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Heterotopic ossification of the hip: A systemic review

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Abstract
Introduction/aims: Ectopic bone formation (heterotopic ossification) is associated with major hip surgery, including total hip replacement, hip resurfacing arthroplasty and pelvic trauma surgery and occurs in up to half of cases. It was hypothesised that increasing grades of heterotopic ossification is associated with increasingly deleterious effects on clinical hip function following arthroplasty.
Methods: A Systematic Review was performed to examine ectopic bone formation following hip arthroplasty and to determine its effect on function in the post-operative setting. Search terms were "Ectopic bone", "Heterotopic ossification (HO)", "Brooker classification", "Arthroplasty" and "Harris Hip Score". Fifty-five studies were identified. Exclusion criteria: non-English language; case studies; book chapter reviews. Forty-four studies were deemed suitable for inclusion, including select 'classic' papers. A search was made of MEDLINE via Pubmed, MEDLINE via Ovid SP, EMBASE via Ovid SP, CENTRAL, and Web of Science for identifying reports of randomised controlled trials, cohort studies and reviews.
Results: The amount of bone deposited in the gluteal muscles varies from small islands to widespread bridging ossification. The underlying basis of heterotopic ossification seems to be related primarily to systemic factors, as well as gender, surgical trauma and concurrent anti-inflammatory use. Radiotherapy has a role in prophylaxis in high risk groups only, given its inherent risks.
Conclusion: The surgical technique and the local tissue trauma moderate both the occurrence and amount of heterotopic ossification, but the condition does not seem to cause pain or decrease hip muscle strength. There is a limitation on hip mobility in cases with significant amounts of ectopic bone formation (Brooker grades III-IV), but not in lesser grades. There is insufficient clinical correlation between function and the Brooker stage.

Keywords: function, surgical, technique, insufficient, Pubmed, Ossification

1. Introduction

Heterotopic ossification (HO) is the formation of pathological bone in ectopic sites, principally in skeletal muscle. In relation to the hip, the focus of HO may be in the gluteal muscles. Indeed, as outlined originally by Brooker *et al*. (1973) [1], it is usually periarticular in nature and ranges from islands of bone to frank ankylosis. The condition is purported to compromise functional outcomes (in relation to stiffness, pain and loss of range of motion), though this is not universally recognized, as supported by Eisenstein *et al*. (2018) [2]. The aetiology and pathogenesis of heterotopic ossification are obscure. For many years, as outlined by Pacifici (2018) [3], its main clinical relevance was as a rare complication of elective joint arthroplasty or neurological trauma and a number of prophylactic approaches were developed to mitigate against it in these settings, however the lack of reliable early detection or means of predicting which patients will develop HO is another barrier to effective prophylaxis. This review seeks to examine the hypothesis that increasing grades of heterotopic ossification is associated with increasingly deleterious effects on clinical hip function following arthroplasty. Rarely, other joints may be involved, but the focus of this paper is on the effects of HO on total hip joint replacement. There is a scarcity of good quality randomized controlled trials in this area of Orthopaedics in which to apply the principles of evidence based medicine.

Background and Aims

Described as early as 1883 by Reidel and formalised by Brooker *et al*. (1973) [1], HO is commonly associated with total hip replacement and pelvic trauma surgery. However, there is a wide variation in the incidence of HO after hip replacement, ranging from 8% to 90%, as outlined in the work of Zeckey *et al*. (2011) [4] and others. There is no consensus as to whether HO should be recognized as a true complication arising from hip surgery, as the bulk of patients with the condition are asymptomatic and this view is supported by Zeckey *et al*. (2011) [4], Balboni *et al*. (2006) [5] and Winkler *et al*. (2015) [6]. Moreover, the incidence of HO depends on numerous confounders, which are difficult to delineate from one another. The condition is associated with an increased prevalence after total hip replacement in men, in those with hypertrophic osteoarthritis, ankylosing spondylitis, previous history of HO at other sites (e.g. contralateral total hip replacement) and in revision joint replacement, which has been outlined in previous studies, including work by Neal *et al*. (2002) [7, 23] and Pakos *et al*. (2006) [35]. This review examines the current state of understanding of heterotopic ossification in relation to total hip replacement, including its clinical context, pathophysiology, current prophylactic strategies and management, as well as potential future therapeutic modalities, with a focus on novel and evolving molecular biological approaches to this challenging problem.

Methods

This study took the form as a systematic review of heterotopic bone formation following hip arthroplasty and its effect on function in the post-operative setting. In order to maximize sensitivity of the search (although reducing its precision) a combination of the following keywords was used: "Ectopic bone", "Heterotopic ossification (HO)", "Brooker classification", "Arthroplasty"; "Function" and "Harris Hip Score". Reference lists of the identified reports as well as of existing systematic reviews and meta- analyses were also hand searched for additional studies. Fifty-five studies were identified. Forty-four studies were deemed suitable for inclusion, including select 'classic' papers from pre-2002. Exclusion criteria were the following: non-English language; case studies; book chapter reviews. There were no other language restrictions to assessment of the retrieved articles.

A search was made of MEDLINE via Pubmed, MEDLINE via Ovid SP, EMBASE via Ovid SP, CENTRAL, and Web of Science for identifying reports of randomised controlled trials, cohort studies and reviews. The databases were comparable and together produced better results than either one would have on their own. This manuscript was written following guidance of the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement. Two independent reviewers were involved in the study selection, data extraction and interpretation. There was no blinding of the reviewers. Instead of reports, studies were considered as the units of interest, thus duplicated reports from the same study were merged.

