Both the Atp6v0d2 and DC-STAMP promoters contain multiple NFATc1 binding sites and are bound by NFAC1 protein in chromatin immunoprecipitation assay[49].

NF-κB

The NF-κB family includes NF-κB1 (p50 and its precursor p105), NF-κB2 (p52 and its precursor p100), RelA, RelB and c-Rel. Homo- and hetero-dimers of the 5 NF-κB proteins activate the transcription of target genes, through the canonical (RelA:p50) and the non-canonical (RelB:p52) pathways. NF-κB (typically refers to canonical RelA-mediated transcription) regulates many aspects of cellular activity[47]. Expression of both NF-κB1 and NF-κB2 are essential for RANKL-induced osteoclast formation[13,42,50]. Basal osteoclast formation is normal in *NF-κB1-/-* or *NF-κB2-/-* mice[51], but TNF and RANKL-induced osteoclast formation is increased in *NF-κB2-/-* mice, indicating that NF-κB2-mediated cellular events negatively regulate osteoclast formation[52]. IL-4 inhibits the RANKL-induced osteoclast differentiation and promotes macrophage fusion. IL-4 inhibition of osteoclastogenesis is mediated by suppressing the RANKL-induced activation of NF-κB. A recent study reported that IL-4 did not block proximal, canonical NF-κB signaling. Instead, IL-4 inhibited NF-κB signaling by inducing NF-κB1 expression. Formation of both RANKL-induced osteoclasts and IL-4-induced foreign body giant cells are impaired in bone marrow-derived macrophages from *NF-κB1-/-* mice, and in WT cells that were treated with the NF-κB inhibitors, IκB kinase 2 inhibitor or NF-κB essential modulator inhibitory peptide. Over-expression of p50, p65, p52, and RelB individually in *NF-κB1-/-* or WT bone marrow-derived macrophages increased the formation of multinucleated osteoclasts and foreign body giant cells. Interestingly, knockdown of NF-κB2 in WT BMM dramatically enhanced both osteoclast and foreign body giant cell formation[53]. NF-κB2 is composed of p52 and its precursor p100. RANKL promotes the processing of p100 to p52 via NIK (NF-κB inducing kinase). Under basal conditions, cells have very low levels of NIK protein because it is degraded in a protein complex inducing TRAF3[54,55]. In mice whose osteoclasts carrying a mutated form of NIK that lacks its TRAF3 binding domain, osteoclast formation and fusion is increased and mice develop mild osteoporosis. Osteoclasts from these mice express high levels of NFATc1 and DC-STAMP[56]. Consistent with this finding, we observed increased RANKL-induced osteoclast fusion in M-CSF-dependent myeloid precursors that are isolated from osteoclast specific TRAF3 knockout mice (Figure 2). Together, these findings suggest that NF-κB1 stimulates while NF-κB2 inhibits osteoclast fusion. The detailed mechanisms by which NF-κB2 negatively regulates osteoclast fusion need to be further studied.

Calcium

RANKL induces calcium (Ca^{2+}) oscillations, leading to up-regulation of NFATc1. Cellular Ca^{2+} comes from both intracellular and extracellular sources. Inositol 1,4,5-trisphosphate affects osteoclast formation by stimulating Ca^{2+}-release from the endoplasmic reticulum[57-59]. However, it is less clear the extent to which extracellular Ca^{2+} influx is involved in osteoclast biology. Ca^{2+} entering cells is mainly mediated by the Ca^{2+}-release-activated Ca^{2+} channel on plasma membrane[60,61]. Orai1 is a subunit of the Ca^{2+}-release-activated Ca^{2+} channel, which provides a major Ca^{2+} influx pathway in hematopoietic cells and plays a critical role in the maintenance of Ca^{2+} oscillations[62]. Orai1 is required for the activation of NFAT in T cells[63]. Knockdown of Orai1 by RNA interference in human monocytes[64] or RAW264.7 cells[65] reduces Ca^{2+} channel and inhibits RANKL-induced osteoclastogenesis by suppressing the induction of NFATc1. *Orai1-/-* cells are defective in cell fusion and bone resorption, which is associated with down-regulation of ATP6v0d2, suggesting that Orai1 might be a potential therapeutic target for the treatment of bone loss caused by osteoclasts.

REGULATION OF DC-STAMP BY FACTORS OTHER THAN RANKL

Recent studies reveal that DC-STAMP can be regulated by factors other than RANKL, indicating the complexity of cell fusion regulation.

Interleukin-32

Interleukin-32 gamma is a cytokine that is produced mainly by T cells and NK cells[66]. The expression of interleukin-32 gamma is increased in synovial tissues from patients with rheumatoid arthritis[67]. Interleukin-32 gamma increases the expression levels of NFATc1, DC-STAMP and ATP6V0d2, and promotes RANKL-induced osteoclast formation and fusion. Interleukin-32 gamma-induced DC-STAMP and ATP6V0d2 up-expression is abolished in cells treated with NFATc1 inhibitor. These data indicate that T cell cytokine interleukin-32 gamma promotes osteoclast fusion via NFATc1-mediated up-regulation of DC-STAMP and ATP6V0d2, and T cells may affect osteoclast fusion via Interleukin-32 gamma in patients with rheumatoid arthritis or other similar types of diseases[68].

Tal1

T-cell acute lymphocytic leukemia 1/stem cell leukemia 1 (Tal1/Scl1) is a basic helix-loop-helix transcription factor essential for hematopoiesis. *Tal1*-/- mice died in early embryo due to failure of hematopoietic stem cell and blood development[69]. Tal1 functions as a transcription repressor or activator, depending on the cofactors with which it is associated[70]. Embryonic stem cells derived from *Tal1*-/- mice fail to give rise to osteoclasts[71]. A recent study indicates that Tal1 is involved in pre-OC fusion. Over-expression of Tal1 in RAW264.7 cells or primary bone marrow-derived macrophages inhibits osteoclast formation, but has no effect on TRAP+ pre-OC formation. Knockdown of Tal1 with RNA interference increases pre-OC fusion. Tal1 binds to the *DC-STAMP* promoter and inhibits DC-STAMP transcription. During osteoclast differentiation, the Tal1 occupancy of DC-STAMP promoter decreases while PU.1 occupancy of DC-STAMP promoter increases, cells fuse[72]. However, the exact role of Tal1 in osteoclast fusion in bone volume needs to be studied in mice with osteoclast specific depletion of Tal1.

CCN2/CTGF

CCN family 2/connective tissue growth factor (CCN2/CTGF) promotes endochondral ossification[73]. *Ccn2*-/- mice have an expanded hypertrophic zone[74], indicating that the resorption of the cartilage extracellular matrix by osteoclasts or chondroblasts is impaired. Expression of the Ccn2 gene is increased along RANKL-induced osteoclast differentiation. Recombinant CCN2 plus RANKL significantly enhances TRAP+ multinucleated cell formation compared with RANKL alone. CCN2 induces DC-STAMP expression and binds to DC-STAMP protein. Furthermore, RANKL-induced osteoclastogenesis is impaired in fetal liver cells from *Ccn2*-/- mice, which can be rescued by the addition of exogenous recombinant CCN2 or the forced expression of DC-STAMP by a retroviral vector. These results suggest that CCN2 expressed during osteoclastogenesis promotes osteoclast formation via induction of and interaction with DC-STAMP[75].

LDLR

Osteoporosis is often associated with atherosclerosis and vascular calcification due to hyperlipidemia. A recent study demonstrates that RANKL-induced osteoclast formation is decreased in bone marrow-derived macrophages from mice with depletion of low-density lipoprotein receptor (*LDLR*). Osteoclast precursors constitutively express LDLR. PreOCs from *LDLR*-/- mice form smaller osteoclasts than WT cells. RANKL-activated downstream Erk and Akt signals and expression of NFATc1, cathepsin K, and TRAP are normal in *LDLR*-/- pre-OCs, but the protein expression of DC-STAMP and ATP6V0d2 is reduced in the cell surface of *LDLR*-/- pre-OCs. *LDLR*-/- mice have high bone mass, which is accompanied by a decrease in bone resorption parameters, with no changes in bone formation parameters. These findings provide a novel mechanism for osteoclast differentiation and improve the understanding of the correlation between osteoclast fusion and lipids[76].

