Clinical Factors, Disease Parameters, and Molecular Therapies Affecting Osseointegration of Orthopedic Implants

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Abstract Total hip and knee arthroplasty are effective interventions for management of end-stage arthritis. Indeed, about seven million Americans are currently living with artificial hip and knee joints. The majority of these individuals, however, will outlive their implants and require revision surgeries, mostly due to poor implant osseointegration and aseptic loosening. Revisions are potentially avoidable with better management of patient-related risk factors that affect the osseointegration of orthopedic implants. In this review, we summarize the published clinical literature on the role of demographics, biologic factors, comorbidities, medications, and aseptic loosening risk. We focus on several systemic and local factors that are particularly relevant to implant osseointegration. Examples include physiological and molecular processes that are linked to hyperglycemia, oxidative stress, metabolic syndrome, and dyslipidemia. We discuss how orthopedic implant osseointegration can be affected by a number of molecular therapies that are antiresorptive or bone anabolic (i.e., calcium, vitamin D, bisphosphonates, calcitonin, strontium, hormone replacement therapy, selective estrogen receptor modulators).

Keywords Arthroplasty · Osseointegration · Aseptic loosening

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Introduction

Total hip (THA) and total knee (TKA) arthroplasties are effective and relatively safe procedures for management of end-stage arthritis of the hip and knee joints. The incidence of these procedures has increased almost exponentially in recent years with over one million procedures performed annually in the USA [1]. As a result of the high incidence and the long life expectancy following surgery, there are currently seven million individuals (about 2 % of the US population) with a history of THA and/or TKA [2]. Unfortunately, a substantial proportion of these individuals will outlive their implants and require expensive revision surgeries. Although revision is considered an avoidable outcome, relatively little is known about factors that influence the risk of revisions in THA and TKA. The etiology of revisions is multifactorial including patient, implant, surgical, and healthcare delivery factors. The causal contribution of each of these factors likely differs during the lifetime of an arthroplasty patient. For example, surgical and healthcare delivery factors have a significant influence on the short-term risk of complications, whereas patient and implant factors can have a large influence on the osseointegration potential of the implants and the subsequent risk of revisions, particularly due to aseptic loosening.

This review paper provides a summary of the published clinical literature on patient-related risk factors, diseases, and molecular therapies that may affect osseointegration of orthopedic implants in THA and TKA patients. We focus almost exclusively on the potential biological and molecular effects of the patient-related risk factors and deliberately exclude implant, surgical, and healthcare delivery factors. Readers are also encouraged to refer to other comprehensive reviews and manuscripts on this topic [3, 4, 5]. Of note, the evidence for each of the patient-related risk factors is variable. Some are studied extensively in large clinical studies, whereas others are

only studied experimentally *in vitro* and *in vivo*. We nevertheless provide a critical discussion of selected disease and treatment factors of interest based on biological plausibility, basic science, and/or clinical evidence.

Demographic Factors

Age Age is a well-known risk factor for revision in both THA and TKA [3, 6–9]. The majority of large, registry-based cohort studies reported a linear increase in the risk of revision with decreasing age. The age effect is not simply due to comorbid joint pathologies in younger patients and persisted when cohorts were restricted to osteoarthritis patients. For example, in one of earliest studies reporting on the prognosis of THA in Sweden, patients younger than 55 years of age at the time of THA surgery had the highest risk of revisions for aseptic loosening followed by decreasing order in the 55–64, 65–74, and >75 years olds [10]. In another large cohort of more than 30,000 TKA surgeries from Finland, the risk of aseptic revisions was almost 5-fold higher among patients younger than 55 years as compared to patients older than 65 years [11]. In studies from our group, younger THA and TKA patients experienced a higher risk of revision irrespective of implant type [12–14]. Although the increased risk of revision in younger patients has been almost entirely attributed to higher activity levels and higher loading on the joints, it is unknown whether other age-related factors affect bone quality and, in turn, contribute to the excess risk of revisions in young patients. We believe that further studies are warranted to better understand the age effect, such as studies of periprosthetic bone remodeling [15] and *in vivo* and *in vitro* studies of the potential role of bone mineral density, bone mineral content, peak bone mass, and bone turnover markers on osseointegration and risk of aseptic loosening in THA and TKA. Because tissue regeneration around implants depends on endogenous mesenchymal stem cells, it will be informative to assess whether the molecular properties of stem cells and their ability to support perimplant bone formation are altered.

