INTRODUCTION

The leading cause of failure and subsequent revision surgery following total ankle arthroplasty (TAA) is aseptic loosening. However, exact rates of aseptic loosening are difficult to define, since definitions and methods of diagnosing loosening vary considerably in the literature.

In general terms, aseptic (i.e., not caused by infection) loosening refers to the failure of fixation at the bone–implant interface, with resultant micro- or macromotion of the implant relative to the adjacent bone. The challenges in diagnosis arise from the difficulty in detecting the presence of such motion, particularly when it is in the submillimeter range. Thus, surrogate measures, such as radiolucent lines adjacent to implants or increased uptake on bone scan, are typically used to determine whether an implant is loose. However, the accuracy and interobserver agreement of these measures are unknown.

Loosening may occur early, through failure of initial ingrowth of bone into the prosthesis or poor cementing technique. Alternately, loosening of a previously solidly fixed implant may occur months or years after implantation, potentially because of mechanical overload, physiologic bone resorption, or a combination of both at the bone–implant interface. This leads to the varied clinical presentations associated with loosening, which may range from no pain to persistent ankle pain beginning immediately after TAA to late-onset pain beginning many months or years after a previously nonsymptomatic TAA.

Further complicating matters is the recognition that implants may be partially loose. Just as recent computed tomography (CT) scan studies have shown that joint arthrodeses often have bone-to-bone healing across only a portion of the joint surface, it is also apparent that bone ingrowth may occur only over a portion of the bone–implant interface. Depending on the location and amount of ingrowth present, a large enough portion of the implant may not be fixed to bone, thereby creating a cantilever effect, much like a diving board, where one side of the implant is stable, but the other side experiences micromotion.

It is these complexities that make a thorough understanding of aseptic loosening a challenge. The goal of this chapter is to define the etiology, epidemiology, and classification and diagnostic approach to aseptic loosening in TAA, within the limits of this challenging context.

EPIDEMIOLOGY

Aseptic loosening, with or without implant subsidence, is the leading cause of TAA failure. It is notable that some authors categorize aseptic loosening and subsidence separately, while others do not. This has the potential to create confusion, since criteria to separate these two categories are not universal. In general terms, subsidence refers to macroscopic motion of the implant relative to bone, a condition that inherently indicates that the implant is loose, while aseptic loosening implies nonmacroscopic loosening. Hence, both of these terms represent loosening, and for the purposes of this chapter, both will be considered.

Glazebrook et al. performed a systematic review of articles reporting on TAA complications and failures. They included all cohorts with at least 25 patients and minimum 2 years of follow-up. They reported a mean failure rate of 12.4% (range, 1.3% to 32.3%) at 64 months for the 2,386 ankles reviewed. Aseptic loosening and subsidence (i.e., macroscopic loosening) were the most common complications, with a combined rate of 19.4% (10.7% and 8.7%, respectively). Aseptic loosening resulted in failure of the TAA 70.2% of the time that it occurred. On the basis of this rate of failure, they classified aseptic loosening as a high-grade complication, along with deep infection and implant failure.

Haddad et al. performed a meta-analysis pooling TAA outcomes in 10 intermediate- to long-term studies evaluating a total of 852 TAAs. They reported a revision rate of 7% (95% confidence interval, 3.5% to 10.9%) at a mean of 4.7 years postsurgery, with the primary reason for the revisions being loosening and/or subsidence. However, the 5-year survival rate was only 78%.

In a recent study with the longest-term follow-up for any contemporary TAA prosthesis, Brunner et al. found aseptic loosening and subsidence requiring revision in 20 (32%) of 62 Scandinavian total ankle replacement (STAR) cases available for follow-up at a minimum of 10.8 years. Younger age at the time of TAA was associated with an increased risk of loosening.

