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GENERAL REVIEW • UPPER LIMB - TUMORS

Patellar complications following total knee arthroplasty: a review of the current literature

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Abstract
Total knee arthroplasty is a common operation for treating patients with end-stage knee osteoarthritis and generally has a good outcome. There are several complications that may necessitate revision of the implants. Patella-related complications are difficult to treat, and their consequences impact the longevity of the implanted joint and functional outcomes. In this review, we explore the current literature on patellar complications in total knee arthroplasty and identify risk factors as well as strategies that can help in preventing these complications. We present pertinent findings relating to patellar complications. They can be classified into bony or soft tissue complications and include bone loss, aseptic loosening, periprosthetic fractures, patella fracture, patellar clunk syndrome, patellofemoral instability, extensor mechanism complications, maltracking, patella baja and malrotation. We conclude that patellar complications in total knee arthroplasty are common and have significant implications for the functional outcome of total knee arthroplasty. A high index of suspicion should be maintained in order to avoid them. Implant malpositioning and other forms of intraoperative technical error are the main cause of these complications, and therefore, primary prevention is crucial. When dealing with these established problems, a clear plan of action should be formulated in advance to allow appropriate management as well as anticipation of adverse outcomes.

Keywords Patella · Patellar complications · Patellar fracture · Patellar dislocation · Prosthesis failure · Total knee arthroplasty

Introduction

Initial total knee arthroplasty (TKA) designs did not include patellar implants and it quickly became apparent there was a high rate of anterior knee pain following these operations [1]. With the advent of cement-free metal patella components in the 1980s, patella-related complications accounted for up to 50% of complications following TKA [2]. In modern TKA designs, patellar implants are all-polyethylene with multiple peripheral pegs, as the older metal-backed implants had high rates of wear and loosening [3].

Patellar resurfacing was introduced and with it came several complications that proved difficult to treat [4]. Therefore, it is not surprising that patellar resurfacing has been subject to controversy for several years [5–9]. Some support routine resurfacing, while others advise against it [10]. A third group of clinicians are proponents of selective resurfacing as required [11]. Although a large number of studies have shown similar functional outcomes and pain levels between resurfaced and non-resurfaced groups, they examined implants which are now obsolete [12]. Patellofemoral complications post-TKA form a large percentage of all TKA-related problems and include anterior knee pain, extensor mechanism injuries and patella fractures [13], but there is considerable overlap in the pathologies responsible for anterior knee pain. Evidence has emerged to suggest that resurfacing reduces anterior knee pain [14] and the

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rate of revision after TKA [15, 16]. However, some suggest that there is no difference in the outcome between the two approaches [17]. Furthermore, it has been demonstrated that patellar resurfacing reduces the patellofemoral contact area to approximately 40% of the native joint [18], thereby increasing contact stress leading to implant loosening and failure [19]. As such, the community remains divided in their opinion towards patellar resurfacing.

Patellar complications in TKA account for one of the commonest indications for revision [20] surgery and should therefore be well understood in order to better plan treatment and manage complications. The incidence of patellofemoral complications following TKA ranges between 2% and 20%. These complications encompass a variety of pathologies that reflect both preoperative and intraoperative risk factors. In 1988, a study by Brick and Scott showed that up to 50% of revision TKA surgery was due to patellofemoral complications [21]. In the recent years, this rate has observed a downward trend. This may be attributed to increased understanding of pathophysiology and greater scrutiny of operator-dependent factors. A common denominator of patellofemoral complications in TKA is implant positioning and consequent maltracking of the patella. An implanted patella component can fail by a number of mechanisms, including aseptic loosening, fracture of the remaining bone and damage to the implant. Failure of the patella implant stems from a combination of implant design characteristics and technical error during implantation. In order to explore patellar complications in TKA, we can classify them into bone-related and soft tissue-related complications. Bone complications include bone loss, aseptic loosening and periprosthetic fractures. Soft tissue complications include patellar clunk syndrome, patellofemoral instability and extensor mechanism failure.