Results

Heterotopic ossification involves the formation and progressive accumulation of extraskeletal bone-like tissue at the expense of local tissues, including muscle and connective tissue elements. An examination of the literature reveals that there are common forms of HO that are triggered by extensive trauma (including surgical insult), severe burns and other systemic insults (severe brain or CNS trauma); Ahrengart (1991) [9] outlined the condition's progressive and at times aggressive nature. There are also rare congenital severe forms of heterotopic ossification that occur independent of a specific cause or local trauma. It has been recognised by Ahrengart (1991) [9] and Liu *et al*. (2017) [10], among others, that at a molecular biological level, heterotopic ossification is often preceded by inflammation, thus current prophylactic modalities usually involve anti-inflammatory agents alone or in combination with local, low-dose irradiation. The amount of bone deposited in the gluteal muscles varies from small islands to widespread bridging ossification. The underlying basis of heterotopic ossification seems to be related primarily to systemic factors, as well as gender, surgical trauma and concurrent anti-inflammatory use. Radiotherapy has a role in prophylaxis in high risk groups only. Liu *et al*. (2017) [10] identified high risk groups, which include men, those with hypertrophic osteoarthritis, ankylosing spondylitis, previous history of HO at other sites (e.g. contralateral total hip replacement) and those undergoing revision joint replacement.

The pernicious effects of HO have been outlined in previous original studies, although, as discussed by Banaszkiewicz (2014) [11], the condition is not universally recognised as a true complication of total hip replacement, because the vast majority of cases are largely asymptomatic and in essence represent incidental radiological findings. It is not recognised as a key driver of pain or gross functional impairment and therefore excision of HO or revision of a total hip replacement in the setting of HO should not be considered best practice considering the presently available literature and cogently summarised by Eisenstein *et al*. (2018) [2].

Role of Approach

Previous systematic comparisons of anterior approach versus posterior approach in primary total hip replacement have largely focused on clinical and functional outcomes. A systematic review with meta-analysis by Miller *et al*. (2018) [12] compared the complication risk of the anterior approach versus posterior approach in primary total hip replacement with at least 12 months mean follow-up and included both prospective and retrospective studies. Reported complications included HO, dislocation/instability episodes, infection and wound breakdown, re-operation for any cause, thromboembolic events (DVT and PE), iatrogenic neurovascular injury and fracture. Miller *et al*. (2018) [12] adhered to the principles of random effects meta-analysis and this was used for all outcomes under review, which is an added strength of the study. Complication risk was reported as rate ratio (RR) to account for differential follow-up durations and this also adds validity to the study. Specifically, values >1 indicated higher complication risk with the anterior approach and values <1 indicated lower risk with the anterior approach.

In all, Miller *et al*. (2018) [12] examined 19 studies, including 15 single-centre comparative studies with 6,620 patients (2,278 anterior approach; 4,342 posterior approach) and four multi-centre registries with 157,687 patients (18,735 anterior approach; 138,952 posterior approach). Median follow-up was 16 (12-64) months) with the anterior approach and 18 (12-110) months with the posterior approach. It was determined that the anterior approach was associated with lower rate of infection (RR =0.55, $p = 0.002$), dislocation (RR =0.65, $p = 0.03$), and re-operation (RR =0.84, $p < 0.001$). No statistically significant differences were observed in the rate of thromboembolic events (RR =0.59, $p = 0.5$), heterotopic ossification (RR =0.63, $p = 0.1$), wound complications such as dehiscence (RR =0.93, $p = 0.8$) or iatrogenic fracture (RR =1.0, $p = 0.9$). Additionally, there was a higher rate of patient-reported nerve injury with the anterior approach (RR =2.3, $p = 0.01$). Based on this recent systematic review comparing anterior and posterior approach to primary total hip replacement, the anterior approach was associated with lower risk of heterotopic ossification, re-operation for any cause, dislocation and infection.

Contrary to the Miller *et al*. (2018) [12] study, others have found no difference in HO rates in terms of surgical approach, whilst also confirming the potential benefits of the anterior approach to total hip replacement. It must also be recognised that any level of muscle trauma around the hip may set off a cascade of events that ultimately leads to the development of ectopic bone formation, especially in high risk groups. Indeed, even 'minimally invasive' hip replacements and hip arthroscopy, the efficacy of which is increasingly recognised by surgeons working in hip preservation surgery, may be complicated by ectopic bone formation, as outlined by Amar, Sharfman and Rath (2015)

[13], in their recent review of the topic.

Thus, in terms of surgical approach and the incidence of heterotopic ossification, the literature is not clear. Mulliken *et al*. (1998) [14] conducted a retrospective review of 770 consecutive primary total hip replacements to determine the complications and utility of a modified direct lateral approach. This direct transgluteal approach involves elevation of the anterior one-third of the gluteus medius and vastus lateralis in continuity. Other studies have demonstrated no statistically significant differences between surgical approach and the subsequent development of ectopic bone formation (Nayak *et al*. (1997) [15]. Mulliken *et al*. (1998) [14] assessed 640 patients or 712 total hip arthroplasties; follow-up was for a minimum of two years (maximum of 6.5 years and with an average of 3.6 years). In their review of outcomes, Mulliken *et al*. (1998) [14] identified two prosthetic joint dislocations which occurred in the follow-up period, for a prevalence of instability of 0.3%. The direct lateral approach has received attention in the literature as having a higher incidence of post-operative limp secondary to abductor deficiency (either due to gluteal muscle injury/fibrosis or superior gluteal nerve injury) or as a consequence of loss of range of motion or stiffness owing to clinically significant ectopic bone formation. This post-operative gait abnormality or Trendelenberg gait is not universal, however (Nayak *et al*., 1997) [15].

In the Mulliken *et al*. (1998) [14] study, a moderate or severe limp was present in 10% of all patients at two-year follow-up. Of note, severe heterotopic ossification (Brooker grade III or IV) developed in fewer than 3% of hips and was functionally limiting in only seven patients. In terms of neurovascular injuries, four sciatic nerve palsies occurred, which is consistent across series and significantly more common with the posterior approach. The direct lateral surgical exposure is considered equal to the posterior approach in relation to ease of exposure, without the need for extensile measures, such as a trochanteric osteotomy, which is easier in the posterior approach. From this review by Mulliken *et al*. (1998) [14], it was concluded that the modified direct lateral approach has greatly diminished the potentially devastating complication of postoperative instability (as compared to the posterior approach) and is associated with an acceptable level and severity of gait disturbance and heterotopic ossification, which is not statistically different to the posterior approach.