In one of the earliest studies on a contemporary TAA in North America, Pyevich et al. found that 21 of 85 Agility TAAs had migrated (i.e., were macroscopically loose), although only two underwent revision. Radiolucent lines of 2 mm or less at the bone–implant interface were found circumferentially around the tibial component in 26% of cases. The authors noted that
ETIOLOGY

Little has been written about the etiology of aseptic loosening in TAA specifically. However, aseptic loosening has long been recognized as a major complication of total hip arthroplasty (THA) and total knee arthroplasty (TKA). As a result, most of what is understood about aseptic loosening is taken from THA and TKA literature and extrapolated to TAA. Although the validity of such a wholesale assumption is debatable, many, if not all, of the same contributory principles present in THA and TKA are also present in TAA in some manner. As a result, this section relies primarily on data from THA and TKA experience, while incorporating TAA-specific data where possible.

Shortly after the introduction of prosthetic joint replacement, periprosthetic bone loss (osteolysis) and eventual component loosening were recognized as a main mode of implant failure. Several theories have been postulated to explain this phenomenon. Initially it was attributed to chronic osteitis secondary to mild sepsis or to hypersensitivity reaction to cement also called “cement disease.”6,5 It is now believed that biologic reaction to particulate wear debris plays a central role in the pathogenesis of osteolysis and aseptic loosening of various prosthetic joints. In general, aseptic loosening could result from a harmful combination of mechanical and biologic factors that jeopardize the formation or the survival of bonding between the implant and the host bone.10 These factors could be divided into six broad categories: (1) biologic response to wear debris, (2) intra-articular fluid pressure, (3) implant design, (4) patient-specific characteristics, (5) dormant unrecognized infection, and (6) genetics.

BIOLIGIC RESPONSE TO WEAR DEBRIS

The role of particulate debris in periprosthetic bone loss has been studied extensively since its initial recognition by Willert and Semlitsch11 in 1977. Biologic response to wear particles is now recognized as the leading cause of periprosthetic osteolysis and aseptic loosening of prosthetic hip and knee implants. Polyethylene liners, metal components, and cement all are subjected to wear and produce wear particles. Of these, polyethylene particles are the most important in the pathogenesis of osteolysis. Particle type, size, and number affect the host biologic response.12–15 Green et al.15 describe a “critical size” range (0.3 to 10.0 μm) that the wear particles must fall within in order to trigger a macrophage-based inflammatory response. Critical-size wear particles are phagocytosed by macrophages, triggering a cascade of intracellular reactions leading to the production of inflammatory mediators, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and macrophage colony-stimulating factor (M-CSF). TNF-α induces fibroblast proliferation, tissue fibrosis, and activation of osteoclasts. This leads to extensive periprosthetic bone resorption.14,15 As well, wear debris has a direct inhibitory effect on osteoblast bone formation.16

Schmalzried et al.17 introduced the concept of effective joint space. The effective joint space is the space surrounding the prosthetic joint and encompassing all of the implant–bone surfaces through which synovial fluid can flow and disperse wear particles. This concept explains how wear particles reach areas far from the articular surface.

INTRA-ARTICULAR FLUID PRESSURE

Inflammation triggered by wear debris particles and/or intra-articular exposure of bone which is normally sealed from the joint results in overproduction of synovial fluid and a potential increase in intra-articular fluid pressure; this, in turn, may result in abnormal bone perfusion and ischemia leading to necrosis, osteocyte death, and osteolysis. This effect was demonstrated in animal experimental studies.18,19 Robertsson et al.20 documented a higher intra-articular pressure in 18 hips diagnosed with aseptic loosening in comparison to stable hips.

IMPLANT DESIGN

Immediate implant stability is critical in achieving strong bony ingrowth at the bone–implant interface21 and failure of ingrowth may lead to early aseptic loosening of the prosthesis. Younger et al.22 have demonstrated significantly greater micromotion immediately after implant insertion for Agility TAA implants compared to STAR implants, and have correlated this with a significantly higher rate of revision due to aseptic loosening in Agility TAAs compared to STARs. This finding suggests that the early circumferential radiolucent lines identified by Pyvich et al.23 in 26% of Agility TAA cases may be due to failure of initial bone ingrowth secondary to insufficient initial implant stability.

Achieving solid initial implant fixation may be affected by several implant design factors. The addition of keels or stems to the implant, for example, may provide a larger fixation surface, increasing the implant initial stability, reducing micromotion and mechanical stresses at the bone–implant interface, thereby potentially increasing the chance of successful bonding.23,24 Ries et al.25 retrospectively compared standard and short-keeled TKA and showed an increased risk of aseptic loosening in the short-keeled TKAs.