Bone loss

Background

Bone loss during revision of a patellar implant is a common and significant complication that may be avoided with careful preoperative planning. In revision TKA, 30–50% of cases can present with a well-fixed patellar implant [22].

Management

The decision on how to proceed depends on the indication for the revision and the compatibility of the existing patellar implant to the new femoral and tibial implants that will be inserted. If the decision to remove a well-fixed implant is made, then significant patella bone loss or even patella fracture should be anticipated. Therefore, careful planning is necessary in dealing with this technically challenging problem.

Techniques that address this issue include the use of morsellised cancellous bone graft, structural iliac crest bone graft and gull-wing osteotomy [23]. Implants with a porous metal domed baseplate (Fig. 1) may also be used; they can be sutured into the soft tissues surrounding the patella [22]. Patellectomy has been shown to produce a considerable reduction in quadriceps strength and causes degree of extensor lag [24]. Patellectomy in revision TKA has poor clinical outcomes and, although not typically recommended, can be used as a last resort. Recently, mid-term results have suggested that the use of tantalum cones in patients with severe bone loss is a successful treatment strategy [25].

Aseptic loosening

Background

Aseptic loosening is the commonest cause for isolated patellar implant failure [26]. Patellar implant failure was more common with the initial metal-backed implants due to the increased risk of peg fracture, metal baseplate fracture,

Fig. 1 Lateral knee radiograph of tantalum porous patella implant in a total knee arthroplasty

loosening due to lack of bone ingrowth and metal–polyethylene dissociation [3]. Exposed metal baseplate leads to rapid metallosis and failure of the entire joint due to metal-on-metal wear between the patellar and femoral implants. This often necessitates revision surgery [27]. Modern all-polyethylene patellar implants have improved complication rates compared to both metal-backed implants and uncemented patellar implants [28].

Risk factors

Certain factors can predispose to aseptic loosening. These include patient, intraoperative or postoperative factors.

Patients with high BMI, high activity level or are male, will have an increased risk of aseptic loosening following TKA. Although all-polyethylene implants often demonstrate cold flow deformation, it does not always translate to significant clinical benefit. All-polyethylene components tend to fail if there is joint overstuffing as a result of increased patellar composite thickness or an oversized femoral component [29]. Increased flexion of the femoral implant, preoperative fixed flexion deformity and the use of uncemented implants [30] are all associated with patellar component loosening [31]. Additionally, König et al. carried out a biomechanical study which showed that joint line elevation after TKA contributes to an increase in the patellofemoral contact forces which may predispose to early implant failure [32].

Management

When managing aseptic loosening, it is important to bear in mind that implant malpositioning is the most common cause and can manifest as patellar maltracking [33]. Consequently, isolated patellar revision can have a high incidence of complications and may result in recurrent implant failure [22]. In the recent years, the use of off-set stem couplers in revision TKAs has produced good results when compared to the use of straight stems. This perhaps holds promise in addressing recurrent implant failure [34]. Aseptic loosening of all-polyethylene patellar implants in the absence of implant malrotation has been well described in the literature. One of the leading causes of this problem is patella osteonecrosis which may occur following insult to the vascular supply during TKA [35]. However, revision surgery is rarely necessary in asymptomatic patients. Aseptic loosening often presents with pain or extensor mechanism failure, which is discussed in the later sections of this review. In symptomatic patients who require revision surgery, several options exist. Re-implantation may be undertaken with bone grafting, metallic frame or cement. Conversely, bone grafting may be performed without re-implantation. Other options include osteotomy, patellectomy and reconstruction of the patella with or without reconstructing the extensor mechanism using an allograft. If unavoidable, reconstruction may be favoured over patellectomy which can result in loss of strength.

Periprosthetic fracture

Background

The incidence of perioperative and postoperative patellar fracture varies in the literature and range from under 1% to over 20% [24, 36]. While less common than periprosthetic fractures of the femur [37], it poses a significant challenge as it is difficult for patients to return to satisfactory function afterwards. Periprosthetic fractures can occur in non-replaced (Fig. 2a, b) and replaced patellae, although there is a clear correlation with patellar resurfacing [38, 39]. There are certain features that predispose to periprosthetic fractures. A systematic review by Chalidis et al. reported that 11.68% of periprosthetic patellar fractures can be directly attributed to trauma, while the remainder occurs without any significant trauma [38].