Although the focus of this review is on the incidence and significance of heterotopic ossification as it relates to total hip replacement, the condition has also been recognised by Bosse *et al*. (1988) [16] and subsequent authors to occur following major pelvic surgery, including operative fixation of pelvic ring and acetabular fractures and sacral fractures. Whether this represents a unique condition or whether it is fundamentally identical to the ectopic bone formation that can occur following hip arthroplasty, which may be driven by gluteal muscle trauma, is currently under debate (Verbeek *et al*., 2018) [17]. The Stoppa approach for acetabular fracture surgery has gained significant popularity and early results have been encouraging, but clinical outcome and extensive follow-up is scarce. Verbeek *et al*. (2018) [17] examined the modified Stoppa approach in relation to its utility in the operative treatment of acetabular fractures and assessed clinical outcome at mid-term follow-up, which appears to be unique in the relevant literature. In this retrospective study by Verbeek *et al*. (2018) [17], all patients treated operatively for an acetabular fracture using the Stoppa approach over a 10-year period were included. The primary outcome measure was native hip survivorship; secondary outcome measures included functional outcome (including Harris hip) scores, health-related quality of life (short-form 36) and radiographic outcome measures, namely the presence and severity of heterotopic ossification and secondary ipsilateral hip osteoarthritis.

The homogenous nature of the study is one of its strengths, especially as it relates to clinical correlates. Indeed, 45 patients received operative fixation for 47 acetabular fractures using the Stoppa approach, demonstrating its excellent clinical utility. Verbeek *et al*. (2018) [17] identified a number of relevant complications requiring further surgical intervention, including one patient who developed a vascular lesion intra-operatively and three patients who developed post-operative wound infections and bleeding-related complications, for example, large retained haematoma. Follow-up was 83% and 74% of native hips survived at mean 59 months (SD 49) postoperatively. Furthermore, excellent-to-good functional scores were found in 76% of patients (Harris hip score) who had retained their native hip. Most (6/8) short-form 36 indices in these patients were comparable to population norms, suggesting that stiffness or loss of range of motion were not significant in this population.

Of 29 native hips with radiographic follow-up (mean 59 months (SD 49), 86% had no or minimal radiographic abnormalities, including heterotopic ossification, and in those who did have ectopic bone identified on plain radiographs, there was no clear clinical relation in relation to impaired function (pain, stiffness or loss of range of motion). The study by Verbeek *et al*. (2018) [17] confirms that the Stoppa approach is a safe and effective technique for acetabular fracture fixation. Additionally, at mid-term follow-up, this approach is associated with good results in terms of hip survivorship, as well as functional and radiographic outcome measures. In those with recognised or established heterotopic ossification, there was no clear statistically significant clinical relationship. Except in the most severe cases of the condition, radiographic findings do not correlate with clinical outcomes and this is consistent with the ectopic bone formation associated with total hip replacement, as confirmed by Bossche and Vanderstraeten (2005) [18] and subsequent authors.

Heterotopic ossification has been noted around total hip replacements components in numerous studies. With hip resurfacing remaining a useful approach is some arthroplasty cohorts (namely, young men), Back *et al*. (2007) [19] prospectively evaluated the incidence in a cohort undergoing hip resurfacing in a high volume arthroplasty centre in Melbourne, Australia. Two hundred and twenty consecutive hip resurfacing procedures (Birmingham hip resurfacing) were prospectively reviewed at a minimum of two years follow up to assess the incidence of heterotopic ossification and its effect on function and clinical outcome. All clinical cases were performed through the posterior approach and two surgeons were involved in all cases. Back *et al*. (2007) [19] also reviewed the preoperative diagnosis, age, sex and previous surgery status of the cohort. It was identified that the overall incidence of heterotopic ossification was 58.63%; the standard Brooker classification system was used by the study's authors. The incidence of Brooker I was 37.27%, Brooker II was 13.18% and Brooker

III was 8.18%. No cases of Brooker IV (frank ankylosis) were identified in this study, which contrasts with other studies of similar patient volumes, including the series by Rama *et al*. (2009) [20].

It was identified by Back *et al*. (2007) [19] that male patients with hypertrophic-type osteoarthritis had the highest incidence of ectopic bone formation; this outcome is supported in the literature and would suggest that this group of patients would warrant prophylactic treatment peri-operatively (Sell *et al*, 1998 and Schara and Herman, 2001) [21, 22]. From this cohort study, three men underwent excision of heterotopic bone, two for pain and stiffness and one for decreased range of movement (Back *et al*., 2007) [19]. Harris hip scores were not identified as good clinical correlates to radiographic evidence of ectopic bone formation. Both anteroposterior and lateral radiographs were reviewed for evidence of HO. Moreover, 12.7% had no evidence of ectopic bone formation in the first view, but clearly had evidence of it in the second view. The incidence of HO also increased from the time of surgery, confirming that the condition takes time to develop following a precipitating event, in this case major arthroplasty surgery. Overall, Back *et al*. (2007) [19] found no evidence that heterotopic ossification affected the clinical or functional outcome of the hip resurfacing at a mean of three years follow-up. Despite this, the study authors concluded that in light of the high incidence of ectopic bone formation seen in a yet unproven long-term prosthesis (at the time of the study), the Cochrane database recommendations with regard to prophylaxis should be implemented. This advice has much support in the aforementioned literature.

Indeed, the work of Rama *et al*. (2009) [20] largely supports this view. With a randomised clinical trial, they compared the incidence and severity of heterotopic ossification in cohorts of patients who have undergone either surface replacement arthroplasty or total hip replacement at a minimum follow-up of one year. Rama *et al*. (2009) [20] discovered that the surface replacement arthroplasty group had a significantly higher rate of severe heterotopic ossification (Brooker grades III or IV) than the total hip replacement group; 12.6% (13/103) compared to 2.1% (2/97, with P = .02. Indeed, grade IV heterotopic ossification was observed exclusively in the surface replacement arthroplasty group, with 4.9% (5/103). Moreover, patients with severe ectopic bone formation had significantly inferior functional outcome scores in a host of measures. It was concluded that arthroplasty surgeons offering surface replacement, such as the Birmingham Hip Resurfacing, must be aware of this increased risk and use meticulous soft tissue handling and careful surgical technique and consider routine prophylaxis against heterotopic ossification in this unique cohort.