For stemmed implants, increased stem flexibility may result in decreased bony ingrowth, increased fibrous ingrowth, and increased risk of implant loosening.26 On the other hand, increased stem stiffness may result in more stress shielding and periprosthetic bone loss.27,28

Adding a porous or hydroxyapatite-coated surface to the implant may help seal the implant–bone interface. This seal prevents the wear particles from reaching the effective joint space surrounding the implant and reduces wear debris-triggered periprosthetic osteolysis.29–32 The presence of unused screw holes may provide a portal for wear particles to flow into the surrounding bone and may increase the risk of osteolysis33 and eventual subsequent loosening.
PATIENT-SPECIFIC CHARACTERISTICS

Patient variables may have an effect on the development of aseptic loosening. Younger patients with higher activity levels generate more stresses across the prosthetic joint, which may increase wear rates and subsequently the risk of aseptic loosening compared to older less-active patients. In a case–control study comparing 725 patients with THA aseptic loosening to 4,310 matched controls, older patients, female gender, and patients with restricted mobility were associated with decreased risk of aseptic loosening. The author attributed this finding to decreased patient activity level. Other authors have reported similar findings.

Theoretically, factors like patient smoking and usage of non-steroidal anti-inflammatory drugs may have an effect on early osteointegration. However, no statically significant association was found between these factors and loosening. Other medical conditions such as hereditary hemochromatosis may result in a higher risk of aseptic loosening.

DORMANT UNRECOGNIZED INFECTION

Although aseptic loosening indicates implant loosening in the absence of deep joint infection, it is postulated that some aseptic loosening cases may be secondary to a dormant low-grade unrecognized infection. Glycocalyx biofilm, which forms on the surface of an infected prosthetic joint, creates a barrier concealing the infecting organisms and makes obtaining a positive culture difficult.

Several studies have documented the detection of bacterial DNA in tissue samples from patients undergoing revision for aseptic loosening of a joint prosthesis. In a recent multicenter study, 175 THA patients undergoing revision surgery for aseptic loosening were investigated for a possible infection with both cultures and rRNA polymerase chain reaction. According to a predefined classification system, 7 patients were classified as infected and an additional 15 patients were classified as suspected of having infection. The authors concluded that between 4% and 13% of patients with the preoperative diagnosis of aseptic loosening were infected.

Parvizi et al. retrospectively reviewed two groups of patients who underwent revision THA for aseptic loosening: one group had an overt infection or a positive intraoperative culture and another group had no evidence of infection. The frequency of abnormal C-reactive protein (CRP) was 48% in the first group and 27% in the second group. They concluded that some patients with presumed aseptic loosening have abnormal serologic indicators suggestive of prosthetic joint infection that either has escaped diagnosis or was not adequately investigated.

GENETICS

Genetic susceptibility has been proposed as a potential factor that may increase the risk of aseptic loosening of prosthetic joints in certain patients. Variations in the genetic coding influence the transcription of certain proteins and subsequently increase the individual’s susceptibility to certain diseases. This variation is known as “genetic polymorphism.” Godoy-Santos et al. investigated the frequency of polymorphism of the genes promoting matrix metalloproteinase (MMP)-1, a metalloprotease responsible for extracellular matrix collagen degradation in a group of 27 patients who underwent uncemented THA and had evidence of early aseptic loosening compared to 31 controls. The allele 2G (responsible for more collagenase activity) was observed at a frequency of 29.97% in the control group compared to 83.33% in the aseptic loosening group. Malik et al. performed a case–control study comparing the frequency of genetic polymorphism of the osteoprotegerin (OPG) and RANK genes in patients who underwent cemented THA. The study included a group of 91 patients with aseptic loosening, 71 patients with deep infection, and 150 controls. They found that the A allele (P < 0.001) and genotype A/A (P < 0.001) for the OPG-163 SNP and the RANK +575 (C/T SNP) T allele (P = 0.004) and T/T genotype (P = 0.008) were associated with aseptic failure. Although studies in this field are still preliminary and their current clinical applications are limited, genetic investigations may eventually help identify patients with high risk for aseptic loosening.