Sex Sex is another well-studied but often ignored risk factor for revision in both THA and TKA. In the majority of studies, men have at least a 1.5- to 2-fold higher risk of aseptic revisions than women [3, 6, 13, 14, 16]. Yet, this is not a universal finding. For example, in our recent follow-up analysis of revision THA, women have a significantly higher risk of repeat revision for aseptic loosening than men [12]. Similarly, within the Kaiser Permanente Joint Registry, women have a higher risk of aseptic THA revision than men, whereas there was no difference between men and women in the risk of aseptic TKA revision [8, 17]. These differences across studies and joint type suggest that more research is justified to better understand the sex differences in osseointegration potential of

implants. Sex differences cannot be solely attributed to anatomical, kinematic, and implant-type differences between men and women. It remains to be seen how anatomical and mechanical differences influence the risk of different failure mechanisms on different joints, and whether hormonal factors across the lifespan may play a role in mediating osseointegration, and potential age-related risk of aseptic loosening. Future studies are warranted in this area to understand the contributions of age, menopausal status, and age at menopause to the risk of aseptic loosening and revision in women. Furthermore, evidence from osteoporosis research indicates that, although estrogen deficiency is traditionally viewed as the main contributor of bone loss [18], other estrogen-independent factors also affect bone quality and some of these are more relevant to the solid fixation of implants during THA and TKA, e.g., mechanical loading.

Race Despite the recognition of racial and ethnic differences in arthritis disease severity and access to THA and TKA surgery [19, 20], surprisingly, little is known about variation in the risk of complications and revisions in different racial groups. In two recent studies from the Kaiser Permanente Registry, Hispanic and Asian Americans had a lower risk of aseptic revisions, whereas African Americans had a higher risk of aseptic revisions in TKA only [7, 8]. Presumably, the etiology of racial and ethnic differences in outcomes is multifactorial and includes healthcare delivery factors, insurance status, and patient preferences as well as interracial differences in lifestyle factors (i.e., nutrition, body mass index, physician activity). Yet, there is also ample evidence from other diseases about the potential role of biological and genetic factors. For example, African American women have stronger bones and have a lower risk for osteoporotic fracture than White women [21]. It remains to be seen whether stronger bones in African Americans also translate into better osseointegration potential and lower risk of revision, independent of the influence of other factors. Therefore, studies of racial differences can provide clues about the etiology of osseointegration in arthroplasty. In this context, ethnically prevalent genetic variations, as well as epigenetic modifications associated with lifestyle and other environmental factor exposure changes, may contribute to new bone formation around implants.

Obesity Obesity is the main risk factor for osteoarthritis, and at least half of the arthroplasty patients are obese with a body mass index higher than 30 kg/m² [22]. Obesity is associated with several adverse outcomes in THA and TKA. Yet, evidence is conflicting in terms of the risk of aseptic loosening [23–27]. This is, in part, due to statistical methodology and information loss through restriction of body mass index (BMI) categories and, in part, by inability to account for activity levels in the majority of studies. In one pooled analysis and two recent studies [26–28], the risk of aseptic loosening was about 2-fold

higher among individuals with a BMI above 35 kg/m². Supported by basic science evidence, this has been attributed to increased mechanical stress and more frequent limb malalignment in obese patients. These findings were not corroborated in other studies [7, 8, 24]. For example, in a large cohort of THA patients from our institution, increasing BMI was not associated with the risk of mechanical failure of the implant or aseptic loosening, but BMI correlated negatively with the risk of revision for bearing surface wear [24]. It has been suggested that obesity-associated stress on implant interfaces may be offset by lower activity levels in very obese patients. Yet, the potential contribution of metabolic effects of the fat mass at different body sites (e.g., visceral versus subcutaneous) on osseointegration of the implants is currently unknown. At the population level, although obesity is traditionally associated with higher bone mineral density and a lower risk of fractures, emerging evidence suggests that this is not universally true [29]. It is unknown whether sex, age, bone mineral density, and the severity or the type of obesity could modulate osseointegration and the risk of aseptic loosening in THA and TKA. Evidence from bariatric surgery studies in arthroplasty patients is also particularly relevant in this regard.