In a previous Australian study by Neal *et al*. (2002) [7, 23], which took the form of a systematic review, heterotopic bone formation was purported to be a well-established complication of major hip surgery, including arthroplasty and pelvic fracture fixation surgery, but it was proposed that traditional reviews of the published literature may have underestimated its frequency. This view was proposed by others in early 2000s (Neal, 2003 and Pohl *et al*., 2005) [24, 25]. Neal *et al*. (2002) [7, 23] undertook a systematic overview of all the relevant studies performed up to that date to determine reliably the incidence of any ectopic bone formation and the incidence of each Brooker grade. By separating the cohorts into arthroplasty and pelvic fracture fixation groups, the authors have made the interpretation of results in regards to radiographic findings and clinical outcomes easier. Neal *et al*. (2002) [7, 23] identified 218 studies with data on the incidence of ectopic bone formation after either hip replacement or acetabular fracture fixation. The studies included data from an estimated 59,121 operated hips among patients who received total hip replacement and an estimated 998 hips among patients that underwent acetabular fracture operative fixation.

It was determined that the incidence of any Brooker grade of heterotopic ossification was 43% after total hip replacement and 51% after acetabular fracture repair. The incidence of severe ectopic bone formation (Brooker grade III and IV) was 9% and 19%, respectively. The authors didn't delineate the surgical approach undertaken for either the total hip replacement or pelvic fracture fixation groups, which is a definite weakness of the study, especially when trying to compare other, aforementioned studies which have examined the surgical approach as a key factor in the formation of ectopic bone formation. It can be concluded from the Neal *et al*. (2002) [7, 23] study that ectopic bone formation occurs more frequently after total hip replacement than is generally recognised. It is possible that heterotopic bone formation is a more important cause of postoperative disability than has previously been recognised and that effective prophylactic strategies may serve to improve clinical outcomes in large numbers of patients. These findings are not replicated in large series or cohort studies, but due to the fact that the systemic review by Neal *et al*. (2002) [7, 23] incorporated such large numbers and very clearly has statistical validity and power, its conclusions should be considered by hip arthroplasty surgeons, especially in the management of high risk patients, namely men with hypertrophic osteoarthritis, those with connective tissue disorders, patients with ankylosing spondylitis and patients who have developed heterotopic ossification of the contralateral hip.

The Role of Prophylaxis

From an interpretation of the existing literature, heterotopic ossification can be defined as a benign condition of abnormal formation of bone in soft tissue and is thought to be driven by trauma to the gluteal muscles. The condition is frequently asymptomatic, though when it is more extensive, it typically manifests as decreased range of motion at the involved joint. Heterotopic ossification has been recognised to occur in three distinct contexts: post-traumatic; neurologic injury; and, rarely, as a consequence of genetic abnormalities. The underlying basis of the condition is incompletely understood. The most plausible molecular biological basis of the condition is thought to be from the presence and activation of osteoprogenitor cells and, indeed, a certain critical level of pathologically induced imbalance, at a local or systemic factor level (Johnson & Sims, 2014) [26]. The process is likely driven by a host of inducible factors, including vascular endothelium growth factor (VEGF), platelet-derived growth factor (PDGF) and other chemotaxis-responsive phenomena (Seavey *et al*., 2017, Davies *et al*., 2017 and Kim *et al*., 2013) [27, 28, 29]. The current best available evidence supports the philosophy of prophylaxis to prevent ectopic bone formation in high risk patients. The two most commonly used modalities for prophylaxis are non-steroidal anti-inflammatory drugs and

low-dose radiation therapy, which has an increasingly strong scientific basis, as outlined by Balboni *et al*. (2006) [5] and Winkler *et al*. (2015) [6].

Given that heterotopic ossification is a potentially severe, if uncommon, complication in total hip replacement surgery, patients do warrant stratification in relation to their potential risk factors. An assessment of the literature does reveal a degree of uncertainty in relation to whether NSAIDs or radiation therapy, or a combination of the two modalities, has the strongest affect in terms of prophylaxis in these high risk groups. Vavken *et al*. (2009) [30] systematically reviewed the literature in EMBASE, MedLine, CINAHL and the Cochrane Controlled Trial Register and, after ruling out publication bias and data heterogeneity, which is a strength of their study, performed a meta-analysis of randomised controlled trials to assess effectiveness, utility and complications of NSAIDs and radiation therapy in the prevention of ectopic bone formation.

Vavken *et al*. (2009) [30] identified nine studies reporting on effectiveness, utility and complications including a total of 1295 patients. A review of this paper revealed that the pooled risk ratio for the effectiveness in heterotopic ossification prevention was 0.96 (95% confidence interval, 0.88-1.06) and was independent of the type of surgery, that is, total hip replacement or pelvic fracture operative fixation. Furthermore, there was no association with gender, age, length of follow-up or other identifiable patient factors. Additionally, the risk ratio for associated complications was 0.79 (95% confidence interval, 0.45-1.41); this was independent of the aforementioned factors. Vavken *et al*. (2009) [30] concluded that there was no evidence for a statistically significant or clinically important difference between NSAIDs or radiation therapy in preventing heterotopic ossification following total hip replacement or pelvic fracture operative fixation. This support of radiation therapy and essentially the proposal of its non-inferiority in 'all-comers' lends credence to the work of many other researchers, including, pivotally, Ayers *et al*. (1986) [31], which is one of the earliest works proposing the utility of radiation therapy in the prophylaxis of heterotopic ossification involving the hip joint.