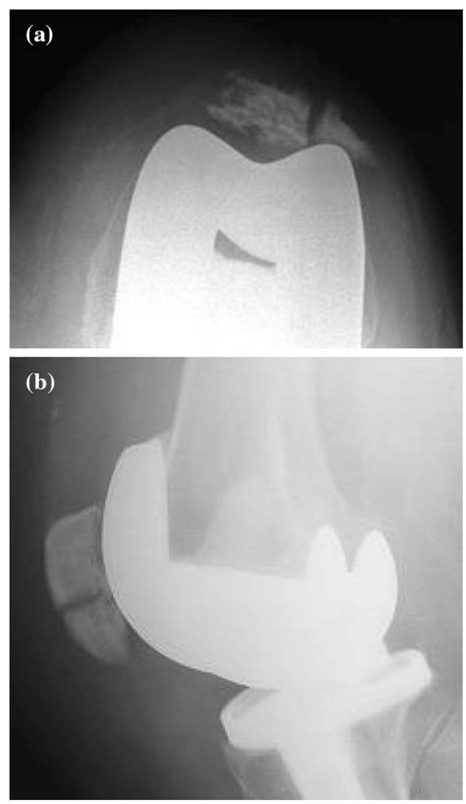

Fig. 2 **a** Merchant view of vertical fracture in a non-replaced patella in a total knee arthroplasty. **b** Lateral view of knee radiograph of a horizontal fracture in a non-replaced patella after total knee arthroplasty

Risk factors

Burnett and Bourne classified the risk factors for these fractures into three groups [7]. The first group relates to patient factors, the second group includes implant design issues and the third group includes intraoperative factors relating to technical error. Patient factors include osteoporosis, the male sex, inflammatory arthropathy and excessive postoperative mobilisation [37]. Implant designs such as cementless implants, implant with single large central lugs and a combination of patellofemoral and abnormally flexed or extended femoral implants are all risk factors for periprosthetic fracture. Technical faults include the inappropriate use of patellar clamps, over-reaming of the native patella, inadvertent asymmetrical reaming of the patella as a result of failing to identify the circumferential osteochondral junction [31], femoral implant malalignment that leads to patellar instability and surgical devascularisation of the patella during the TKA. These are also common causes of anterior knee pain following TKA [40]. It has been shown that routine exposure in TKA carries a significant insult to patellar perfusion. Aggressive excision of the fat pad, which carries blood supply to the inferior pole and concomitant lateral retinacular release in attempt to optimise tracking, greatly increases the risk of perioperative patellar fracture [41]. To achieve exposure, some suggest gentle lateral retraction rather than eversion in order to minimise ischaemia [42]. This is supported by studies which show that eversion of the patella causes ischaemia to the bone, which can lead to avascular necrosis and stress fractures of the patella [43]. The degree of ischaemia has been quantified by laser Doppler flowmetry which showed that eversion reduced blood flow to the patella by 87%, whereas lateral retraction reduced the flow by 47% [42]. Similar findings have been reported by multiple groups who suggested lateral retraction of the patella as an alternative to the practice of everting it [44, 45]. Additionally, disruption of arterial supply in procedures such as bone-patellar tendon-bone autograft harvest may significantly diminish patellar vascularity. This causes reduced gadolinium uptake which has been demonstrated using magnetic resonance imaging (MRI) [46]. Large patellar fixation was a common causative factor of fractures in earlier implant designs. Significantly reduced residual bone thickness is another common factor; a residual bone thickness of less than 15 mm may predispose towards a patellar fracture [47]. However, some studies have reported good outcomes with bone thickness in the order of 12 mm [48]. A patella bone thickness of equal to or less than 10 mm in a revision would indicate a high risk of patellar fracture [46]. To minimise the risk, one could elect not to resurface the patella and perform a gull-wing osteotomy. The use of modern implants with or without grafting may help to restore the original patella thickness. Such implants include cemented bi-convex all-polyethylene implants and trabecular metal (usually tantalum) prostheses [49]. An overstuffed patellofemoral joint (Fig. 3) results in significantly increased joint reaction forces; this is suggested to be a causative factor in periprosthetic fractures. A reduction or complete loss of vascularity of the patella secondary to intraoperative technical error has been linked to multifragmented fractures [24]. Finally, patella maltracking, significant elevation or depression of the joint line and asymmetrical resection of the patella have all been associated with patellar fractures. In the case of significant maltracking, the fractures are often of shear type. Postoperative fractures are more common than intraoperative fractures. They typically present with anterior knee pain which is made more apparent when using stairs. On examination, there is usually pain on palpation of the patella with an associated effusion [50].