Vitamin E

Vitamin E is an antioxidant that inhibits lipid peroxidation by scavenging reactive oxygen species and is believed to be protective against arteriosclerotic changes and the aging process[77]. Vitamin E is a mixture of tocopherols and tocotrienols. In liver α-tocopherol transfer protein (α-TTP) mediates the transfer of α-tocopherol into lipoproteins[78] and α-tocopherol is the most predominant isoform of vitamin E in the body. Dr. Takeda's lab recently examined bone phenotypes of mice deficient in α-TTP (*Ttpa*-/- mice) and found that these mice develop high bone mass phenotypes. *Ttpa*-/- mice have normal osteoblasts and decreased osteoclasts *in vivo*. Interestingly, *in vitro* RANKL-induced osteoclast formation is normal when bone marrow-derived macrophages from *Ttpa*-/- mice are used. Serum from *Ttpa*-/- mice inhibits RANKL-induced WT osteoclast formation, suggesting that circulating α-tocopherol negatively regulates osteoclast formation. Consistent with this, additional α-tocopherol increases RANKL-induced osteoclast formation and the size of osteoclasts. α-tocopherol promotes DC-STAMP expression via mitogen-activated protein kinase and microphthalmia-associated transcription factor. It is directly recruited to the DC-STAMP promoter. These studies reveal a new role for vitamin E in bone homeostasis through regulation of osteoclast fusion[79].

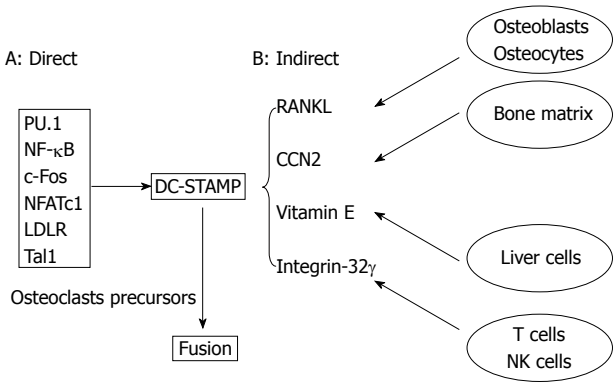

Figure 3 Osteoclast fusion is regulated by various factors mainly through dritic cell-specific transmembrane protein. A: In osteoclast precursors, factors including transcription factors essential for osteoclastogenesis control DC-STAMP expression, which regulates osteoclast fusion directly; B: Various cell types produce soluble factors that affect DC-STAMP expression in osteoclast precursors, which regulates osteoclast fusion indirectly. DC-STAMP: Dritic cell-specific transmembrane protein.

DC-STAMP HAS FUNCTIONS OTHER THAN FUSION

DC-STAMP is expressed on the cell surface. A recent study reveals two new functions of DC-STAMP apart from that of a master fusion factor using osteoclasts and precursors from human peripheral blood. One is that DC-STAMP can serve as an osteoclast precursor biomarker in patients with psoriatic arthritis. In this study, peripheral blood mono-nuclear cells are isolated from psoriatic arthritis patients and healthy controls, and stained with FITC-labeled anti-DC-STAMP antibody. DC-STAMP+ and DC-STAMP- cells are used in RANKL-induced osteoclast formation assays. The majority of osteoclasts are derived form DC-STAMP expressing monocytes. Interestingly, psoriatic arthritis patients have a higher percentage of DC-STAMP expressing monocyte cells than those of healthy controls. Another new discovery is that DC-STAMP functions as a signaling molecule within the osteoclasts. The cytoplamic tail of DC-STAMP contains an immunoreceptor tyrosine-based inhibitory motif, which is phosphorylated on its tyrosine residues and physically interacts with SHP-1 and CD16, an SH2-domain-containing tyrosine phosphatase and an ITAM-associated protein, respectively[11].

OC-STAMP

DC-STAMP was originally identified on the cell surface of dendritic cells[81] and in IL-4-treated macrophages and osteoclasts[9,41,81]. To isolate factors that are specifically expressed on multinucleated osteoclasts after they are formed from pre-OC fusion, the OC-STAMP (osteoclast stimulatory transmembrane protein) is cloned in RANKL-treated RAW264.7 cells[82]. *OC-STAMP*-/- mice have a fusion defect in both osteoclasts and foreign body giant cells, both of which are macrophage-lineage cells. Interestingly, DC-STAMP expression in *OC-STAMP*-/- osteoclasts and foreign body giant cells is normal. Similarly, OC-STAMP expression in *DC-STAMP*-/- osteoclasts and foreign body giant cells is normal, suggesting that OC-STAMP and DC-STAMP may regulate cell-cell fusion in osteoclasts and foreign body giant cells independently[83]. The regulation of OC-STAMP and its relationship with DC-STAMP is currently not known.

Pro-inflammatory cytokines

Osteoclast fusion is also promoted by pro-inflammatory cytokines. In RAW264.7 cells, RANKL, lipopolysaccharide (LPS), and TNFα all induce cell fusion, but M-CSF has no effect. The cell fusion induced by RANKL, TNFα, and LPS is specifically blocked by osteoprotegerin (OPG), anti-TNFα antibody and polymyxin B, respectively. LPS-induced cell fusion is partly inhibited by the anti-TNFα antibody, but not by OPG. Osteoclast fusion induced by these cytokines is accompanied by the activation of signaling pathways including PI3K, Src, ERK, JNK, and p38. Consistently, the specific chemical inhibitors LY294002 (PI3K), PP2 (Src), U0126 (ERK), and SP600125 (JNK) effectively reduce cell fusion. However, the expression levels of NFATc1 and DC-STAMP are unchanged. Thus, pre-inflammatory induced cell fusion may involve factors other than DC-STAMP[84].

CONCLUSION

Many advances have been made in recent years for understanding of osteoclast fusion and its regulation, which is involved in numerous molecules and pathways. Among them, DC-STAMP is the major fusion regulator. DC-STAMP expression is regulated through direct and indirect mechanisms (Figure 3). In the direct mechanism, RANKL/RANK downstream transcription factors that are essential for RANKL-mediated osteoclast formation are also important for osteoclast fusion, which include PU.1, NF-κB, c-Fos, and NFATc1. Factors that do not work through the RANKL/RANK pathway control osteoclast fusion include LDLR and Tal1. These factors function in the osteoclast precursors to up-regulate DC-STAMP transcription. In the indirect mechanism, cells in the non-osteoclast lineage regulate DC-STAMP expression by producing soluble factors such as RANKL. Osteoblasts and osteocytes are major cell types that produce RANKL under physiological condition, which is a strong inducer of DC-STAMP production. CCN2, vitamin E, and integrin-32 are newly identified factors that regulate osteoclast fusion via DC-STAMP despite of precise mechanisms by which regulate DC-STAMP expression are not clear. ATP6V0d2 is another important fusion regulator and is regulated by the RANKL-NFATc1 pathway under certain conditions.

However, there are still many open questions. For instance, all current fusion factors regulate the fusion process of both foreign body giant cell and osteoclast formation. It is not clear if osteoclast specific fusion factors exist. It has been proposed that in order to fuse, cells need to become fusion-component status. The

techniques of identifying these fusion-component cells and their regulation are lacking. M-SCF is another factor that is essential for osteoclastogenesis, but M-SCF itself cannot induce TRAP+ pre-OC formation. It will be interesting to determine if M-CSF is the factor for fusion-competency while RANKL induces fusion mediators such as DC-STAMP. Because osteoclasts a play central role in physiologic bone remodeling and pathologic bone destruction, manipulation of their fusion is a promising therapeutic strategy to treat bone disorders due to the abnormality of osteoclasts.