Discussion

As has been established in an analysis of the literature thus far, heterotopic ossification is a complication after major tissue trauma, fractures and hip surgery. Prophylaxis is the most effective therapy once established and includes a combination of anti-inflammatory medications (NSAIDs) and low-dose radiation therapy. If ectopic bone formation becomes symptomatic and limits patients' quality of life (usually Brooker grades III and IV), revision surgery can be indicated and is usually combined with a perioperative oral prophylaxis (NSAIDs) and/or irradiation regime (Ranganathan *et al*., 2015) [32]. However, the long-term use of NSAIDs can induce gastrointestinal or cardiovascular side effects and possible bony non-unions during fracture healing. The German study by Winkler *et al*. (2015) [6] assessed the current status of heterotopic ossification prophylaxis after injuries or fractures and evaluated the current indications and strategies for excision of symptomatic heterotopic ossification.

Between 2013 and 2014, a questionnaire was sent to 119 Orthopaedic and Trauma Surgery Departments in Germany. The cumulative feedback rate from the Winkler *et al*. (2015) [6] study was 71%. Trauma and Orthopaedic Surgery Departments in Germany recommend oral prophylaxis with standard NSAIDs after acetabulum and femoral neck fractures, elbow dislocation and fracture or dislocation of the radial head as a means of mitigating ectopic bone formation. This group did not look at total hip replacement itself as a cause of ectopic bone formation. Pain with movement and an increasing loss of range of motion in the affected joint were considered to be clear indications for HO extirpation, although this is not universally supported in the literature, due to high recurrence rates, especially in the setting of an underlying prosthetic joint (Vasileiadis *et al*., 2015) [33].

A partial removal of ROM-limiting HO formations was also considered important, although can be technically challenging to even the most skilled revisionists (Aljurayyan et al., 2016). The vast majority of all Orthopaedic Departments in Germany now include perioperative oral HO prophylaxis and/or irradiation if surgical HO removal is planned. The choice and duration of NSAIDs is highly variable and depends on the patients' general health and associated medical conditions; there is no consensus in the available literature on the type and duration of oral prophylaxis regimes. Indeed, from the Winkler *et al*. (2015) [6] study, it can be concluded that ectopic bone formation, especially of Brooker grades III and IV involving the hip, but also affecting other joints and in the post-operative phase following fracture fixation surgery, is of considerable clinical significance.

Certain fractures and injuries are prone to ectopic bone formation and prophylactic measures should be taken in such high risk cases. The respondents in the Winkler *et al*. (2015) [6] survey assessed current therapeutic strategies for HO formations in a similar, standard fashion and their recommendations are in line with the current best available literature. However, the duration of perioperative oral HO prophylaxis varied greatly among the specialist centres; this is also seen globally (Vasileiadis *et al*., 2015 and Pakos *et al*., 2009) [33, 35]. This is a significant issue, as a long-term use of NSAIDs creates potential risk for patients' safety and could influence their ultimate clinical outcome. National and international guidelines need to be developed to further reduce heterotopic ossification rates and improve patients' health and safety in relation to oral prophylaxis with NSAIDs.

Current total hip replacements utilise a variety of different stem and acetabular component options, including cemented, non-cemented and hybrid fixation options. Hip replacement components come in a variety of designs and varying material compositions. An examination of the literature reveals that most papers have examined heterotypic ossification in arthroplasty in general, but have failed to examine the potential impact of different materials and fixation methods on the development of the condition. A study by Nayak *et al*. (1997) [15] attempted to determine the prevalence of ectopic bone formation in cemented versus non-cemented total hip joint replacement; such a study had not been constructed previously. Nayak *et al*. (1997) [15] designed a prospective randomised controlled trial; follow-up ranged from two to six years all patients were recruited by a university hospital. Two hundred and twenty-six patients, who had primary or secondary osteoarthritis of the hip, were stratified according to surgeon, age and type of fixation. Patients were randomised

within subgroups; 112 received non-cemented total hip prostheses and 114 received cemented prostheses. The two groups were well matched for age, sex and other factors. In the cemented group, standard bone cement (polymethylmethacrylate) was used. In both groups, all femoral prostheses were inserted through a direct lateral surgical approach.

The standardisation of surgical approach in the study by Nayak *et al*. (1997) [15] removes any confounders related to differences in ectopic bone formation in relation to the approach itself, with any differences in outcome being attributable to differences in the fixation method alone. The Brooker classification was used to grade ectopic bone formation from post-operative x-rays. Overall, 148 (66%) hips had no heterotopic ossification, 56 (25%) were Brooker grade I; 14 (6%) were grade II; 8 (3%) were grade III and no grade IV cases were identified in this time interval. Nayak *et al*. (1997) [15] identified, that in the non-cemented group of patients, 76 (68%) hips had no heterotopic ossification; 25 (22%) were Brooker grade I; 7 (6%) were grade II; 4 (4%) were grade III and none were grade IV. Comparably, in the cemented group of patients, 72 (63%) hips had no heterotopic ossification; 31 (27%) hips were Brooker grade I; 7 (6%) were grade II, 4 (4%) were grade III and none were grade IV. From this study is can be concluded that there is no significant difference in the prevalence of heterotopic ossification between cemented and non-cemented total hip replacements in patients with osteoarthritis; this supports the work of Ahrengart (1991) [9] and, more recently, Rama *et al*. (2009) [20], where approach and local muscle trauma is proposed to be the underlying basis of the condition, with 'patient risk profile' serving as the significant modifying factor.

Given the current paradigm, deserved or not, that surgical approach itself may drive or modify ectopic bone formation following total hip replacement, an analysis of studies which have high patient volumes, sound methodology and are free from bias, is essential in addressing this clinical problem. Alijanipour *et al*. (2017) [36] had posited that the severity of heterotopic ossification, not just its presence radiographically or clinically, may be influenced by the type of surgical approach. It was hypothesised that because of differences in soft tissue dissection, clear differences exist in ectopic bone formation in primary total hip replacement using the direct anterior compared with the direct lateral approach. With this assumption, Alijanipour *et al*. (2017) [36] recruited a total of 1482 consecutive patients with either the direct lateral (736) or the direct anterior (746) approach and utilised a standardised perioperative protocol over a two year period.