Fig. 3 Lateral view of knee radiograph illustrating an overstuffed patellofemoral compartment in a knee arthroplasty with close approximation of the patella to the tibial component

Management

Ortiguera and Berry classified these fractures into three types based on the bone stock of the patella, the integrity of the extensor mechanism and implant stability [36]. Type I fractures have stable implants and intact extensor mechanism, type II fractures are characterised by disruption of the extensor mechanism and type III fractures have loose patellar implants. Type III is sub-categorised into IIIa when there is adequate bone stock and IIIb when there is inadequate bone stock. Other less frequently used classification systems also exist. Fortunately, a significant proportion of these fractures are marginal or vertical. If the extensor mechanism is not disrupted and does not cause implant loosening, it may be treated non-operatively with a good prognosis [51]. In managing these fractures, it is imperative that operative intervention is carefully planned with a view of restoring the integrity of the extensor mechanism, addressing the underlying cause that led to the fracture and ensuring that fixation does not compromise implant stability. Treatment of these fractures includes non-operative management with splinting or operative management. Operative options include open reduction and internal fixation (Fig. 4) with or without implant revision, partial patellectomy with repair of the extensor mechanism or total patellectomy [38]. With intraoperative fractures, it is feasible to fix the fracture and avoid resurfacing while it heals, and to carry out resurfacing later on, should the patient remain symptomatic [24]. Several studies have reported high complication and revision rates alongside poor patient satisfaction in fractures that were fixed with cerclage wiring or tension band technique [36]. This approach is also associated with a high non-union rate of up to 92% [43]. It appears that, in general, the presence of a stable implant and an intact extensor mechanism should be strong indications for non-operative management of these injuries [24].

Fig. 4 Lateral view of knee with a periprosthetic fracture of a non-replaced patella following total knee arthroplasty that has required internal fixation

Patellar clunk syndrome

Background

Patellar clunk syndrome is the most common impingement-related issue following TKA. In this syndrome, a fibrosynovial peripatellar hyperplastic tissue nodule develops adjacent to the patellar implant and engages the patellofemoral articulation when in flexion [52, 53]. In extension, the nodule migrates proximally and gives rise to a painful clunk [54]. This is usually experienced between 30 and 60 degrees of knee flexion, as the knee extends [24]. A milder form of this pathology presents as patellofemoral crepitus and may occur without any associated pain. The incidence varies between 0 and 20% depending on the implant used and usually presents within a year postoperatively [55]. In a recently published series, an incidence of 2.76% was observed with a modern posterior stabilised implant, whereas an incidence of 6% was seen with the use of a different posterior stabilised design [56]. Although not as devastating as periprosthetic infection or fracture, patellar clunk syndrome is one of the commonest reasons for non-revision surgery following TKA [57]. In the past, patellar clunking has been associated with posterior cruciate sacrificing implants, but femoral implant design changes such as trochlea elongation and deepening appear to have reduced the incidence of this problem [27, 58].

Risk factors

Several factors may predispose to patellar clunk syndrome. Patellar clunking may occur in TKA without resurfacing of the patella [59]. Some associated factors include the male sex [60], a small patellar component size [57], patella baja or alta [54], femoral implants with an increased intercondylar box ratio [56, 61], anterior placement of the tibial implant, reduced patellar composite thickness, an increased degree of postoperative knee flexion and previous knee surgery. The individual effect of these risk factors has not been clearly established [58].