Smoking and Alcohol Consumption Smoking and alcohol consumption are two important behavioral risk factors for a number of adverse outcomes following surgery, including THA and TKA. Excessive amounts can theoretically increase the risk of aseptic loosening due to delayed bone healing and bone regeneration [30, 31]. In a pooled analysis of THA studies, smokers had a 3-fold higher risk of aseptic loosening than non-smokers [32]. Yet, in a recent study by our group, smoking was not associated with the risk of aseptic revisions, whereas alcohol use was associated with a significantly lower risk of revision [33]. Heavy alcohol use was associated with dislocation but not aseptic loosening in two earlier studies [34, 35]. The reasons for the discrepant findings are unknown but potentially include methodological differences, because risk factor data collection is typically limited to the immediate perioperative period. More studies are warranted that examine risk of aseptic revisions with longitudinal risk factor data collection. This is important since both smoking and alcohol can theoretically affect osseointegration potential through their detrimental effects on bone mineral density [36, 37].

Surgical Indications

Although the majority of patients undergoing THA and TKA are degenerative osteoarthritis patients, about 10–15 % have other underlying diseases and operative indications, including post-traumatic degenerative arthritis, as well as rheumatoid arthritis and other joint-related inflammatory processes, avascular necrosis (steroid-induced, post-traumatic, or idiopathic),

congenital hip conditions (developmental dysplasia), and neoplasias. Rheumatoid arthritis is perhaps the best studied condition. THA patients with inflammatory arthritis had a significantly lower risk of aseptic loosening than osteoarthritis patients [16]. In contrast, THA patients with hip dysplasia had twice the risk of aseptic loosening than osteoarthritis patients. In more recent studies, patients with rheumatoid arthritis experience a higher risk of revision due to infection and dislocation, but the long-term risk of aseptic loosening is similar to patients with osteoarthritis [6, 38–41]. There are no data on the long-term revision risk in patients with other forms of inflammatory arthritis. Developmental dysplasia of the hip is associated with poor bone stock and various technical problems resulting in a higher risk of aseptic loosening in THA [42]. Similarly, THA for femoral neck fractures is associated with a higher risk of aseptic loosening [43]. TKA following open reduction and internal fixation of a tibial plateau fracture presents similar technical challenges but does not increase the risk of aseptic loosening [44]. Even though evidence for a direct impact of skeletal degeneration and inflammatory processes on patient risk remains inconclusive, it is likely that the physiological condition of the patient will modify the cellular and molecular processes that guide skeletal tissue repair around the implant after surgery.

Comorbidities

Osteoporosis Osteoporosis is the most common condition affecting bone quality in the elderly. It affects about one third of women and one fifth of men aged 50 years and older in the USA [45]. Although osteoarthritis and osteoporosis are traditionally viewed to have an inverse relationship [46], contemporary understanding of both diseases recognizes different disease phenotypes, including the presence of osteoporotic, erosive, and bone-forming osteoarthritis phenotypes [46, 47–49]. Indeed, several studies found a high prevalence of osteoporosis in THA and TKA patients [50–53]. Yet, little is known about the effects of low bone mineral density on arthroplasty outcomes and the potential beneficial or adverse effects of antiresorptive (i.e., bisphosphonates) and bone anabolic osteoporosis medications. So far, studies in osteoporosis patients are relatively small and focused mostly on implant fixation with cemented versus uncemented prostheses or implant migration [54]. There are no studies examining the interactions of bone mineral density, BMI, and other factors (e.g., inflammation) to modify arthroplasty outcomes. Consequently, at present, there is little emphasis on the evaluation of bone quality in arthroplasty candidates. This is unfortunate because bone mineral density and bone turnover markers may offer potential for risk stratification [55]. As summarized below, there is increasing in vivo and in vitro evidence for the potential beneficial effects of bisphosphonates in arthroplasty patients.