In summary, multiple factors contribute to the development of aseptic loosening. Given the relatively early state of TAA compared to THA and TKA, an understanding of which of these factors is of foremost importance is lacking. However, the relatively higher rates of early loosening and cystic osteolysis seen in TAA suggest that implant design and initial stability, along with the biologic response to wear debris, are likely to critical issues.

CLASSIFICATION

Despite numerous studies reporting on aseptic loosening as a common complication and cause of failure of total ankle arthroplasty, there is no validated or commonly cited classification for aseptic loosening.

The creation of a classification for aseptic loosening is made challenging by the lack of validated and agreed-upon criteria as to what constitutes “loosening.” In broad terms, an implant can clearly be deemed to be loose if it is seen to visibly move in relation to bone under direct or arthroscopic vision or on real-time fluoroscopy. Beyond these obvious situations, however, clearly defining what constitutes a loose component is difficult. To further complicate matters, Easley et al. have pointed out that not all radiologically identified changes in implant position or radiolucencies are associated with failure and revision. Hence, even if an implant is clearly demonstrated to have features suggestive of loosening, it can still be debated as to whether it should be considered “loose” if it is not clinically problematic.

As a surrogate for loosening, some authors have defined classifications of subsidence and radiolucencies adjacent to TAA implants. However, Hanna et al. have clearly demonstrated that plain radiographs fail to detect 35% of osteolytic lesions associated with TAA and underestimate the size of the lesions by a factor of 3 when compared to CT scans. Similar findings have recently been demonstrated by Kohonen et al. as well. In view of this, any future radiologic classification of loosening or periprosthetic lucencies will almost certainly require CT scan imaging.
DIAGNOSTIC APPROACH TO ASEPTIC LOOSENING

The diagnosis of aseptic loosening in TAA is often a diagnosis of exclusion. Typically, a patient presents with either persistent or new-onset ankle pain, sometime after undergoing TAA. The diagnostic approach to aseptic loosening is therefore, in actuality, the approach to evaluating the painful TAA.

CLINICAL EVALUATION

A thorough clinical history is necessary to identify other potential causes of post-TAA ankle pain. Of foremost importance is the determination of any history of infection in the ankle, either prior to the TAA or at any time after. A history of slow wound healing is common after TAA, and may raise the possibility of deep infection as well. Any history of current skin redness, significant swelling, or fever should raise suspicion of possible infection as well.

The nature and location of the ankle pain may also be important, though may not readily differentiate between pain secondary to bone or soft tissue impingement and loosening. Pain secondary to loosening may be expected to be activity-mediated, while pain due to infection less so.

Clinical examination is also important, though there are no clear distinguishing features of loosening as compared to many other causes of ankle pain. Ultimately, the primary goals of clinical evaluation are to aid in ruling out the possibility of ankle infection and to define the severity of the patient’s problem. It is only through an understanding of how debilitating the patient’s ankle pain is that appropriate indications for further evaluation and surgery can be determined.

LABORATORY EVALUATION

Since low-grade infection may be a possibility in all painful TAAs, each patient presenting with a painful TAA should undergo CRP and erythrocyte sedimentation rate (ESR) testing, in keeping with the Clinical Practice Guideline of the American Academy of Orthopaedic Surgeons. If the CRP and/or the ESR are abnormal, then an aspiration of ankle joint fluid should be obtained and sent for culture and cell count.

RADIOGRAPHIC EVALUATION

Standing anteroposterior (AP), mortise, and lateral radiographs of the ankle are necessary, and ideally are compared to prior radiographs. Evidence of any change in implant position or the development of periprosthetic lucencies is sought. Additionally, other potential causes of ankle pain, including bony impingement in the medial or lateral gutters of the ankle, significant implant malalignment, the development of heterotopic ossification, or arthrosis in the subtalar or talonavicular joints, should be identified.

CT scanning is recommended to better assess the presence and sizes of periarticular lucencies, to assess the subtalar and talonavicular joints, and to further clarify any signs of impingement. On its own, however, CT scanning cannot be relied upon to clearly define the presence of implant loosening.