Management

Management of patellar clunk involves both primary prevention and management of secondary complications. During TKA, surgeons should avoid excessive proximalisation of the patellar implant or flexion of the femoral implant. Hypertrophied synovial tissue should be carefully excise from the distal quadriceps tendon undersurface. In dealing with patellar clunk syndrome, a thorough assessment should be carried out as an audible clunk may be the only symptom, in the absence of pain. Persistent knee pain and failure of conservative management approaches such as knee flexion exercises can be seen in 50% of patients with patellar clunk [52]. In such cases, arthroscopic debridement of the soft tissue lesion can be considered [62]. Prophylactic antibiotics should be administered during this procedure and superior arthroscopic portals should be used if possible [24]. Care should be exercised to avoid damaging the implant surfaces during arthroscopic debridement. This is often technically challenging due to the presence of intraarticular adhesions [53].

Patellofemoral instability

Background

Patellofemoral instability has an incidence that ranges from 1 to 20% and is generally a consequence of intraoperative technical error [20, 63].

Risk factors

Risk factors that predispose to patellofemoral maltracking and instability can be related to the patient, the implant fitted and the intraoperative surgical approach [64].

Patient-related factors include significant preoperative valgus deformity and preoperative patellar subluxation. Both of these problems are associated with an increased incidence of lateral retinacular release in TKA. Implant type can contribute to patellofemoral instability in several ways. Femoral implants with symmetrical shallow trochlear grooves predispose to patellar subluxation. This issue was addressed by implants with deeper trochlear grooves that are elongated [65], extend more distally and have an elevated asymmetrical lateral trochlear flange [66]. The concept of the Q-angle is important in the prosthetic knee. Alterations to the Q-angle in TKA occur with changes in positioning of the femoral and tibial implants; this can occur without causing a change in the mechanical axis of the knee [67]. If a tibial tray is implanted in excessive internal rotation, the tibial tuberosity becomes displaced laterally along with the line of pull of the patellar tendon. Consequently, this increases the Q-angle. Similarly, if a femoral component is placed in internal rotation, it can cause preferential loading of the lateral facet of the patella and increase the risk of patellar maltracking and subluxation [68]. In femoral implants, referencing rotation of the cuts from the epicondylar axis is a safer practice than referencing off the posterior condylar line [69]. In the latter, erroneous positioning may occur as the posterior femoral condyles are often deficient, especially in knees with valgus deformities [70]. One radiological study has shown that patellofemoral off-set following TKAs with a resurfaced patella does not always translate to worsened postoperative outcomes [71].

Management

Patellofemoral instability can manifest in different ways and management differs accordingly. Patellar subluxation with associated pain is more common than dislocation. Non-operative conservative management is usually inadequate. Therefore, it is crucial for the exact cause to be identified prior to surgically correction. Preoperative radiographic assessment of the patellofemoral joint and CT evaluation of the femoral and tibial implants may provide valuable information such as the degree of implant rotation [72]. For accurate assessment of the anatomical joint line, contralateral knee films can be captured prior to revision in order to determine the degree of joint line elevation. Restoration of joint line according to contralateral films has been correlated to good functional outcome [73]. Furthermore, CT imaging and MRI imaging have both been used alongside computerised algorithms that measure the relationship between bony landmarks to obtain an accurate joint line calculation [74, 75]. Other studies have correlated the degree internal rotation of the femoral and tibial components to the severity of patellar maltracking. They described that with small amounts of internal rotation, the patella tracks laterally and tilts. Moderate internal rotation causes subluxation, whereas severe internal rotation leads to early patellar dislocation and implant failure [76]. The studies used CT imaging to establish the implant rotational profile in cases of patellofemoral complications that did not have a clear cause. The position of the patellar implant is important in cases of maltracking of a resurfaced patella. Medialising the patellar implant may be beneficial as it reduces the need for lateral retinacular release [70]. It may also reduce the patellofemoral joint reaction force in deep flexion [64, 68]. However, excessive medialisation should be avoided as it can lead to lateral tilt of the resurfaced patella. In a significant implant malpositioning with internal rotation of the femoral or tibial component, revision of the component is likely to produce good outcomes [33]. In the