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REVIEW

Male osteoporosis: A review

Antonio Herrera, Antonio Lobo-Escolar, Jesús Mateo, Jorge Gil, Elena Ibarz, Luis Gracia

Antonio Herrera, Antonio Lobo-Escolar, Jesús Mateo, Jorge Gil, Department of Orthopedic and Trauma Surgery, Miguel Servet University Hospital, 50009 Zaragoza, Spain
Elena Ibarz, Luis Gracia, Department of Mechanical Engineering, University of Zaragoza, 50009 Zaragoza, Spain
Author contributions: All the authors contributed to the conception and design of the work, revised carefully the content and approved the final version of the manuscript.
Correspondence to: Antonio Herrera, MD, PhD, Professor, Department of Orthopedic and Trauma Surgery, Miguel Servet University Hospital, Avda Isabel la Católica, 1, 50009 Zaragoza, Spain. aherrera@salud.aragon.es
Telephone: +34-976-765664 Fax: +34-976-765652
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Abstract

Osteoporosis in men is a heterogeneous disease that has received little attention. However, one third of worldwide hip fractures occur in the male population. This problem is more prevalent in people over 70 years of age. The etiology can be idiopathic or secondary to hypogonadism, vitamin D deficiency and inadequate calcium intake, hormonal treatments for prostate cancer, use of toxic and every disease or drug use that alters bone metabolism. Risk factors such as a previous history of fragility fracture should be assessed for the diagnosis. However, risk factors in men are very heterogeneous. There are significant differences in the pharmacological treatment of osteoporosis between men and women fundamentally due to the level of evidence in published trials supporting each treatment. New treatments will offer new therapeutic prospects. The goal of this work is a revision of the present status knowledge about male osteoporosis.

Key words: Male osteoporosis; Skeleton involution; Etiology; Fracture risk; Osteoporosis; Non-pharmacological treatments; Pharmacological treatments

Peer reviewers: Toru Yamaguchi, MD, PhD, Associate Professor, Internal Medicine 1, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo-shi, Shimane 693-8501, Japan; Claudine JC Lamoth, Assistant Professor, Centre for Human Movement Science University Medical Centre Groningen Ant. Deusinglaan 1, 9713 AV Groningen, The Netherlands

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INTRODUCTION

Osteoporosis has generally been considered a female disease; this may explain why this pathology has focused less attention on men. While osteoporosis has been underestimated and poorly treated in female patients, the situation is even worse in male patients, despite the fact that up to one third of hip fractures are suffered by men[1]. In Spain, 26% of these osteoporotic hip fractures are diagnosed in male patients[2]. In addition, the first-year mortality has been reported to be higher among male patients (37.5 %)[3]. The risk of suffering a hip fracture among men is linked to age, although 50% of these fractures are experienced by patients under 80 years old[4]. The incidence of vertebral osteoporotic fractures has been published as being 50% lower in men[5,6], but many of these fractures are diagnosed in male patients with bone mineral density (BMD) levels above the osteoporotic standard criteria[7]. The high incidence and mortality rates of hip fractures, together with the incidence of vertebral fractures in men and their impact on quality of life[8,9], highlight that osteoporosis is also a male disease, and that it must be diagnosed and treated as it is in

female patients[9].

The association between osteoporosis and aging has been well documented. It seems clear that we face a serious problem due to a marked increase in life expectancy in the United States[10,11] and the Western world[12]. In addition, this increase is higher among men[13]. In Spain, mean life expectancy among men was 76.6 years in 2000[14], reaching 77 years in 2005[15]. These data emphasize the relevance of male osteoporosis. Some studies conducted in Sweden[13], which compared BMD in the femoral neck among men and women based on DXA scan determinations, proved that the higher incidence of male osteoporosis is found in patients aged 70 to 85 years. Up to 34.7% of individuals in that interval fulfilled osteoporosis criteria. Moreover, according to the same authors, about 47% of men older than 50 suffered osteopenia. If the group aged between 50 and 80 years is studied, the prevalence of osteoporosis remains around 21% in the female sex and 6.3% in the whole population.

DEVELOPMENT AND INVOLUTION OF THE SKELETON IN MEN

The appendicular skeleton grows twice that of the axial skeleton during the prepubertal period. In males, puberty starts later than in females, so the male appendicular skeleton is bigger in size and width. However, these differences in the prepubertal period are lesser in the axial skeleton[16].

The male skeleton shows a progressive increase of BMD during childhood. This increase becomes exponential during adolescence. Although BMD of trabecular bone is similar in both genders, this density is higher in men's cortical bone when compared with that of women, even when adjusted by body mass index[17]. The human male bone is also bigger in size. These biomechanical advantages provided by the thickness of cortical bone, make the male skeleton more resistant, and thus, less prone to suffer fragility fractures. Androgenic male hormones might explain this advantage[18]. The bone size enlarges more in males than in females during normal aging. This is due to a greater periosteal apposition in males that increases the previous differences which occurred during adolescence. Volumetric BMD in vertebrae is similar in both genders of the younger population, and the ulterior losses of trabecular bone are also similar. Nevertheless, the male skeleton preserves a higher BMD in the spine during aging due to the greater periosteal apposition. On the contrary, an increased endosteal resorption in men compensates for previous differences in other locations like the hip, where the volumetric BMD is similar in both genders. Cortical porosity is also lower, and the trabecular architecture and connectivity are much more preserved in men than in women[19]. In a recent study conducted by Patsch *et al*[20] analyzing iliac crest biopsies of men with idiopathic osteoporosis concludes that there are an osteoblast dysfunction and a different microstructural pathology than age-related bone loss.

In male idiopathic osteoporosis there is a microstructural alteration in relation to age. In women, bone stock decreases markedly during the sixth decade of life, because of an estrogenic hormone deprivation[13]. In men this decrease is found in patients beyond the age of 70 years[21], but the trabecular bone is preserved more years[22] than in females. There is a relationship between trabecular bone loss in men and the insulin-like growing factor. On the contrary, cortical bone loss is due to a decrease in testosterone and estrogenic hormones[23,24], that leads to an increased bone turn-over process. These differences between sexes in the bone stock involution make male individuals more resistant to fragility fractures, therefore generally suffering these fractures later in life than women[25].

ETIOLOGY AND PATHOGENESIS OF MALE OSTEOPOROSIS

Osteoporosis in men has been categorized, classically, into three types: (1) Involutional or senile osteoporosis; (2) Idiopathic in middle aged males; and (3) Secondary osteoporosis[26]. Up to 50%-65% of the diagnoses in male patients are secondary to metabolic diseases, toxic substances or iatrogenic side effects[24,27].

In men, testosterone plays a major role in bone metabolism, similar to the role of estrogens in females. Several studies have reported the importance of the estrogen receptor (ER)-alfa[28] and aromatase inhibitors[29] on the growth and development of pathological conditions of bone. Other authors[30] have demonstrated the importance of the androgen receptor (AR) whose function is essential for male-type bone formation and remodeling, because promotes osteoblastic activity. Furthermore they showed that deficiency of AR has a essential effect on the expression of the receptor activator of NF-κB ligand (RANKL) gene, which encoding an osteoclastogenesis inducer.

Up to 70% of bone turnover and resorption appear to be modulated by estrogens and 30% by testosterone[31]. Moreover both hormones are substantial in bone formation mechanisms[26].

Although hormonal changes in men are not so marked as in females, they are also important in the pathogenesis of osteoporosis. Sex-hormone binding globulin (SHBG) levels increase with aging in men[32]. On the contrary, serum bio-available (or non-SHBG bound) estradiol and testosterone levels decrease with age. BMD is clearly related with steroid levels, especially with bio-available estradiol levels[26].

The trabecular and endosteal resorption in osteoporosis patients is not compensated by bone formation. The periosteal apposition, capital in the male bone metabolism, is directly related with bio-available levels of testosterone. A deficit in testosterone levels leads to bone loss and increases the risk of fracture[23,26].

The association between aging and serum SHBG levels remains unclear. Nevertheless, an inverse relation of insulin-like growth factor I (IGF-I) levels and SHBG levels has been widely proven. IGF-I directly inhibits SHBG production by liver cells[33].

Periosteal apposition, that compensates endosteal resorption, especially in men, is modulated not only by testosterone, but also by growth hormone (GH) and IGF-I levels[26].

An inadequate peak bone mass is involved in the pathogenesis of osteoporosis in males. Inherited factors such as gene regulation of steroids production, GH or IGF-I, are directly related with the peak bone mass. The lower the peak bone mass, the greater the possibility of developing an age-related osteoporosis.

