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White paper

The Paradox of Prosthetic Joint Infection and the Microbiome: Are Some Bacteria Actually Helpful?

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ABSTRACT

Periprosthetic joint infection (PJI) is a potentially catastrophic complication of total joint arthroplasty of the lower extremity. PJI is associated with significant burden of illness and economic cost. There are a number of well-established modifiable risk factors for PJI. Myriad perioperative protocols are used with the intent of reducing the incidence of PJI. However, it remains unclear why infections occur despite correction of modifiable risk factors and/or adherence to prophylactic protocols. There is emerging evidence that the microbiome—the diverse population of commensal microorganisms that inhabit the human body—may play a role in the pathogenesis of musculoskeletal infections. The impact of the microbiome on PJI warrants further investigation and may change how we conceptualize, prevent, and treat PJI.

Introduction

Total joint arthroplasty (TJA) of the hip and knee is among the most successful surgical innovations of the past century given the restoration of function and reduction of pain. The problem of the greatest magnitude in TJA is perhaps one that we understand the least, periprosthetic joint infection (PJI). PJI is conceivably the most devastating complication after TJA as it is associated with potentially catastrophic outcomes, such as loss of limb or life [1]. PJI is the primary mode of failure of total knee arthroplasty (TKA) and the 3rd most common reason for revision in total hip arthroplasty (THA) [2]. Although PJI occurs in less than 1%-2% of primary TJA cases, the impact is substantial given the high volume of TJA cases performed nationally [2]. By 2030, THA and TKA cases performed annually in the US are projected to grow to 1.26 million and 935,000 cases, respectively [3], and hence, the absolute number of infections will unfortunately only rise over time.

Problem statement

Complications of PJI including local recurrence of infection and systemic sepsis pose a significant burden of illness. The treatment of chronic PJI often involves revision surgery and, in some instances, requires permanent implant removal, fusion or amputation, or prolonged antimicrobial therapy [4-6]. The cost associated with these treatments including patient time lost from work and productivity, along with the impact on family members and friends, all amounts to a substantial economic burden. It is estimated that the combined annual hospital costs related to PJI of the hip and knee in the US will be $1.85 billion by 2030 [2].

Multiple patient and surgical factors play a role in the pathogenesis of PJI. A number of modifiable risk factors for PJI have been identified, including smoking, obesity, diabetes, vitamin D deficiency, and malnutrition, and these are now the central focus of perioperative optimization and infection prevention [7-9]. Surgical strategies to reduce PJI pertain to reducing bacterial bioburden at the surgical site, which has led to a number of potential strategies including preoperative methicillin-resistant and methicillin-

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sensitive *Staphylococcus aureus* screening and decolonization, appropriately timed and selected intravenous (IV) antibiotic prophylaxis, preoperative skin decolonization, and using alcohol-based skin preparation solutions [10-13]. Other methods involve attempts to decrease bacterial contamination in the operating room (OR) environment, including limiting OR traffic, utilizing laminar flow, and donning exhaust suits [14,15]. Many of these techniques remain controversial and are not universally used. Despite implementation of patient and surgical optimization techniques, and extensive efforts to reduce infection, PJI still occurs, indicating that current modes of prevention are insufficient.

Proposed solution

A new paradigm of the role of bacteria in the pathogenesis of PJI

The continued threat of PJI, often in the absence of known patient risk factors or deviation from preventative protocols, calls into question the current paradigm of the pathogenesis and prevention of these infections. The human body is inhabited by a host of commensal microbes in the skin, respiratory tract, genitourinary tract, oral cavity, and gastrointestinal (GI) tract, also known collectively as the "microbiome" [16]. Colonization of the microbiome with bacteria, fungi, protists, and archaea, collectively called "microbiota," starts at birth and in the first year of life whereby a newborn is exposed to maternal and environmental microbes that initiate the gut microbiota [16].