Fig. 5 Lateral knee radiograph demonstrating extensor mechanism failure with patellar tendon rupture and passive traction of quadriceps causing a high riding patella

presence of appropriately aligned implants, management could include an initial lateral retinacular release, followed by more extensive procedures such as proximal or distal realignment [77, 78]. Distal realignment procedures have been associated with an increased risk of patellar tendon ruptures (Fig. 5), non-union of the tibial tuberosity osteotomy and wound complications. A no-thumbs technique may be used with or without interrupted sutures to the medial retinaculum and capsule when assessing patellofemoral tracking and soft tissue tension [24, 64, 70]. When performing lateral retinacular release, the lateral patellofemoral ligament should be released, as this may be sufficient. If further release is necessary, tension should be applied to the lateral soft tissues, such that the lateral superior and inferior genicular arteries may be bluntly dissected and protected. This helps to preserve patellar blood supply, which reduces the incidence of postoperative patellar fractures [64, 79]. Once the superior lateral genicular artery is identified, a full lateral release can be performed from deep to superficial planes, via an incision 1–2 cm lateral to the patellar margin. The synovial membrane, capsule and retinacular fibres are all incised in this process. At this point, subcutaneous fat should become visible. The release can be carried out with Gerdy's tubercle as the margin. The need for lateral release is increased with preoperative valgus deformity, with patellar subluxation and in patients with significantly reduced preoperative range of movement. The use of a vastus-splitting or a sub-vastus approach instead of a medial para-patellar approach has been shown to reduce the need for a lateral retinacular release [70].

Extensor mechanism failure

Background

Failure of the extensor mechanism is an infrequent, yet devastating patellar complication in TKA [65]. Although not directly related to the patella implant, this complication occurs when the patella is everted in order to expose the joint or to prepare the retro-patellar articular surface for arthroplasty. The incidence of extensor mechanism failure ranges from 1 to 10% [24, 79] and includes avulsion of the tibial tuberosity, rupture of the patellar or quadriceps tendons and fracture of the patella [80].

Risk factors

It has several causes, including closed manipulation of a stiff TKA in an attempt to increase the range of movement, intraoperative technical error, poor local vascularity, periprosthetic infection, significant iatrogenic elevation of the joint line, previous knee surgery prior to the TKA and patient factors [33]. The latter include obesity, inflammatory arthropathy, diabetes mellitus and renal disease. It may also occur as a consequence of direct trauma to the knee. Technical errors that may lead to disruption of the extensor mechanism include implant malrotation, an oversized flexed femoral component, excessive resection of the fat pad, inappropriate proximalisation of a lateral retinacular release which weakens the vastus lateralis tendon and insufficient fixation of a tibial tubercle osteotomy [33, 81].

Extensor mechanism failure presents more often in revision TKA [82] and the patellar tendon is more likely to be implicated than the quadriceps tendon. Patellar tendon ruptures present at a mean of 7 months after surgery [83] and usually involves the distal attachment as opposed to intra-substance or proximal ruptures [35]. Clinical presentation varies from the sudden onset of knee pain with an inability to walk or climb stairs, to the progressive onset of these symptoms, without a preceding traumatic event [81].

Caution should be given intraoperatively in order to avoid this complication, especially in revision cases and preoperatively stiff knees. Release of the lateral patellofemoral ligaments prior to patellar eversion, performing a quadriceps snip, tibial tubercle osteotomy, V-Y quadriceps turndown and retracting the patella laterally instead of everting it are a few techniques that can be helpful in avoiding rupture of the extensor mechanism. Although performing a quadriceps snip or a V-Y turndown may improve exposure during the TKA and reduce the tension in the extensor mechanism, it has been reported that this confers a high risk for subsequent quadriceps tendon rupture [35].