No patients received prophylactic radiotherapy, nor NSAIDs. Preoperative and six month postoperative x-rays were reviewed based on the Brooker classification system. It was determined that the incidence of overall ectopic bone formation was higher in the direct lateral (36.1%) compared to the direct anterior approach group (19.4%, $P < .001$), but that high-grade heterotopic ossification (Brooker III or IV) was not significantly different among the groups (3.9% for direct lateral and 3.0% for direct anterior groups). Moreover, no patient required further surgery for ectopic bone resection, which is comparable to other studies, including the work of Bossche & Vanderstraeten (2005) [18]. It can be concluded, on the basis of the prospective study by Alijanipour *et al*. (2017) [36], that the type of approach (direct anterior or direct lateral) does not seem to have a major influence on the short-term incidence of high-grade heterotopic ossification (Brooker III or IV) based on an established and well-validated radiographic analysis.

Anthonissen *et al*. (2016) [37] undertook a retrospective review to determine the incidence and severity of heterotrophic ossification following acute revision total hip arthroplasty and whether this represents a significant risk factor for HO that warrants a prophylactic approach. A total of seven patients (three male and four female) with a mean age of 55 years (39-70 years) who underwent a re-operation of their hip replacement for any reason that required a hip arthrotomy within three weeks of the index arthroplasty were included. Despite the lack of high patient numbers, the mean follow-up of 8.8 years (2-12 years) is one of the strengths of this study. Anthonissen *et al*. (2016) [37], as part of their study design and essential to its success, ensured that all patients were both evaluated radiographically for any evidence of HO and clinically using the Harris hip score.

All seven hips developed HO, with 71% being severe (Brooker grade III and IV). One hip developed Brooker IV heterotrophic ossification, four hips (57 %) developed Brooker III heterotrophic ossification and two hips developed Brooker II heterotrophic ossification. In relation to clinical/functional outcome measures, the patient's range of motion varied, but was very limited in three patients. Three patients were dissatisfied with their surgery; one patient had Brooker IV heterotrophic ossification and two patients had Brooker III heterotrophic ossification. It can be concluded that acute re-operation after primary or revision total hip replacement is a significant risk factor for the development of extensive heterotrophic ossification and this may in itself require a philosophy of care that incorporates a focus on prophylactic treatment (Anthonissen *et al*., 2016) [37]. This view is supported by more recent studies, including the work of Alijanipour *et al*. (2017) [36] and Redmond *et al*. (2017) [38].

The Efficacy of Radiation Therapy

Ayers, Evarts and Parkinson (1986) [31] performed a well-constructed prospective study to evaluate the efficacy of treatment with 1,000 rads of radiation in the prevention of heterotopic ossification after total hip arthroplasty in high risk patients. Patients who were considered high risk for heterotopic ossification after total hip replacement were identified and an effective regimen for its prevention was established. It was demonstrated that treatment with 2,000 rads of radiation that was initiated within four days after the total hip replacement was effective in the prevention of ectopic bone formation and in the prevention of recurrence after resection of existing ectopic foci. Ayers, Evarts and Parkinson (1986) [31] examined whether 1,000 rads of radiation, which was administered in increments of 200 rads over a period of five to seven days, is as effective as treatment with 2,000 rads. Their protocol of 1,000 rads was found to be preferable because it reduces the risk of malignancy and the length of stay in hospital. Other Radiation Oncology specialists have since expanded on this work and have determined that there is indeed a critical volume of total radiation, as well as dose and frequency, that must be delivered, to impart a prophylactic effect in relation to the prevention of ectopic bone formation; the study by Balboni *et al*. (2006) [5] best encapsulates this

current paradigm.

More recently however, and building on this previous work, Liu *et al*. (2017) [10] supported the view that radiation is an effective prophylaxis, but that an optimal protocol has yet to be determined that is truly evidence based. Liu's group performed a randomised, double-blinded clinical trial in high risk patients to determine the efficacy of 400 vs 700 cGy doses of radiation (considered low dose treatment). One hundred forty-seven patients undergoing total hip replacement and at high risk for ectopic bone formation were randomised to receive either a single 400 or 700 cGy dose of radiation postoperatively. Liu *et al*. (2017) [10] defined high risk as being a diagnosis of diffuse idiopathic skeletal hyperostosis (DISH), hypertrophic osteoarthritis, ankylosing spondylitis or history of previous heterotopic ossification, especially of the contralateral hip. Radiation was administered on the first or second postoperative day. A single-blinded reviewer graded x-rays taken immediately postoperatively and at a minimum of six months postoperatively using the Brooker classification system.

Liu *et al*. (2017) [10] defined progression as an increase in Brooker classification grade by a minimum of one grade. Operative data including surgical approach, implant fixation method, revision surgery status, and postoperative range of motion were also collected. One deficiency of the study was that it did not clearly delineate primary from revision or re-revision surgery. Nevertheless, it was determined, that a significantly greater proportion of patients who received the 400 cGy dose demonstrated progression of HO than patients who received the 700 cGy dose, indicating that there is indeed a critical value of radiation dose in relation to heterotopic ossification prophylaxis. No preoperative factors were associated with a higher rate of progression of Brooker grade, but patients who progressed in grade had less flexion on physical examination than patients who did not progress, but this was not clinically significant. It was therefore concluded that 700 cGy was superior to 400 cGy in preventing ectopic bone formation following total hip replacement in high risk patients and may be the more effective treatment in this cohort of patients.

Aside from radiation therapy and NSAIDs, novel methods are in development to address ectopic bone formation. Johnson & Sims (2014) [26] have outlined one useful strategy that has shown promise to inhibit chondrogenesis, which has been proposed as an essential component of the molecular profile of heterotopic ossification. This novel study outlined the role of retinoic acid receptor gamma (RARγ) agonism to inhibit chondrogenesis. It was postulated that without a cartilage scaffold, the endochondral processes that generates heterotopic ossification are blocked and no mineralised osteoid can be deposited. Moreover, it was noted in this rodent model, that there was a transient prolongation of fracture healing associated with RARγ agonism, owing to the decreased capacity to form mineralised osteoid as the fracture callus matures. Much work remains to be done in this potential future therapy.