Idiopathic osteoporosis

Idiopathic osteoporosis can be present in any age group, but it is more prevalent in younger individuals. It is known that low bone mass may be inherited. Genetic factors linked with gene polymorphisms are the supposed etiology for this type of osteoporosis. Polymorphisms have recently been reported in collagen specific proteins (COLIA 1 and COLIA 2), in vitamin D receptors; and in lipoprotein receptor-related protein[34]. All of these factors might be involved in the development of a low bone mass of uncertain origin[35]. Up to 40% of the cases affecting male patients are diagnosed as primary or idiopathic osteoporosis[24].

Secondary osteoporosis

Frequent causes of secondary osteoporosis are:

Hypogonadism: This is one of the most frequent etiologies of secondary osteoporosis in men. Studies carried out in nursing homes showed that, among geriatric individuals who had suffered a hip fracture, up to 66% had hormonal levels lower than the standard[36].

Other authors[37] have documented a marked increase in the risk of suffering fragility fractures among patients with low levels of testosterone and estradiol. Moreover, these low levels of sexual hormones lead to muscle atrophy and total muscular mass decrease. Therefore, a hormonal deprivation on muscle function damages the defensive mechanism against falls, thus increasing the incidence of fractures in these individuals.

Nowadays, it is widely accepted that bone metabolism disorders in patients with low levels of estradiol can increase the risk of fractures[38,39]. This might be caused by a deficit of testosterone transformation into estradiol due to an aromatase enzyme dysfunction. There are several reports along these lines documenting severe male osteoporosis induced by mutations of the estrogen-receptor of the aromatase enzyme[40,41].

Low serum levels of vitamin D: Vitamin D plays a major role on bone health in all age groups. In younger individuals it contributes to achieving a good peak bone mass whereas in adults, lower levels of vitamin D lead to substantial losses in bone mass and subsequently to osteoporosis[42]. Two sources of vitamin D are found in humans: (1) Epidermal synthesis of Vitamin D3 (colecalciferol) under sunlight influence (UV-B radiation); or (2) Absorption in the gastrointestinal tract, from the diet or nutritional supplements [in some countries certain food is supplemented with Vitamin D2 (ergocalciferol)]. Vitamin D is then metabolized in the liver into 25-hydroxivitamin D (25-(OH) D)[42].

Vitamin D stimulates intestinal calcium absorption. Few food groups contain high concentrations of vitamin D: fatty fish, fish-liver oils (cod liver oil), and liver. Not all of them are available in all countries or they are not consumed regularly by the adult population. Moreover, certain foods such as milk, margarine, butter, orange juice and cereals are not regularly supplemented with Vitamin D in many countries, such as Spain. Therefore, daily requirements of Vitamin D are frequently insufficient in some regions[43,44]. Similarly, the substantial epidermal synthesis of Vitamin D in younger populations is reduced in the elderly[44]. Curiously, in Spain, where the amount of sunlight radiation is high, the older population is usually poorly exposed to this radiation, and the synthesis of Vitamin D is even lower[45].

The European SENECA Study, carried out in 12 European countries, showed serum levels of 25 hydroxivitamin D lower than 30 ng/mL in 36% of the elderly population[46]. In our country, a recent study also showed low levels of 25-hydroxyvitamin-D serum in elderly people, with a 95% sensibility to detect secondary hyperparathyroidism[47].

The presence of low levels of vitamin D in men over 65 years of age is very common. It has been considered that about 15% of male osteoporosis cases are caused by this deficiency[48]. Several studies[49-51] have found a high prevalence of 25-hydroxyvitamin-D serum levels below 25 ng/mL in the population over 65 years of age (standard levels are above 35 ng/mL).

This has a major impact on bone metabolism[52]. Firstly, a decrease in the intestinal absorption of calcium decreases the serum ionized calcium concentration. This gives way to an increased production of parathyroid hormone (PTH) which stimulates bone osteoclasts, releasing calcium into the bloodstream. PTH also increases renal resorption of calcium and renal excretion of phosphorus.

All these metabolic disorders, triggered by the vitamin D deficiency, lead to a significant increase of bone resorption and, consequently, to a decrease of BMD.

Our experience with 267 patients sustaining a hip fracture, with a mean age of 80.3 years, proved that 67% of them had vitamin D serum levels below 25 ng/mL at the time of admission. These results assert the high frequency of this deficiency in men with osteoporosis.

Poor calcium intake: The correct daily calcium intake is essential for bone metabolism[44]. An intake below the

recommended 1.200 mgrs per day is quite usual in the population over 65 years of age. This is directly linked with a low mineral bone density. If, as usual, it is also associated with low vitamin D serum levels, the negative consequences for the mineral metabolism and the health of the individuals are even greater[39].

Influence of tobacco: Among the toxic substances involved in the etiology of osteoporosis, tobacco plays a major role[53]. Smokers have been found to have lower BMD and consequently a significantly higher risk of fragility fracture. Smoking is endemic within the Spanish population over 65. It should also be noted, that this harmful effect has usually been maintained for many years, in most cases since adolescence.

Alcohol: Alcohol is another toxic substance affecting BMD[54,55]. It is also quite well rooted in the Spanish population. A significant percentage of people in this country are regular drinkers, particularly men. A recent population study of a large, representative sample of the population aged 55 or more in Zaragoza (Spain) has documented that, among men, the proportion of heavy drinkers (WHO criteria) is 16.7%, in comparison to only 0.7% among women[56]. Heavy drinking may lead to significant adverse effects, not only in the mineral metabolism, but also in the whole metabolic system. It might also be hypothesized that different rates of osteoporotic fractures in men and women are influenced by differences in alcohol consumption.

Coffee consumption: Contrary to what was classically thought, we now know that there is not enough evidence to link heavy coffee consumption with osteoporosis in men[57].

Hormonal treatments: Prostate cancer, a prevalent male disease, can be treated in some cases with androgenic suppression, which is a major risk factor for osteoporosis. In a recent study carried out by Adler[58], 33% of patients with prostate cancer who were treated with androgenic deprivation therapy, showed low BMD, fulfilling osteoporosis criteria in DXA scanning of their hip and spine.

Adler applied the new fracture prediction algorithm tool (FRAX) with corrected femoral neck T-score, reporting that 17% of these patients required treatment. Without any correction this percentage increased to 54% of the patients. In our experience with 87 patients undergoing hormonal treatment for prostate cancer for more than one year, and whose mean age was 78.3 years, 27.58% of them showed a BMD lower than 2.5 standard deviations in the DXA scanning.

Other causes: Other causes involved in the etiology of secondary osteoporosis in men are: (1) Anticonvulsant therapy; (2) Prolonged steroid therapies; (3) Patients with rheumatoid arthritis or ankylosing spondylitis; (4) Primary hyperparathyroidism; (5) Hepatic or renal disease; (6) Malabsorption syndromes; (7) Transplanted patients or those treated with immunomodulators; (8) Thyrotoxicosis; (9) Diabetes mellitus; (10) Hypercalciuria; and (11) Patients with human immunodeficiency virus (HIV). Overall we can say that there is no specific pathology affecting male bone metabolism, but various conditions or medical treatments can cause secondary osteoporosis. And these conditions may affect similarly individuals of both genders.

DIAGNOSIS

The key question is how to establish the diagnosis in men with no apparent causes of secondary osteoporosis, nor previous history of fragility fractures. An accurate assessment of risk factors should be carried out in patients over 50 years old. Special attention should be paid to patients with a fragility fracture before the age of 50 years, as well as to those patients suffering diseases or treated with drugs that can cause a loss of BMD[11]. Several clinical guidelines recommend routine DXA scanning after the age of 70 years in the general population[11]. In a recent study conducted by Schousboe[59], the cost-effectiveness of a DXA study was assessed. This author studied men aged 65 or older treated with oral bisphosphonates for 5 years and with a history of fragility fractures, in addition to the male population aged from 80 to 85 with or without a history of previous fractures. The author concluded, after studying quite a large sample, that bone densitometry may be cost-effective for patients aged 70 years or older, with the cost of oral treatment using bisphosphonates below 500$ per year.

It seems evident that an accurate medical history should be completed prior to the densitometric studies in older men. The main risk factor is the presence of a previous fragility fracture, especially if it happened before 50 years of age. We can also say that male population over 70 years old is at risk for osteoporosis. This risk would be even higher in cases with disorders affecting bone metabolism.