Management

In the case of tendon rupture, acute repairs tend to offer better clinical results compared to repairs of chronic ruptures [84]. When dealing with acute ruptures, non-surgical treatment may have a place in managing elderly sedentary patients with multiple co-morbidities who are unsuitable for extensive reconstructive surgery. In this group of patients, the use of a hinged knee brace locked in extension may be adequate. It has also been described that conservative management is effective in cases of quadriceps tendon ruptures with an associated extension lag of less than 20 degrees [80]. Surgical management should be the mainstay of treatment in any other case. Techniques such as augmentation using a hamstring autograft may be helpful in acute ruptures [85]. In the absence of periprosthetic infection, treatment options for ruptures include direct repair (Fig. 6) or reconstruction. In either case, the prognosis is guarded and patient satisfaction is not great [24]. Reconstructive surgery has produced better clinical results compared to primary repair, due to high rates of re-rupture when simple repair is performed without augmentation [81]. Several reconstructive methods have been described, including the use of fresh-frozen allograft, autograft, synthetic graft and soft tissue flaps [82]. Popular allograft choices include the Achilles tendon and whole extensor mechanism allografts (Fig. 7) [82]. Soft tissue flap options include the local medial gastrocnemius rotational flap, which conveys the benefit of simultaneous soft tissue cover of the knee. The two studies that have presented the results of this technique showed favourable results at 21 and 33 months after surgery [86, 87]. This has also been reported in the treatment of infected TKA and has shown to achieve satisfactory results [88]. For patellar tendon repairs, soft tissue cover and wound healing may pose significant challenges. In such cases, additional soft tissue cover in the form of local or free flaps should be utilised. Regardless of the choice of management, compliance to postoperative rehabilitation is a

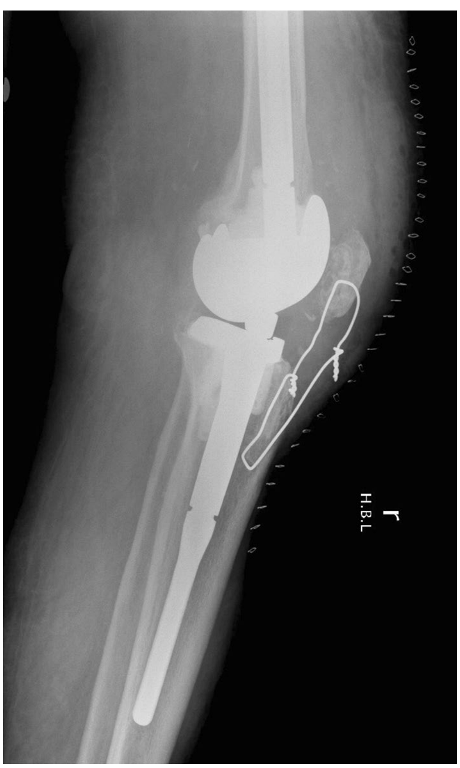

Fig. 6 Lateral view of knee radiograph of repaired patellar tendon rupture protected with cerclage wire

Fig. 7 Lateral left knee radiograph of extensor mechanism Achilles tendon allograft used in the reconstruction of quadriceps rupture following total knee arthroplasty

significant factor affecting functional outcome. In postoperative rehabilitation, it may be better to cast or brace the knee in full extension rather than flexion. This is because persistent extension, caused by casting in full flexion, is a more frequent complication than knee stiffness which can result from casting in full extension [82].

Conclusion

Patellar complications following TKAs have a significant impact on functional outcomes. Careful planning prior to TKA may reduce their incidence. Every patellar complication can be managed in several ways and there remains much contention to the effectiveness of each approach. When revision surgery is necessary, the knee must be approached carefully in order to prevent further complications. Conservative management remains valuable in dealing with a significant number of patellar complications. Moving forward, innovation in prosthesis technology may help to prevent patellar complications and new surgical techniques may be needed to treat them effectively.

Author contributions AA and KT contributed equally with writing the manuscript in consultation with WK and IP. RMJ was involved with the acquisition of images, and KT and WK reviewed the final manuscript.

Compliance with ethical standards

Conflict of interest Angelos Assiotis, Kendrick To, Rhidian Morgan-Jones, Ioannis P. Pengas and Wasim Khan declare that they have no conflict of interest.

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