NUCLEAR MEDICINE EVALUATION

Bone scans are commonly ordered for the evaluation of painful TAA. Although very sensitive, the results are nonspecific and can be misleading (Fig. 13.1).

More recently, high-resolution bone scans have been combined with CT scans to create single-photon emission computed tomography (SPECT)–CT scans. Such imaging allows for highly accurate identification of areas of increased physiologic activity in bone adjacent to the prosthesis, allowing differentiation of pathology that involves the implants versus that which does not (Figs. 13.1 and 13.2).

Figure 13.1. An illustration of bone scan use in the assessment of the painful total ankle replacement in a 73-year-old woman 4 years after TAR with worsening diffuse ankle pain.

A: X-rays demonstrate no evident problems.

B: Bone scan shows diffuse uptake in both tibial and talar regions.

C: CT scan demonstrates bone well apposed to both tibial and talar implants (arrows) with no evident loosening.

D: SPECT–CT, used to clarify status, clearly demonstrates gutter impingement and “hemiarthroplasty pain,” with no evidence of loosening at bone–implant interface.
Figure 13.2. An illustration of SPECT–CT scan used to rule out loosening in a 57-year-old woman 2 years after TAR with persistent medial and lateral ankle pain. A: Bone scan shows diffuse uptake in both tibial and talar regions, worrisome for loosening. B: SPECT–CT clearly demonstrates syndesmosis degeneration and medial gutter impingement (arrows). There is no bone scan signal adjacent to implants, ruling out loosening.

Localized high-intensity signal on SPECT–CT adjacent to the tibial or talar component is highly suspicious for implant loosening (Fig. 13.3). Although the sensitivity and specificity of SPECT–CT for aseptic loosening in TAA remain to be defined, it currently remains the most valuable diagnostic tool in the authors’ practice.

ANKLE ARTHROSCOPY

The use of ankle arthroscopy after TAA to treat impingement lesions has recently been described. The authors have utilized this technique as well, and have also used ankle arthroscopy to assess TAAs for potential loosening in
six cases. In all of these cases, no loosening of the implants could be detected, though eventual revision surgery in two of these cases did demonstrate loosening. As a result of these false negatives, the authors have moved away from the use of ankle arthroscopy as part of the diagnostic workup for aseptic loosening.

**INDICATIONS FOR REVISION SURGERY**

The primary indication for revision surgery in the setting of aseptic loosening is debilitating ankle pain. However, if pain is not severe or limiting, but loosening is present or suspected, treatment must be individualized. The option to defer revision surgery is generally reasonable in such situations, though regular reassessment is mandatory to ensure that progressive bone loss, which might preclude future revision, does not occur.

In the authors’ current practice, in patients with a clinical evaluation that is not suggestive of past or current infection and a CRP and ESR that are within the normal range, deep infection is considered to be excluded and aseptic causes for the pain are sought. If radiographs and SPECT–CT scan do not demonstrate evidence of significant impingement, malalignment, adjacent joint arthritis, or heterotopic ossification, then aseptic loosening is suspected. If SPECT–CT scan demonstrates high-intensity uptake at the bone–implant interface of the tibial or talar components, then aseptic loosening is considered highly likely and revision surgery is considered. However, it is important to recognize that aseptic loosening may be present concurrently with other causes of ankle pain, and differentiating between them may not be possible.

A challenging scenario may arise where multiple potential causes of pain are identified and low-intensity uptake at the bone–implant interface is found on SPECT–CT scan. In these circumstances, if the patient’s pain warrants surgical intervention, then an operative plan is formulated to address all of the potential causes of pain identified preoperatively. This includes readiness to revise one or both of the components if they are found to be loose. The techniques necessary to successfully perform revision TAA are described in the subsequent chapters.
Aseptic loosening is the major cause of failure and revision surgery in TAA. The underlying causes are currently under study, and are likely analogous to the factors leading to aseptic loosening in THA and TKA. The diagnosis of aseptic loosening is often one of exclusion and can be clinically challenging, although the addition of SPECT-CT scanning offers the potential to improve this considerably. Revision TAA is warranted after infection has been ruled out and all other aseptic causes of ankle pain have been accounted for and loosening is confirmed or strongly suspected.

REFERENCES