Diabetes Mellitus Emerging evidence in the last decade suggests that diabetes mellitus is a risk factor for osteoarthritis, leading to the concept of a “diabetes-induced osteoarthritis” [56, 57, 58•, 59, 60]. In vivo evidence suggesting potential role of diabetes control in reducing the severity of osteoarthritis led to studies that specifically examine the potential protective role of antidiabetic drugs in delaying osteoarthritis progression and the risk of arthroplasty [61]. Despite promising in vivo data, clinical studies to date are negative. It remains to be seen whether insulin and/or other antidiabetic drugs delay the progression and severity of osteoarthritis and delay the need for joint arthroplasty. In contrast, individuals with type 2 diabetes may have an increased fracture risk, despite normal bone mineral density [62]. The mechanisms underlying bone fragility associated with diabetes are not completely understood but include effects of obesity, hyperglycemia, oxidative stress, and accumulation of advanced glycation end products, which lead to altered bone metabolism, structure, and strength [63, 64]. In THA and TKA, diabetes mellitus strongly affects functional and perioperative clinical outcomes [65–70], but long-term effects on the risk of aseptic revisions are mostly negative. In two large studies from the Scandinavian Arthroplasty registries, diabetes mellitus was associated with an increased risk for revision due to deep infection but not aseptic loosening [71, 72]. In the Kaiser Permanente Registry, presence of diabetes was a risk factor for aseptic loosening in TKA but not in THA [7, 8]. In a recent study from our institution [73], insulin-dependent diabetes was associated with a 2-fold higher risk of revision in TKA, but not necessarily due to aseptic loosening. Collectively, even though there is no clear clinical evidence yet, conceptually, it is quite plausible that diabetes and hyperglycemia have systemic and/or local effects on healing of the bone-implant interface [58•].

Metabolic Syndrome and Dyslipidemia There is emerging evidence suggesting that dyslipidemia, and particularly high oxidized LDL-cholesterol, has a role in osteoarthritis pathology independent of obesity and mechanical overload [74–77]. The hip, knee, and hand joints may have different susceptibility to metabolic and non-metabolic factors [78, 79]. In fact, osteoarthritis is currently recognized not as a single entity, but a variety of conditions with distinct genetic, developmental, metabolic, and traumatic causes that converge on a common disease phenotype [47, 58•]. Unfortunately, despite the high prevalence of obesity, metabolic syndrome, and dyslipidemia in the arthroplasty population and higher risk of associated complications [80], it is unknown whether the presence of a metabolic syndrome affects osseointegration and aseptic loosening risk in THA and TKA. If this is the case, lowering cholesterol levels or local inflammation systematically or locally can be an effective treatment strategy for improving osseointegration. Progress in the bone and fat tissue connection is remarkable [81] with

demonstration of several systemic and local interactions that are particularly relevant in implant osseointegration research.

Collectively, our review of the clinical literature indicates that, first, indirect evidence from osteoporosis and obesity studies provides etiological clues about the potential effects of comorbidities on osseointegration potential of implants. Second, recognizing the heterogeneous nature of osteoarthritis, the main underlying indication for THA and TKA, future clinical studies should distinguish osteoarthritis phenotypes by reporting outcomes separately in men and women, patients with or without history of trauma, athletes, and non-athletes, as well as obese and non-obese patients. Figure 1 broadly illustrates the emerging paradigms in pathogenesis of arthritis and how osseointegration potential and prognosis likely vary in different osteoarthritis phenotypes. A range of systemic and local factors affect osseointegration, and the relative contribution and host response likely differ in each osteoarthritis phenotype. Third, a number of other common diseases of aging and their treatments are also of interest, including hypertension, renal disease, various forms of cardiovascular disease, heart failure, depression, Parkinson’s disease, and Alzheimer’s disease [72]. Yet, at the time of this review, evidence is limited for inclusion in this review. Finally, both direct and indirect evidence for the role of genetic and epigenetic risk factors on age-related changes in bone metabolism and osteoarthritis may offer solutions for improving osseointegration [82–85].

Medications

The medication classes of interest within the context of orthopedic implant osseointegration are antiresorptive drugs (i.e., calcium, vitamin D, bisphosphonates, calcitonin, strontium, hormone replacement therapy, selective estrogen receptor modulators), bone anabolic drugs (i.e., parathyroid hormone, teriparatide), and other drugs for comorbidities that are common in elderly patients.

Calcium and Vitamin D Calcium and vitamin D are essential for bone development, skeletal remodeling, and fracture repair. Yet, there is no evidence to support the efficacy of vitamin D supplementation in fracture prevention, and screening and supplementation are not recommended among asymptomatic adults. Similarly, vitamin D supplementation has no benefit in knee osteoarthritis patients [86]. Vitamin D deficiency is common in arthroplasty patients [52], but uncertainty remains concerning whether vitamin D supplementation may help with osseointegration in THA and TKA patients, particularly among those with low bone mineral density and/or low vitamin D levels.