In patients with a BMD under 2.5 or more standard deviations, measured by DXA scanning, standardized laboratory tests should be performed[11,50].

These laboratory tests should include: calcium and creatinine serum levels, biochemical markers of bone remodeling e.g., bone resorption markers: serum C-Telopeptide (CTx) and urinary N-Telopeptide (uNTx); and bone formation markers: serum bone-specific alkaline phosphatase (BSAP) and osteocalcin.

High levels of BSAP in primary hyperparathyroidism and low levels of osteocalcin in endogenous hypercorticism are the most relevant data reported in endocrine diseases associated with osteoporosis, high level of bone turnover markers, may be associated with prevalent vertebral fractures[60]. Depending on the type of patient, se-

rum proteins, protein electrophoresis, and Bence-Jones protein should be determined, as well as serum levels of testosterone and vitamin D in individualized cases. Finally, in specific cases, anti-HIV antibodies should be investigated.

RISK OF FRACTURE

A quantification of the fracture risk is essential to initiate the treatment of osteoporosis. Several authors have studied the BMD decrease and its predictive value for the estimation of fracture risk[61-64]. There is no agreement in literature about the hypothetic linear association of BMD declining with fragility fracture risk. Similarly, there is no consensus in the predictive value of BMD depending on the sex of the patient. The EVOS study of vertebral fractures, suggested that the risk of fracture is similar in men and women[61]. De Laet *et al*[65], in the Rotterdam study in 1998, reported a significant predictive value of BMD for fracture risk; and a similar relationship between hip fracture and femoral neck BMD in men and women. Later studies, using the same database, found a higher incidence of vertebral fractures in women[66]. Although BMD is an important predictor for fracture risk[67], a tool with which to obtain an accurate determination of fracture risk in men is still necessary[68]. The importance of age as a fracture predictor was reported by Kanis *et al*[13], in addition to the relevance of previous fragility fractures[69]. In a recent meta-analysis work[70] to analyze the risk factors in men that provide evidence for association with low bone mass and fractures, showed statistical significance the following: age, low body mass index, history of prior fractures, history of falls, current smoking, excessive alcohol use, chronic corticosteroid therapy, stroke and diabetes. None of these associations were of large magnitude from the statistical point of view. This heterogeneity of factors difficulties the decision to counsel a screening in men to determine bone mass by DXA scan. However, the American Society of Endocrinology in a recent publication[71] recommended practice of measuring bone mass to all men over age 70 and men aged 50-69 who have risk factors.

A tool integrating predictive clinical factors with or without BMD measurements has been developed by the WHO in collaboration with the group of Sheffield Metabolic Bone Diseases[72]. The FRAX tool has been reported to be a useful predictor at 10 years follow-up, for fractures in the hip and in other locations[73]. Nevertheless, it seems that this tool needs to be validated in other countries[74-76].

Optionally, BMD can be included for fracture risk calculation since bone strength is closely related to BMD. In this regard, both micro and macro-mechanical models have been suggested, with different characteristics and methodologies to correlate bone strength and BMD. These models can be used for prediction of bone strength at different ages, or to prediction of fracture risk[77-80].

Concerning finite element (FE) simulation, as alternative tool to predict fracture risk, several works can be found in the literature[77-87]. The development of new techniques for measuring BMD has focused much of the recent research in the clinical setting, but the mechanical aspects have not been adequately studied[88-91]. Nonetheless, all models assume that BMD is the basic measurement, and it should therefore be used as a benchmark in predicting fracture risk.

From the mechanical point of view, the exposition of the bone to cyclic loads decreasing in strength over the time produces a progressive damage which can lead to a final fracture. It seems apparent that Damage Mechanics and Fracture Mechanics criteria should be incorporated in any model intending to obtain reliable results. Recent works are focused in that direction[92]. However, till now no model considering the complete correlation between clinical and mechanical magnitudes related to fracture behaviour has been developed.

TREATMENT OF THE OSTEOPOROSIS IN MEN

The indication for treatment of osteoporosis in men with a previous fragility fracture is clear. The key question is whether a DXA screening should be carried out on the rest of the male population, as has been previously recommended by several clinical practice guidelines[59,93,94]. The use of the FRAX tool could help us make a therapeutic decision for individualized cases. The National Osteoporosis Foundation (NOF) recommends drug therapy in patients over 50 years of age with vertebral fracture; in those with BMD below 2.5 SD; and depending on the risk of fracture estimations at 10 years, in those with BMD figures from -2.5 to -1 SD.

Non-pharmacological treatment

As a general rule, a healthy lifestyle, a proper nutrition and the suppression of toxic substances should be recommended. An adequate daily intake of calcium and Vitamin D should also be encouraged. Low blood calcium levels are often present in men older than 70. The intestinal absorption of calcium is usually diminished in the elderly population[94]. Oral treatments for chronic comorbidities that interfere with calcium absorption[40] and the age related decline in glomerular filtration contribute to this situation. In individuals from 50 to 70 years of age with a low calcium intake, oral supplementations of 1000 mg/d of calcium carbonate are usually recommended. In those older than 70, the estimated daily requirements are 1200 mg.

An adequate vitamin D supplementation is also required. We recommend 600 U.I/d in individuals from 50 to 70 years of age and 800 U.I/d in patients older than 70 years[42,95].

Bone is a living tissue that responds to repetitive loadings with increased biomechanical resistance. Weight

Table 1 Published articles on the pharmacological treatment of male osteoporosis

Ref.	No. cases	Follow-up	Type of trial	BMD increase	Outcome parameter	BTMs
Bisphosphonates treatment						
Orwoll *et al*[108]	241	2 yr	Double-blind	+	Vertebral fracture	NS
Ringe *et al*[110]	316	1 yr	Open label, randomized	+	Vertebral fracture	NS
Ringe *et al*[109]	90	2 yr	Comparative	+	NS	NS
Boonen *et al*[111]	284	2 yr	Double-blind	+	Vertebral fracture	+
Orwoll *et al*[112]	132	1 yr	Placebo-controlled, randomized	+	NS	+
Lyles *et al*[114]	2127	1.9 yr	Double-blind	+	Vertebral fracture	NS
Adachi *et al*[116]	2127	3 yr	Double-blind	NS	HRQoL improve	NS
Sambrook *et al*[115]	265	1 yr	Double-blind	+	NS	NS
Genant *et al*[113]	89	1 yr	Placebo-controlled	+	NS	NS
Anabolic treatment						
Orwoll *et al*[121]	437	11 mo	Randomized	+	NS	NS
Kaufman *et al*[122]	325	42 mo	Placebo-controlled	+	Vertebral fracture	NS
Leder *et al*[124]	17	42 mo	Prospective	+	NS	+
Finkelstein *et al*[123]	42	30 mo	Randomized controlled	+	NS	+
Testosterone treatment						
Finkelstein *et al*[125]	21	31 mo	Prospective	+	NS	NS
Katznelson *et al*[126]	36	18 mo	Controlled	+	NS	+
Amory *et al*[127]	70	36 mo	Randomized	+	NS	NS
Benito *et al*[128]	10	24 mo	Prospective	+	NS	NS
Monoclonal antibody therapy						
Smith *et al*[131]	1468	36 mo	Double-blind	+	NS	NS
Smith *et al*[133]	1468	36 mo	Double-blind	NS	NS	+
Toremifene						
Smith *et al*[134]	847	2 yr	Placebo-controlled	NS	Vertebral fracture	NS

Bone mineral density (BMD) increase mean: Sign +: Increase of BMD. Outcome parameter meaning: (1) Vertebral fracture (decreases); and (2) Health-related quality of life improve the health-related quality of life. BTMs: Improvement of biochemical markers; HRQoL: Health-related quality of life. NS: Not studied.

bearing physical activity has been shown to optimize bone mass[96]. Recommended exercises are: weight training, jogging, walking, climbing stairs, gardening, dancing and aerobic sports in general[42]. Strength training machines for resistance exercises can be recommended as well. Significant benefits have been proven with the practice of these activities for just half an hour every day: (1) Increased muscular strength; (2) Preserved or increased bone mass; (3) Improved coordination and (4) Improved general health, self-care and activities of daily living[42,96].