It is estimated that 500-1000 distinct species live in the human body at any given time [16,17]. The composition of the microbiome is affected by host genotype and early bacterial exposure that remains relatively stable in an individual; however, the microbiome can be altered by other environmental factors such as antibiotic use and diet [16-18]. The unique, symbiotic interplay between microbiome and host is thought to play a major role in the immune function and overall health of the host.

In 2007, the National Institute of Health launched the Human Microbiome Project to evaluate human microbiota [17]. This endeavor led to a number of findings pertaining to disease pathogenesis and treatment for a variety of disease states. The microbiota of the gut comprises the majority of the human microbiome [16,18]. Disruption of these symbiotic relationships, called "dysbiosis," is attributed to a broad array of disease states including inflammatory bowel disease (Crohns' disease and ulcerative colitis), upper respiratory disease, autoimmune disorders, liver disease, obesity, cancers, and major depressive disorder [16,19,20]. Conditions specifically associated with an increased risk of PJI of the hip and knee, including obesity and diabetes mellitus, are related to an imbalance of the microbiome [21,22]. Alterations in the microbiome have been linked to other musculoskeletal conditions including increased incidence of bone fragility [18,23].

Hence, we are presented with a paradox: some bacteria may actually help our cause. More than 100 trillion organisms inhabit the human GI tract, rendering it the primary site of interactions between microbes and the immune system [24]. More than 70% of the body's lymphocytes are located in the GI tract, making it the largest immune organ [24]. The microbiota of the GI tract stimulates and enhances the function of the immune system [18]. Strains of commensal bacteria isolated from the human gut have been shown to confer immunomodulatory capabilities, such as regulation of a range of cytokines including interleukin (IL)-10, IL-17a, IL-22, and interferon gamma [25]. Disruptions of the gut microbiome have been demonstrated to reduce the number and effectiveness of macrophages, thus rendering the host less able to respond to pathogenic bacteria [26]. The link between dysbiosis and increased infection risk has been established; reduced diversity of the gut microbiota has been shown to increase the risk of infection after hematopoietic stem cell transplantation [27,28]. A paucity of diversity of the gut microbiome has also been linked to PJI in preclinical studies, as Hernandez et al. demonstrated in a murine model that a change in the microbiome that decreased the presence of normal gut flora increased the incidence of PJI and impaired the immune response to infection [18].

Imbalance in the microbiome may also explain the seemingly incongruous connection between malnutrition and obesity with PJI. It is well established that morbid obesity increases the risk of PJI [8]. However, the mechanism for this is not well understood; it remains speculative whether the increased adipose layer results in incisional complications that lead to superficial infections then become deep PJIs. Inexplicably, patients who undergo bariatric surgery and weight loss remain at a high risk for PJI after primary and revision TJA [29]. Conversely, undernourished patients with low body mass index are also at an increased risk of PJI [30]. The unifying link between underweight patients, overweight patients, and those who underwent weight reduction surgery that results in increased PJI risk may be nutritional deficits [31]. Malnutrition and obesity are both conditions that are linked to dysfunction of the microbiome, as obese and undernourished patients both have reduced diversity of the gut microbiota [32]. Perturbations in the gut microbiome have a profound effect on nutrient absorption [33]. This common finding in obese and undernourished patients paired with the increased risk of PJI in these patients suggests that dysbiosis may be involved in the pathogenesis of PJI.

It remains unclear why microflora of one region, such as the gut, appears to be protective against PJI, whereas other commensal bacteria are pathogenic. *Staphylococcus aureus* that colonizes the nares and skin of 20% of the population is the target of decolonization protocols before TJA [10]. In rare instances, microbiota of the oral cavity or genitourinary tract has been identified as pathogens in osteoarthritis and PJI [34,35]. There are at least 2 case reports of PJI with *Fusobacterium nucleatum,* an anaerobic gram-negative bacillus of the oral microbiota, and 2 cases of hip PJI involving *Gardnerella vaginalis* of the genitourinary tract [36,37]. In these unusual cases, PJI was treated successfully without reported recurrence, suggesting that these commensal bacteria may have resulted in a less virulent form of PJI. Further investigation is needed to distinguish which commensal bacteria are pathogenic vs beneficial in PJI.