Bisphosphonates Bisphosphonates are the most commonly used antiresorptive drugs for the treatment of osteoporosis.

Fig. 1 Etiological paradigm of osseointegration in total joint arthroplasty

They are also studied extensively in animal models, in vitro experiments, and clinical studies to improve the osseointegration of implants in THA and TKA patients [87]. Clinical evidence strongly supports bisphosphonate effects on both the intermediate (i.e., periprosthetic bone loss and implant migration) and clinical outcomes. Systemic, long-term use of bisphosphonates significantly reduces the risk of revision in arthroplasty patients [87–93, 94, 95–97]. For example, in a meta-analysis of four studies, THA and TKA patients who used bisphosphonates for a long period had a 50 % reduction in their risk of implant revision [94]. Yet, the optimal timing for initiation of bisphosphonates in arthroplasty patients is unknown, especially considering the periprosthetic changes during the early months. It is possible that an early initiation may, in fact, delay osseointegration [98]. It is also unclear whether local administration is more efficacious than systemic use, particularly in patients with normal bone mineral density.

Calcitonin Calcitonin is another antiresorptive agent that inhibits osteoclast formation and activity. Data supporting the possible effects of calcitonin on osseointegration has been collected from animal studies [99], although the homeostatic balance between osteoblasts and osteoclasts in bone-forming tissues needs to be further investigated in human subjects.

Strontium Strontium has both antiresorptive and bone anabolic properties and affects fracture healing differently in normal and osteoporotic bones. Experimentally, it improves osseointegration, but clinical studies are lacking.

Hormone Replacement Therapy Hormone replacement therapy has antiresorptive effects and has been the cornerstone of prevention of postmenopausal bone loss and osteoporosis-related fractures until adverse cardiovascular effects were recognized in late 1990s. Although the prevalence of hormone replacement therapy is currently low, its use was high during the 1980s and 1990s, and investigators observed a 40 % reduction in the risk of revision among patients who continued use for at least 6 months after THA-TKA surgery [100]. This finding provides further support for potential adverse effects of estrogen deficiency and possible beneficial role of antiresorptive drugs on the osseointegration of orthopedic implants. It remains to be seen whether the local enhancement of implants with estrogen can improve osseointegration, particularly in estrogen-deficiency-related osteoarthritis.

Selective Estrogen Receptor Modulators Selective estrogen receptor modulators do not have the steroid structure of estrogen but have a tertiary structure that allows binding to the estrogen receptors to exert agonistic effects on the bone. The effects of selective estrogen receptor modulators on bone mineral density may be less than bisphosphonates [101]. So far, there are no animal or clinical studies that relate selective estrogen receptor modulators to the outcomes of THA and TKA.

Vitamin C Vitamin C is a micronutrient found in fruits and vegetables and has been shown to mediate osteoclastogenesis and osteoblastogenesis resulting in better bone health [102, 103]. Studies reporting on associations between vitamin C intake and fracture risk are promising, but there are no in vivo

or in vitro studies on the possible effects of vitamin C in arthroplasty patients.

NSAIDs and Opioids NSAIDs and opioids play an important role in pain management both before and after THA and TKA. Several studies, mostly in fracture patients, suggest that NSAIDs and opioids interfere with bone growth [104, 105]. Yet, so far, studies in THA and TKA are few and conflicting with respect to osseointegration and the subsequent risk of aseptic loosening [106–109].

Insulin Insulin is generally regarded as a bone anabolic agent [60, 110]. Although some studies showed an excess risk of fracture in insulin users, this is likely due to insulin use serving as a marker of diabetes severity rather than direct effects of insulin on the bone. Among other oral hypoglycemic agents, data for metformin is neutral, whereas thiazolidinediones are associated with a doubling of fracture risk in women [111]. Clinical studies on the effects of insulin and oral hypoglycemic agents are lacking in THA and TKA patients.