Daily practice of aerobic activity, such as walking and coordination exercises (tai-chi) should be encouraged in the elderly population[42]. The practice of regular physical exercise has shown not only to be effective in preventing BMD declining, but also in preventing falls[97-100]. Falls are a major risk factor in patients with osteoporosis. In relation to this, fall prevention programs have also proved to be very effective[101-106].

Pharmacological treatment

There are significant differences in the pharmacological treatment of osteoporosis between men and women. The list of pharmacological agents approved by United States FDA for the treatment of female osteoporosis is larger than the one approved for male osteoporosis. The main differences are due to the level of evidence in published trials supporting each treatment. Drugs approved for female osteoporosis have been tested in large, multinational, randomized control and placebo-controlled trials that included thousands of patients. These drugs have shown efficacy in the prevention of vertebral fractures, and less consistently in the reduction of the incidence of non-vertebral fractures. In contrast, the available articles dealing with the pharmacological treatment of male osteoporosis are mainly based on the increase of BMD. Trials that, either provide evidence on vertebral fracture prevention or the decreased number of new vertebral fractures after suffering a prior fracture, are scarce. Furthermore, the size of samples studied and the follow up periods tested are significantly more reduced in males than in females[107]. The methodology used is shown in different studies, from which the number of patients treated and the effects demonstrated by the drugs used are detailed in Table 1.

The drugs most widely used are antiresorptive agents, anabolic agents, hormonal therapy and more recently, for secondary osteoporosis, monoclonal antibody therapy.

Treatment with bisphosphonates: The most extended treatment for osteoporosis is oral therapy with bisphosphonates. However there is little evidence in literature of their effectiveness in male patients.

Several studies have demonstrated that alendronate improves BMD after 2 years of treatment in both spine and femoral neck. There is also evidence of a significant decrease in the incidence of vertebral fractures, although this decrease has not been demonstrated for fractures in

other locations[108]. Another study showed that a combination of weekly alendronate with alfacalcidol, compared to a combination of alendronate, vitamin D and calcium, was more effective in the increase of BMD in the lumbar spine and in the hip at the two year follow-up[109].

Other studies assessing oral treatment with risedronate have also confirmed an increase in BMD in both spine and hip, and a significant reduction in the incidence of vertebral fractures[110]. Once-weekly risendronate for 24 mo showed a significant increase of BMD in lumbar spine and hip, but showed no difference in the number of new fractures when compared with the placebo group[111].

After a monthly dosis of Ibandronate over a 2-year period, it has been demonstrated that it increases BMD in lumbar spine and hip, to decrease the bone resorption marker serum C-terminal telopeptide of type 1 collagen (sCTX) and to increase the bone formation marker BSAP, in people with low BMD[112]. One year of ibandronate treatment was associated with a significant improvement in some parameters of hip geometry, suggesting that ibandronate may improve strength of the hip[113].

However, further investigation is needed to confirm the effectiveness of oral bisphosphonates in decreasing the incidence of hip and other non-vertebral fractures.

Intravenous bisphosphonates (zoledronic acid) have been reported to decrease the incidence of fractures, but their use has not shown a significant reduction in the rate of new hip fractures in those patients who suffered a previous fracture[114]. A study published in 2012 shows that the zoledronic acid clearly increases the BMD[115].

In a recent study about men and women who had suffered a hip fracture, the effectiveness of zoledronic acid was evaluated by means of the health-related quality of life, demonstrating a significant improvement of their functional scores[116].

Although there are not as many studies on the use of bisphosphonates in men as there are in women, some authors claim that their effectiveness is similar in both genders[117].

Finally, in prostate cancer patients treated with androgenic deprivation and presenting a strong BMD decrease, bisphosphonates have been proved as an effective therapy for bone loss[118,119].

Treatment with anabolic drugs: Anabolic treatment with parathyroid hormone derivatives has been approved by the FDA for the treatment of men at high risk of fragility fracture; and for patients treated with steroids suffering a significant reduction in their BMD.

According to Hodsman, the main indications for treatment with parathyroid hormone in men are severe osteoporosis or an unsatisfactory response to antiresorptive therapy[120].

Parathyroid hormone has demonstrated to be effective in the treatment of male osteoporosis. A significant increase in the BMD of patients treated with subcutaneous doses of 20 micrograms of teriparatide per day has been documented. This BMD increase was demonstrated in both femoral neck and spine, as well as in patients with or without hypogonadotropic hypogonadism[121]. Evidence has shown that teriparatide may decrease the incidence of vertebral fractures, but the reduction of fractures in other anatomical locations has not been proved[122]. Another recent investigation has demonstrated the efficacy of teriparatide in increasing BMD in eugonadal men and in a group of men and women with BMD below the standard figures corresponding to their age[123,124].

The controversy of treatment with parathyroid hormone derivatives remains in their possible side effects. These side effects have not been extensively studied so far. Therefore, these anabolic treatments should be kept in use for up to a maximum of two years. A good option, after the anabolic interruption, would be to continue the therapy with bisphosphonates.

Treatment with testosterone: Testosterone treatments for male osteoporosis are not usually recommended in the clinical practice guidelines. This hormonal therapy may produce severe secondary effects which include: polycythemia, sleep apnea, benign prostate hypertrophy, and even prostate cancer. Due to these side effects it has not been used as a standard treatment for osteoporosis.

However, it seems apparent that testosterone, as was demonstrated in 1989[125], could markedly increase the quality and quantity of bone in young patients with hypogonadism. In 1996 the same group demonstrated the positive effects of testosterone in order to increase the lean muscle mass and trabecular bone density[126].

Subsequent investigations[127,128] have found positive effects on BMD and bone quality in osteoporotic elderly patients treated with testosterone. Positive effects have been detected not only on bone but on muscle mass[129]. However, it still does not represent a treatment of choice in male osteoporosis. The main problem of treatment with testosterone is little published evidence and safety problems with testosterone replacement therapy[130].

Other treatments: Many recent studies carried out on prostate cancer patients undergoing hormonal treatment, showed good results using a monoclonal antibody (Denosumab)[131-133]. This antibody, which acts on the RANK-ligand, demonstrated an increase in BMD and a significant decrease in the incidence of vertebral fractures for these patients.

A recent study with a drug in phase Ⅲ (Toremifene) has proved effective to prevent occurrence of new vertebral fractures in patients treated with androgenic deprivation therapy[134].

In a near future we might use other drugs, currently in development, which could be effective in the treatment of male osteoporosis.

CONCLUSION

The adequate diagnosis and management of male osteoporosis remain controversial. The origin of idiopathic male osteoporosis should be further investigated. Mechanisms of trabecular bone loss in men are not fully defined. We don´t know if the same range of standard deviations applied to women in DXA studies to assess osteoporosis, are applicable to men, especially considering that many fractures occur in men with less than 2.5 SD in densitometric studies. There are no standard criteria for the implementation of diagnostic screening tests in men. There are obvious differences in bone structure and properties between men and women, but further investigations are needed to ascertain the fracture risk assessment in men, prior to its clinical application. A research area in the future could be the use of simulation models using the Finite Element Method, these researches should be focused to establish an appropriate and reliable correlation between clinical and mechanical magnitudes, in order to develop more robust models that can be applied to evaluate the bone strength, and therefore the fracture risk, at different ages and in any conditions of the patient (without or under treatment).

Bone loss and fracture risk in men are clearly associated with decreased levels of bio available estrogens. There is little evidence on the effectiveness of bisphosphonates or treatments using anabolic steroids in humans, indicating the need for further studies. Testosterone is indicated just for symptomatic hypogonadism.

Recent research in to new treatment options, like the use of RANK-ligand monoclonal antibody (Denosumab) and other drugs still in phase Ⅲ (Toremifene) opens new perspectives, although more evidence is still needed.

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BRIEF ARTICLE

Do osteoporosis-related vertebral fractures precede hip fractures?