Minimally Invasive Approaches

In current clinical practice, there is a clear trend to embrace a minimally invasive approach, regardless of the surgical interval, given that it is supposedly less traumatic than standard techniques and promises a faster return to activity, with potentially less complications, such as infection, blood loss and hospital length of stay (von Rottkay et al., 2018). Hürlimann *et al*. (2017) [40] investigated the idea that minimally invasive surgery (MIS) may lead to less ectopic bone formation after total hip replacement, as this has been described by others, including by DiGioia III *et al*. (2003) [41], as an additional benefit of this philosophy. Hürlimann *et al*. (2017) [40] undertook a retrospective study which included 134 consecutive patients undergoing primary total hip replacement.

In 42 (31.3%) patients a standard modified anterolateral (Watson-Jones), in 28 (20.9%) patients a standard transgluteal or Hardinge approach, in 39 (29.1%) a MIS direct anterior approach (AMIS) and in 25 (18.7%) patients a MIS anterolateral (MIS-AL) approach was utilised. Hürlimann *et al*. (2017) [40] performed standard preoperative anteroposterior and lateral x-rays to assess for occurrence of heterotopic ossification. As in the established fashion, heterotopic ossification was classified according to the Brooker system. A strength of this study was the addition of short and long-term adverse events. Additionally, data was statistically analysed using Chi-square tests, analysis of variance, multivariate data analysis and Pearson's correlation.

It was determined, that overall, heterotopic ossification was found in 38 patients (28.4%) after total hip replacement. The Watson-Jones group showed the highest heterotopic ossification rate (45.2% $n = 19$) with a significant difference to the AMIS (23.1% $n = 9$) and the Hardinge approach (14.3% $n = 4$). No statistical difference, however, was found in the MIS-AL approach (24.0% $n = 6$). Postoperative complications did not differ significantly, except for a higher incidence of Trendelenburg`s sign in the Hardinge approach, a complication well recognised as occurring secondary to 'gluteal deficiency'. It can be concluded from the study by Hürlimann *et al*. (2017) [40] that the rate and degree of heterotopic ossification after primary total hip replacement were significantly different with regards to the surgical approach. The standard modified anterolateral approach resulted in the highest rate of ectopic bone formation, however, MIS approaches showed higher heterotopic ossification rates than the Hardinge approach, which conflicts with other studies, including that of Banaszkiewicz (2014) [11].

Insights from Animal Models - Local Tissue Trauma

Studies on human subjects has the greatest applicability for the arthroplasty surgeon, however animal experiments can provide important additional information, especially in relation to the underlying biology and pathoanatomy of an underlying systemic disorder, such as heterotopic ossification. Indeed, murine models have demonstrated their utility in this domain and the subsequent extrapolation to human subjects has a sound scientific basis. As outlined throughout this analysis, the pathophysiological entities responsible for the formation of heterotopic ossification remain largely unclear, but muscle trauma is alleged to play a central role in the pathogenic mechanisms underlying ectopic bone formation in muscle. However, for this observation, made by many surgeons for decades, no objective evidence has been provided yet in the form of well-constructed animal models which have applicability to the human condition.

In the face of this apparent lack of objective scientific data, Anthonissen *et al*. (2016) [37] devised an experiment using 50 male Wistar rats. These animals were subjected to

surgery of the right hip. The femoral canal was reamed in three steps up to 2 mm. In terms of stratification, animals formed two groups. In Group One (25 animals), the intervention was carried out with preservation of the surrounding muscles. In contrast, in the rats of Group Two (25 animals), an additional 'muscle lesion' was created, the details of which are not well described, but the idea essentially was create local injury to the muscles around the hip. One strength of the study was the relatively prolonged follow-up period. Twelve weeks after surgery, the volume of heterotopic bone was assessed using micro-computed tomography and classified using a modified Brooker classification system. A chi-square test was used to assess the statistical hypothesis comparing Group One and Two. It was identified by Anthonissen *et al*. (2016) [37] that a significantly higher amount of heterotopic bone was observed in animals that underwent additional muscular trauma. It can be concluded, at least in principle, that during surgery, particular care should be taken to not injure the surrounding musculature.

Other Local Factors

It has been increasingly recognised that one of the local factors contributing to the formation of heterotopic ossification, aside from local tissue trauma, is the bone debris generated during surgery, namely from reaming of the acetabulum and femoral canal preparation. Kantak & Shah (2017) [42] proposed that this risk can be partially mitigated by liberal use of saline lavage. Indeed, extensive intraoperative lavage can reduce the incidence and severity of heterotopic ossification in primary total hip replacement. To examine this idea, Kantak & Shah (2017) [42] designed a retrospective case control radiological study of 145 patients (175 total hip replacements). The control group received minimal intra-operative lavage (less than one litre) and consisted of 90 primary hip replacements. The treatment group received extensive saline lavage (more than three litres) and consisted of 85 primary total hip replacement patients. The Brooker classification was used to grade x-rays at one year for development of heterotopic ossification. It was determined that 66 patients in the control group had heterotopic ossification, with six patients demonstrating a significant grade (Brooker III or IV). Thirty-five patients in the index group had heterotopic ossification with no incidence of severe disease. Moreover, the majority of patients in the index group showed predominantly grade I heterotopic ossification (28 out of 35, compared to 37 out of 66 in control group). Indeed, there was a statistically significant difference in the incidence, as well as the severity of heterotopic ossification between the groups, with extensive lavage having a significant beneficial effect.