Statins Statins have previously been shown to be associated with higher bone mineral density and reduced fracture risk in a number of observational studies [112–114], but these findings are not corroborated in clinical trials [115, 116]. The discordance between observational studies and randomized trials is explained by selection bias, confounding by indication, or a “healthy-user” phenomenon [117]. Systemically administered statins are associated with a reduced risk of aseptic revision and osteolysis in at least two THA studies [118, 119]. Yet, evidence from local delivery of statins on orthopedic implants is so far inconclusive. It remains to be seen whether long-term oral statin therapy, at least in selected patients, or local application can improve osseointegration and reduce the risk of aseptic loosening.

Disease-Modifying Drugs Disease-modifying drugs (DMARDs) or biologic DMARDs are of significant interest in the context of osseointegration of implants due to the high prevalence of arthroplasty procedures in patients with rheumatoid arthritis [120]. There is evidence to suggest that extensive use of biologic DMARDs led to a decline in arthroplasty rates in some joints. Controversy exists on how best to manage DMARDs during the perioperative period due to a higher risk of infections. Regarding the effects of various DMARDs on osseointegration potential, there are theoretical grounds that they can reduce the risk of aseptic loosening by suppressing the particle-mediated chronic inflammation at the bone-implant interface. This hypothesis is, in part, supported by a large cohort study from Finland that showed a slightly reduced risk of revision in patients using biologics when compared with patients on traditional DMARDs [121]. Further studies are warranted about the potential effects of commonly used DMARDs.

Antidepressants Antidepressants, and particularly selective serotonin reuptake inhibitors (SSRI), can have negative effects on the bone and increase the risk of fractures [122, 123]. Depression is also one of the strongest risk factors for revision in arthroplasty patients [72]. However, it is unknown whether the risk is mediated primarily by the disease pathology or secondarily by antidepressant medications.

Thiazide Diuretics Thiazide diuretics reduce renal calcium excretion, regulate intracellular calcium, inhibit osteoclastic bone resorption, and can therefore affect bone metabolism in an osteo-protective manner. In contrast, loop diuretics increase renal calcium excretion and have opposite effects on the bone. Empirical data are consistent with theoretical mechanisms and suggest that thiazide diuretics are associated with a reduced risk of fractures in a dose-dependent manner, whereas loop diuretics are potentially harmful to the bone [124, 125]. There is only one clinical report on arthroplasty patients [126]. In a nationwide Danish study, loop diuretics were associated with an increased risk of revision following primary THA, but there was no protective effect with thiazides [126].

Conclusions

To date, there is a limited understanding of how patient-related, biological factors affect the osseointegration of orthopedic implants. Similarly, the local and/or systemic effects of various classes of antiresorptive and bone anabolic medications are poorly understood. Our review of the published clinical literature highlights a number of important observations. Notably, based on evidence accumulating in osteoarthritis and osteoporosis research, we believe that there is a need to better recognize the phenotypical and genetic heterogeneity and host response in arthroplasty patients (Fig. 1). Likewise, interventions aiming to improve the osseointegration of hip and knee implants possibly differ depending on the joint, etiology of joint damage, and comorbid conditions. For example, young, post-traumatic arthroplasty patients may require different interventions than the obese, metabolic syndrome patients. Furthermore, it is important to distinguish systemic risk factors that would require systemic interventions and local risk factors that possibly require local interventions. More pre-clinical and clinical research remains to be done to identify effective interventions to improve osseointegration of orthopedic implants. Improvements can be achieved by pharmacological, molecular, and stem cell-based methods that biologically enhance bone healing around the implant. A firm understanding of the clinical parameters that complicate osseointegration will permit development of proper animal models that recapitulate the most prevalent clinical conditions with increased failure risk. This combination of clinical and translational studies offers the greatest opportunity to improve patient outcome.

Compliance with Ethical Standards

Conflict of Interest Hilal Maradit Kremers, Eric A. Lewallen, and Andre J. van Wijnen declare that they have no conflict of interest.

David G. Lewallen reports personal fees, non-financial support, and others from Zimmer Biomet; personal fees, non-financial support, and others from Pipeline Mako Stryker and others from American Joint Replacement Registry; and personal fees from Accutiv and personal fees from Link, outside the submitted work. In addition, Dr. Lewallen has a patent Zimmer issued.

Human and Animal Rights and Informed Consent Among the cited articles where one of the authors of the current report was an author, local institutional review board approval was obtained and maintained for studies where human (or animal) subject research was performed.

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