Mir Sadat-Ali, Abid Hussain Gullenpet, Md Quamar Azam, Ammar K Al-Omran

Mir Sadat-Ali, Md Quamar Azam, Ammar K Al-Omran, Department of Orthopaedic Surgery, College of Medicine, University of Dammam and King Fahd Hospital of the University, Al Khobar 31952, Saudi Arabia
Abid Hussain Gullenpet, Department of Radiology, College of Medicine, University of Dammam and King Fahd Hospital of the University, Al Khobar 31952, Saudi Arabia
Author contributions: All the authors contributed to this article.
Correspondence to: Mir Sadat-Ali, MBBS, MS, FRCS, Professor, Department of Orthopaedic Surgery, College of Medicine, PO box 40071, King Fahd University Hospital, AlKhobar 31952, Saudi Arabia. drsadat@hotmail.com
Telephone: +966-50-5848281 Fax: +966-3-8820887
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Abstract

AIM: To evaluate the relationship between a vertebral fracture and a hip fracture in Saudi Arabians with osteoporosis.

METHODS: In this retrospective study, 154 Saudi Arabian patients with osteoporosis-related hip fractures were analyzed for the presence of a vertebral fracture. Radiographs were retrieved from the IPAC (Image Picture Archiving and Computing) System, an imaging retrieval system, and were reviewed independently by two of the authors, Abid Hussain Gullenpet, and Mir Sadat-Ali, and later reviewed jointly. Patients admitted with proximal hip fracture who were $\geqslant$ 50 years and had undergone Thoraco-lumber imaging and a dual energy X-ray absorptiometry (DEXA) scan were included in the study. Patients with a history of significant trauma to the spine and those with a malignancy or connective tissue disorder were excluded from the analysis.

RESULTS: Out of 154 patients with hip fractures, 78 had a fracture of the femoral neck while 76 had an intertrochanteric hip fracture. Of the 111 patients who were finally included in the study, after applying inclusion and exclusion criteria, 76 patients with an average age of 67.28 ± 12 years had no fractures of the spine. Thirty-five patients with an average age of 76.9 ± 14.5 years (31.53%) had a total of 49 vertebral fractures. Patients with vertebral fractures were significantly older than those without fractures $P < 0.001$. Overall, 24.7% of these patients had an asymptomatic vertebral fracture. Further analysis showed that 11 males (18.96%) and 24 females (45.28%) had suffered a previous asymptomatic vertebral fracture. Interestingly, all women who participated in this study and who presented with a femoral neck fracture had experienced a prior asymptomatic vertebral fracture.

CONCLUSION: We recommend that all elderly patients who go to the radiology department for a chest X-ray also have a DEXA scan and a lateral thoracic spine radiograph.

Key words: Fragility fracture; Osteoporosis; Vertebral fractures; Hip fractures; Saudi Arabia

Peer reviewers: Cheung Wing-Hoi, Research Associate Professor, Department of Orthopaedics and Traumatology, Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China; Stefan Grote, MD, Department of Orthopaedic and Trauma Surgery, University of Munich, Nußbaumstr. 20, 80336 Munich, Germany

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INTRODUCTION

Osteoporosis is reported to be common among Saudi Arabians, and researchers report a prevalence of 30%-35%[1-5].

Fragility fracture is a major health care concern because of its relationship to morbidity and mortality. The incidence of fragility fractures in Saudi Arabia jumped from 2.9/1000 in 1999[6] to 6/1000 in 2007 at an annual cost of SR 4.27 billion[7]. Only 30% of the patients who were still alive remained ambulatory[8] and this put an extreme burden on the patient's family and caregivers[9-11]. Prevention of fragility fractures, particularly those of the femur, is an important part of the management of osteoporosis. In a 2012 paper, Chan *et al*[12] suggested that vertebral fractures are probably the most common fragility fractures and that they are often followed by a second fracture. In 2004, Johnell *et al*[13] studied the risk of a second fracture, particularly of the femur, after a fracture of the spine or the proximal part of the humerus and concluded that the risk of a second fracture is highest immediately after the first one. Studies also showed that some who experiences a vertebral fracture have a five-fold increased risk of experiencing a subsequent hip fracture[14-17].

The objective of this study was to evaluate the relationship between an asymptomatic vertebral fracture and a second hip fracture among patients living on the east coast of Saudi Arabia.

MATERIALS AND METHODS

One hundred and fifty-four patients with osteoporosis-related hip fractures and no history of a previous fracture were analyzed for the presence of a vertebral fracture. Demographic data about the patients, including their age, co-morbidities, and ASA score, was retrieved from their medical records and the QuadruMed database. All radiographic images were retrieved from the IPAC imaging system. Patients admitted with proximal hip fracture who were ≥ 50 years and had undergone thoraco-lumbar imaging and a dual energy X-ray absorptiometry (DEXA) scan were included in the study. Patients with a history of significant trauma to the spine, a malignancy, or a connective tissue disorder were excluded from the analysis. After applying inclusion and exclusion criteria, 111 patients were finally included in the study. The fracture morphology was entered in a database, including the side, site, type, and operative implants used. Patients were divided into two groups: a non-elderly group (50-64 years old) and an elderly group ≥ 65 years old, following the accepted definition of elderly patients[15]. Radiographs were reviewed independently by two authors, Abid Hussain Gullenpet (AHG), and Mir Sadat-Ali (MSA), and later they reviewed them jointly. The data was analyzed using SPSS software, version 14. Data were expressed as mean ± SD. Statistically significant differences between the two groups were determined with the Student's *t*-test using a ratio of $P < 0.05$, which is considered to be significant, and precision was ascertained at a CI of 95%.

RESULTS

Of the 154 patients with proximal hip fracture, 78 of them had a fracture of the neck and 76 had an intertrochanteric fracture. Of the 111 patients included in the study, 58 were male and 53 female with an average age of 70.6 ± 13.7 years (Figure 1). The demographic data and associated diseases of the patients are provided in Table 1. Sixty-five patients (58.55%) were classified as elderly patients (≥ 65 years). Seventy-six patients (68.47%), 47 males and 29 females, had no fractures of the spine and an average age of 67.28 ± 12 years. Thirty-five patients (31.53%), 11 males and 24 females, had a total of 49 vertebral fractures and an average age of 76.9 ± 14.5 years. [The odds ratio was calculated as 0.4605, 95%CI (0.2852 to 0.74) and $P = 0.0015$]. Patients with vertebral fractures were significantly older than those without fractures $P < 0.001$. The majority of the fractures (55%) occurred between thoracic 11 and lumbar 2nd vertebra (Figure 2). Women sustained a fractured neck of the femur more often than men $P < 0.001$. All women who had experienced such an injury had a vertebral fracture.

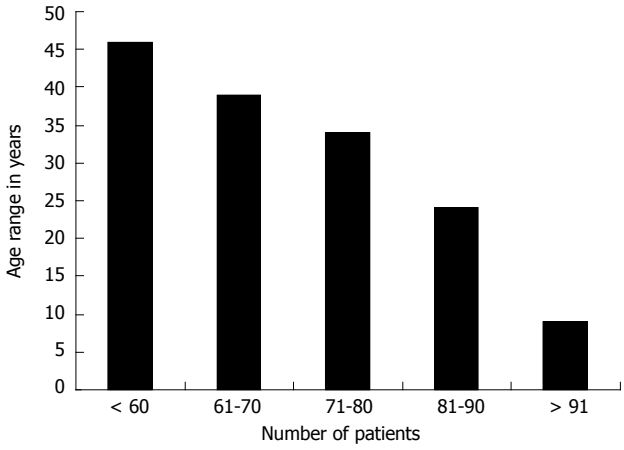

Figure 1 Shows the age range of patients with osteoporosis-related hip fractures.

Overall, 24.7% of our patients had an asymptomatic vertebral fracture. Further analysis showed that 11 males (18.96%) and 24 females (45.28%) had a previous asymptomatic vertebral fracture. Interestingly, in our sample all women who presented with a fractured neck of the femur had a prior asymptomatic vertebral fracture.

DISCUSSION

In this study we found that 24.7% of patients who presented with a hip fracture also had an asymptomatic vertebral fracture, and the remaining 75.3% patients had never experienced spine fractures. This indicates that proximal femoral fracture may be the first presenting complaint that indicates underlying osteoporosis. It also underlines the fact that asymptomatic spine fracture remains undiagnosed in almost 25% of elderly patients until they experience a debilitating hip fracture. Further analysis showed that 45.28% of elderly females and 18.96% of the males had experienced an asymptomatic vertebral fracture.