It is well known that prolonged antibiotic therapy, which eradicates helpful commensal organisms, inadvertently allows pathogens to thrive including *Candidiasis* or *Clostridium difficile* that can lead to bowel infections [38,39]. Short-term prophylactic antibiotics are unlikely to cause dysbiosis, whereas prolonged or suppressive antibiotic therapy has been demonstrated to reduce the diversity of the microbiome, resulting in increased susceptibility to infection [40]. It is thus possible that prolonged antimicrobial therapy may likewise increase the risk of PJI. While hematogenous spread of an infection from one location (such as oral abscess or recurrent urinary tract infection) to a TJA is a cause for concern, it is possible that the antibiotics used to treat that infection can create an additional risk owing to disruption of the microbiome. Paradoxically, treatment for PJI with prolonged antimicrobials and long-term suppressive antibiotics used for the treatment of PJI may also pose a risk of recurrence or new infection by virtue of disrupting the microbiome. Further study is required to determine the extent and duration of dysbiosis after antimicrobial therapy and whether this poses a risk for PJI during that timeframe.

Future directions and long-term focus

If dysfunction within a microbiome can result in disease, it follows that interventions to restore the microbiome could potentially

prevent or treat the disease state. An expert panel was convened in October 2013 by the International Scientific Association for Probiotics and Prebiotics to discuss the field of probiotics [41]. The Food and Agriculture Organization of the United Nations and the World Health Organization definition of probiotics is "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [41]. Probiotics have been demonstrated to enhance innate immunity and suppress the growth of pathogenic organisms. The mechanisms by which this is accomplished include inhibition of IL-10 and stimulation of secretory IgA and reduction of inflammatory cytokines [42].

Probiotics (beneficial bacteria), prebiotics (fiber), and a combination of both (synbiotics) have been found to reduce the incidence of surgical site infections after colorectal and hepatobiliary surgery and have been shown to confer incisional wound healing properties after surgery [43,44]. A meta-analysis by Skonieczna-Zydecka et al. identified 35 randomized control trials investigating the preoperative and/or postoperative use of probiotics, prebiotics, and/or synbiotics compared with controls (placebo or standard of care) after a variety of surgical procedures, including liver transplant, colectomy, esophagectomy, pancreaticoduodenectomy, hepatectomy, and other major abdominal surgery. This analysis revealed that the use of probiotics and synbiotics conferred a significant reduction in superficial surgical site infections and deep-space surgical infections [43]. The use of probiotics and synbiotics also reduced surgery-related complications, including pneumonia and urinary tract infections, and was associated with shorter length of stay in hospital. The authors concluded the effect of perioperative treatment with probiotics and synbiotics to be a complex one that was also associated with a reduction in post-surgical serum inflammatory markers, including C-reactive protein (CRP) and IL-6 [43].

Based on preclinical studies that suggest an altered microbiome plays a role in PJI development and clinical studies that have shown a reduction in SSI with correction of dysbiosis in other surgical fields, the microbiome's role in PJI is a promising and worthy area of further investigation [18,43]. The incidence of dysbiosis in patients with PJI needs to be evaluated. If found to play a significant role, treatments for dysbiosis such as probiotics or fecal transplant may prove effective in the prevention of PJI.

Recommendations

We as arthroplasty surgeons ascribe to an ingrained dogma that all bacteria are bad. Without a doubt, impeccable sterility in the OR environment remains non-negotiable. However, we may need to broaden our thinking about microorganisms and their varying roles in PJI. The role of probiotics and synbiotics in the prevention of PJI warrants further investigation. The current notion that all bacteria should be annihilated with broad-spectrum antibiotics administered intravenously, topically, and in antibiotic cement may ultimately need to be abandoned for a more laser-focused approach, whereby antibiotics and other treatments that target specific pathogens while preserving symbiotic microbial species are developed and used. [40] The cornerstone of PJI prevention may ultimately involve coexisting with and even promoting "good" bacteria to fight the "bad" bacteria.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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