Functional Considerations

As has now been established, heterotopic ossification represents one of the most frequent complications following any type of hip arthroplasty, including resurfacing. However, disagreement exists regarding the clinical significance of heterotopic ossification after total hip replacement. Kocic *et al*. (2010) [43] evaluated the effect of different grades of heterotopic ossification on range of hip motion, pain and the clinical outcomes in patients after primary total hip replacement. The study included 198 patients with primary total hip arthroplasty because of unilateral hip osteoarthritis, followed for a minimum of one year post-operatively. The diagnosis and classification of heterotopic ossification was according to the Brooker classification system and was achieved on anteroposterior x-rays one year postoperatively. These radiographic measures were then correlated with the clinical outcomes, which were assessed with the use of the Harris hip score. Pain was assessed as the pain component of the Harris hip score and hip range of motion was measured passively in the supine position with a goniometer and recorded in degrees according to the method suggested by the American Academy of Orthopaedic Surgeons 1988.

Overall, the incidence of heterotopic ossification was just under half, at 47% and the incidence of severe ectopic bone formation was 11% (Brooker grade III or IV). It was determined that the severe heterotopic ossification significantly reduced clinical outcome, overall range of hip motion and certain components such as flexion, abduction and external rotation (FABER), but had no significant effect on pain nor true stiffness. Moreover, lesser degrees of ectopic bone formation did not significantly influence the clinical outcome, hip motion and pain. It can be concluded from this study that only severe heterotopic ossification is of clinical significance and should be mitigated against through the aforementioned approaches (gentle soft tissue handling, liberal use of saline lavage and haemostasis).

In another most recent study, Ranganathan *et al*. (2015) [32], calculated the range of motion and Harris hip score in 104 patients with known heterotopic ossification after total hip replacement and 208 matched controls without heterotopic ossification. The patients with heterotopic ossification were radiographically divided into high and low grade groups, based on a qualitative assessment of the volume of ectopic bone deposition. This division into two groups made comparisons easier when analysing the study, but clearly the use of the Brooker classification system allows for a more nuanced assessment of radiographic and clinical or functional correlation. Nevertheless, it was determined that there was no statistically significant association of clinical hip scores with high or low grade heterotopic ossification. It was demonstrated that high grade heterotopic ossification had a statistically significant 6° loss of terminal hip flexion, 4° loss of abduction, and 6° loss of internal rotation at the hip, although the overall clinical detriment of this range of motion loss is not significant. Therefore, the small changes in terminal hip range of motion and lack of association with hip clinical scores may be the result of false radiographic continuity resulting in an overestimation of the functional compromise in high grade heterotopic ossification states.

Future Directions

As outlined previously, the aetiology and pathogenesis of heterotopic ossification are still obscure. Rath *et al*. (2002) [44] evaluated the impact of necrotic gluteus minimus muscle debridement on the formation of heterotopic ossification after operative treatment of posterior wall and associated transverse-posterior wall acetabular fracture fixations utilising a Kocher–Langenbeck surgical exposure. It was determined that necrotic gluteus minimus muscle debridement resection diminishes ectopic bone formation comparably to other reported series in which non-steroidal anti-inflammatory medications were used. Resection of the necrotic gluteus minimus muscle from the zone of injury has proved to be an efficient and safe method of preventing significant heterotopic ossification in patients after operative

fixation of posterior wall and associated transverse-posterior wall acetabular fractures treated through a standard Kocher–Langenbeck approach.

Furthermore, a clinical observation is that such heterotopic bone formation mainly occurs in the gluteus minimus muscle, i.e. not in the gluteus medius muscle belly. In this regard, further studies to compare gene expression profiles could be performed in those two gluteal muscles. During elective hip surgery (total hip replacement using a lateral transgluteal approach), it is proposed that muscle belly samples could be harvested from gluteus minimus and gluteus medius. The assay and biopsy technique for gluteal muscle sampling is still in development and in the future could be used to assess the differences in gene expression.

If the genetic markers that drive ectopic bone formation following hip replacement can be characterised, it may be possible to delineate potential therapeutic modalities to attenuate this deleterious process and improve function for this subgroup of patients.

Conclusion

Heterotopic bone formation is associated with major hip surgery, including hip arthroplasty and pelvic trauma surgery and occurs in up to half of such cases. The aetiology and pathogenesis of heterotopic ossification are obscure. Heterotopic bone formation can cause stiffness and pain following hip arthroplasty, but recent literature is contentious. The condition is recognised, especially in its more severe forms, as one which can adversely affect the performance of an otherwise well positioned, stable and clinically satisfactory total hip joint replacement. Although the pathophysiological basis of heterotopic ossification remains unclear, gluteal muscle trauma is proposed to play a central role. Post-operative heterotopic bone formation can cause hip stiffness and rarely pain following total hip replacement, but seems to be relevant only in Brooker grades III-IV.

The utility of heterotopic ossification classification systems is debatable, although the Brooker system is the most used, best validated and easiest to apply for the arthroplasty surgeon in clinical practice. It has been demonstrated in the best available studies that the surgical technique and the local tissue trauma moderate both the occurrence and amount of heterotopic ossification, but the condition does not seem to cause pain or decrease hip muscle strength. There is a limitation on hip mobility in cases with significant amounts of ectopic bone formation (Brooker grades III-IV), but not in lesser grades; the loss of terminal range of motion is not thought to be detrimental to normal function. It is unclear whether the surgical approach (posterior, lateral, anterior) has any statistically significant impact on the development of the condition, as the evidence for this is mixed and largely underpowered.

Moreover, there is insufficient clinical correlation between function and the Brooker stage, especially as it relates to the earliest, most undeveloped stages of the disease process. Is prophylaxis against heterotopic ossification worthwhile, if the majority of ectopic bone formation is largely asymptomatic? By correlating the Brooker stage with well-established clinical hip scores in larger patient populations, the potentially deleterious effects on hip function may be further clarified. Heterotopic ossification has a strong genetic basis with a unique and as yet fully delineated molecular profile. Should we, however, be concerned? Is the condition a driver for hip revisions in the future? Will the incidence of heterotopic ossification increase in the future and should we adjust our way of performing total hip replacements to meet this challenge? Understanding the biochemistry and molecular biology of heterotopic ossification is clearly important and should be seen as one of the many tools in our armamentarium to combat the challenge of ectopic bone formation.

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