Table 1 Demographic details of patients (mean ± SD)

	Hip fracture with vertebral fracture	Hip fracture without vertebral fracture	*P* value
Number of patients (n = 111)	35	76	
Mean age	76.9 ± 14.5	67.28 ± 12.2	0.001
BMD at hip (g/cm^2) non fractured side	0.511 ± 2.5	0.692 ± 3.1	0.7
BMD at spine (g/cm^2) non fractured vertebra	0.496 ± 4.3	0.728 ± 3.6	0.6
HTN/CAD (hypertension/ coronary artery disease)	14	45	0.06
Diabetes mellitus	25	49	0.5
Endocrine diseases	2	2	0.4
Stroke	3	7	0.9
Family history of osteoporotic fracture	3	0	0.7
Chronic kidney disease	9	4	0.01
Dementia	1	5	0.01
Asthma	5	2	0.06
Drugs, steroids, anticoagulants	4	7	0.7

BMD: Bone mineral density.

The results of this study cause us to emphasize the issue of a second fracture, which has been raised by many other researchers. Lönnroos *et al*[18] reported that this occurs at an incidence of 5.08%, but Berry *et al*[19] found the incidence of a second fracture was 14.8% in a follow-up study after 4.2 years. Recently Kaukonen *et al*[20] reported a second femoral fracture occurred in 12% of their patients. A recent study reported that in a cohort of 178 women, grade 1 vertebral fractures were identified in 33.1% and grade 2 and 3 fractures in 20.2%, and the researchers concluded that age, vitamin D levels, and osteoporosis as defined by DEXA were not factors influencing vertebral fractures[21]. Clinton *et al*[22] reported that the risk of a subsequent hip fracture after a proximal humeral fracture was highest within one year after the proximal humeral fracture, with a hazard ratio of 5.68 (95%CI = 3.70 to 8.73). We agree with Rouzi *et al*[23] that various clinical factors, including elderly age and sex, are independent risk factors that predict osteoporotic fractures.

This study was limited because of its retrospective nature and the relatively small patient population, which may not adequately represent the whole country. However, in the absence of literature published by researchers in Saudi Arabia, the current study may stimulate more prospective studies on this subject. We conclude by repeating that proximal femur fracture may be the first presenting complaint of a patient with underlying osteoporosis. It is not, as a rule, necessarily preceded by a spine fracture. However, asymptomatic vertebral fracture is a harbinger of a subsequent hip fracture, especially in elderly females. A health care worker needs a high degree of awareness to diagnose the underlying osteoporosis before his or her patient ends up suffering a fragility fracture. We recommend a DEXA scan and a lateral thoracic spine radiograph for all elderly patients who go to the radiology department for a chest X-ray. This strategy has the potential to allow health care professionals to diagnose osteoporosis at an early stage and to detect at least 25% of asymptomatic vertebral fractures. If appropriate medical therapy is instituted for such patients, it is possible that the morbidity and mortality that result from a fragility fracture of the hip can be minimized significantly.

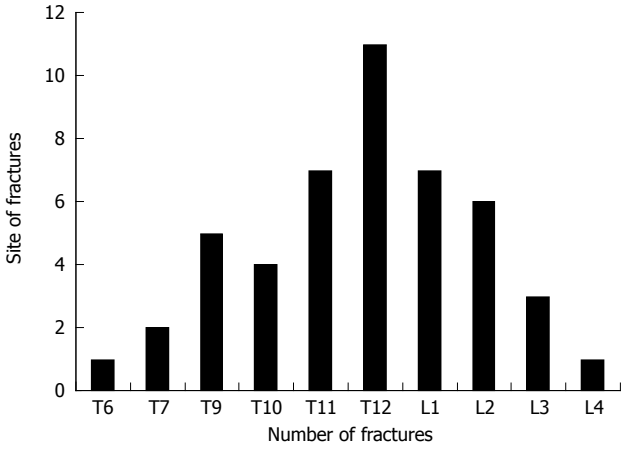

Figure 2 Shows the site and number of vertebral fractures seen is patients with hip fractures. T: Thoracic; L: Lumbar.

COMMENTS

Background

Fractures related to osteoporosis in men and women can cause high rates of morbidity and mortality. Others have reported that vertebral fractures precede a hip fracture. The objective of this study was to evaluate the relationship between a vertebral fracture and a hip fracture in Saudi Arabians with osteoporosis.

Research frontiers

A vertebral fracture does not precede hip fracture in all patients with osteoporosis. Other co-morbidities play an important role. Patients with vertebral fractures due to osteoporosis need to be closely monitored, particularly if they have other diseases, so that a femoral fracture may be prevented.

Innovations and breakthroughs

It is not essential to see a vertebral fracture in a patient with a proximal femoral fracture related to osteoporosis.

Applications

Patients with osteoporosis-related vertebral fractures and associated other diseases should be followed regularly to prevent other fragility fractures.

Peer review

This is a retrospective study to review the clinical data in Saudi Arabia and investigate the relationship between a vertebral fracture and a hip fracture in the population with osteoporosis. The study aims to look into whether vertebral fractures precede the occurrence of hip fractures. The study design is straightforward to review the X-ray retrospectively by two investigators independently and count the number of vertebral fracture cases.

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World J Orthop 2012 December 18; 3(12): I
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Events Calendar 2012

January 12-15, 2012
ICJR 4th Annual Winter Hip and Knee Course
Colorado, CO, United States

January 23-25, 2012
8th Middle East Orthopaedics Conference "Future Challenges and Directions in Orthopedic Surgery"
Dubai, United Arab Emirates

February 7-11, 2012
American Academy of Orthopaedic Surgeons
San Diego, CA, United States

February 14-15, 2012
7th National Conference: Orthopaedics and Sports Medicine 2012 London, United Kingdom

February 16-19, 2012
Orthopaedic MRI and Small Parts
Scottsdale, AZ, United States

March 4-8, 2012
The 30th Annual Emergencies in Medicine Conference
Utah, UT, United States

March 8-10, 2012
ICJR 2nd Annual Advances in Orthopaedic Trauma and Arthroplasty Course
Florida, FL, United States

March 17-24, 2012
Orthopaedics and Sports Medicine for Primary Care Practitioners
Honolulu, HI, United States

May 2-6, 2012
Association of Bone and Joint Surgeons
Charleston, SC, United States

May 4-5, 2012
8th Annual Spine Care Conference for the Primary Care Practitioner
Sacramento, CA, United States

May 9-11, 2012
Pan-African Orthopaedics Conference 2012
Nasrec, South Africa

May 11-21, 2012
Rheumatology and Orthopaedics
Civitavecchia, Italy

July 8-15, 2012
Practice Management and Technology for The 21st Century Practice
Lauderdale, FL, United States

August 13-15, 2012
International Conference and Exhibition on Orthopedics
Chicago, IL, United States

September 14-21, 2012
Orthopaedics and Sports Medicine
Barcelona, Spain

September 21-25, 2012
36th Annual UC Davis Fingers to the Toes Comprehensive Review of Primary Care Orthopaedics
Lake Tahoe, CA, United States

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GENERAL INFORMATION

World Journal of Orthopedics (*World J Orthop*, *WJO*, online ISSN 2218-5836, DOI: 10.5312) is a monthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 261 experts in orthopedics from 30 countries.

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

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Name of journal

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Editor-in-chief

Bao-Gan Peng, MD, PhD, Professor, Department of Spinal Surgery, General Hospital of Armed Police Force, 69 Yongding Road, Beijing 100039, China

Editorial Office

World Journal of Orthopedics
Editorial Department: Room 903, Building D,
Ocean International Center,

No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjo@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-8538-1892
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Key words

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

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Acknowledgments

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

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Format

Journals

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

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

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

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

In press

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

Organization as author

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

Both personal authors and an organization as author

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

No author given

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

Volume with supplement

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

Issue with no volume

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

No volume or issue

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

Books

Personal author(s)

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

Chapter in a book (list all authors)

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

Author(s) and editor(s)

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

Conference proceedings

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

Conference paper

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

Electronic journal (list all authors)

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

Patent (list all authors)

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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

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

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pres-

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

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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Editorial: http://www.wjgnet.com/2218-5836/g_info_20100723140942.htm

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