The Role of Tetracyclines in Joint Arthroplasties

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ABSTRACT

Tetracyclines have various connections to total joint arthroplasties, including their potential use in perioperative infection prophylaxis, treatment of periprosthetic infections and mitigation of complications such as osteolysis and aseptic loosening. The present study is a narrative review focusing on the potential association of tetracyclines with joint arthroplasties. Tetracyclines have several potential uses in the context of arthroplasties, although they are not commonly used as prophylactic antibiotics during surgery due to concerns about their efficacy against the typical pathogens associated with surgical site infections. However, in the case of prosthetic joint infections, tetracyclines may be considered as part of the antibiotic regimen. After successful treatment of a prosthetic joint infection, some patients may require long-term antibiotic suppression therapy to prevent the recurrence of infection. Tetracyclines, such as doxycycline, may be one option for long-term oral antibiotic therapy in these cases. Minocycline-induced black bone disease and skin pigmentation are adverse events that should be taken into consideration, in terms of joint arthroplasties. The use of doxycycline in the prevention of osteolysis and aseptic loosening is an area of interest and ongoing research in orthopedic surgery, particularly in the context of total joint arthroplasties. Finally, tetracycline labeling in bones can provide valuable insights into implant incorporation and aseptic loosening of prosthetic joints.

Keywords: Arthroplasty, doxycycline, minocycline, tetracyclines.

1. INTRODUCTION

Tetracyclines represent a class of broad-spectrum antibiotics that have been integral in the treatment of various bacterial infections since their discovery in the mid-20th century. Over the years, their versatility has expanded beyond their initial uses, with applications ranging from common infections to emerging therapeutic avenues. Tetracyclines are characterized by a polycyclic nucleus composed of four fused rings [1]. Common members include tetracycline, doxycycline, minocycline, and demeclocycline. Tetracyclines exhibit bacteriostatic activity by inhibiting bacterial protein synthesis. They achieve this by reversibly binding to the bacterial 30S ribosomal subunit, thereby blocking the attachment of aminoacyl-tRNA to the mRNA-ribosome complex. This interference disrupts the elongation phase of protein synthesis, ultimately halting bacterial growth. Additionally, tetracyclines possess anti-inflammatory, immunomodulatory, and antiprotease properties, contributing to their therapeutic efficacy in non-infectious conditions [2].

Tetracyclines are well-absorbed orally, with variable bioavailability influenced by factors such as food and divalent cations. They distribute widely into tissues and body fluids, including bone and the central nervous system. Metabolism primarily occurs in the liver, with excretion primarily via renal and fecal routes. Different tetracyclines exhibit variations in pharmacokinetic parameters such as absorption, tissue distribution, and elimination half-life. For example, doxycycline demonstrates enhanced bioavailability and tissue penetration compared to tetracycline [3], [4].

Tetracyclines are indicated for a wide range of bacterial infections, including respiratory tract infections, skin and soft tissue infections, urinary tract infections, sexually transmitted infections, and atypical infections such as those caused by Mycoplasma and Chlamydia species. Beyond their antimicrobial properties, tetracyclines have therapeutic utility in non-infectious conditions such as acne vulgaris, rosacea, and periodontal diseases due to their anti-inflammatory ability and ability to inhibit matrix metalloproteinases. Furthermore, tetracyclines have shown
promise in the treatment of various non-infectious conditions, including rheumatoid arthritis, inflammatory bowel disease, and certain dermatological disorders [5]. In recent years, tetracyclines have garnered attention for their potential beyond traditional antimicrobial therapy. Ongoing research explores their role in modulating cellular signaling pathways, inhibiting matrix metalloproteinases involved in tissue remodeling, and combating multidrug-resistant bacterial infections. Furthermore, tetracycline derivatives are being investigated as adjunctive therapies in cancer treatment, neurodegenerative disorders, and periodontal regeneration, highlighting their diverse pharmacological properties and therapeutic potential [6].

Despite their efficacy, tetracyclines are associated with several adverse effects, primarily gastrointestinal disturbances such as nausea, vomiting, and diarrhea. Photosensitivity reactions, tooth discoloration (particularly in children), and hepatotoxicity are also recognized adverse effects. Additionally, tetracyclines may pose risks during pregnancy and childhood due to their affinity for calcium deposition in developing teeth and bones. Rare instances of hepatotoxicity have been reported with tetracycline use, necessitating monitoring of liver function tests during therapy [7]–[9].

Arthroplasty, also known as joint replacement surgery, is a surgical procedure performed to restore function and relieve pain in a diseased or damaged joint by replacing it with an artificial prosthesis. Arthroplasties are commonly performed for degenerative joint conditions such as osteoarthritis, rheumatoid arthritis, post-traumatic arthritis, and avascular necrosis. Total joint arthroplasty involves replacing both the articulating surfaces of the joint with prosthetic components. The artificial components, which are usually made of metal, plastic, or ceramic materials, are implanted to recreate the joint’s function and movement. Common examples include total hip replacement and total knee replacement. Partial joint arthroplasty involves replacing only one of the joint surfaces. Examples include unicompartmental knee replacement. Revision arthroplasty is performed to replace a failed or worn-out joint replacement with new prosthetic components [10]–[13].

While arthroplasty is generally safe and effective, complications can occur. These may include infection, venous thromboembolic events, implant loosening or failure, nerve or blood vessel injury, stiffness, instability, and persistent pain. Osteolysis and aseptic loosening are common complications of total joint arthroplasties, particularly in the long term, which can lead to implant failure, revision surgeries, and decreased patient satisfaction [14]. Osteolysis refers to the gradual loss of bone around the prosthetic joint due to a chronic inflammatory response to wear debris, leading to implant instability and eventual loosening. Aseptic loosening occurs when the bond between the implant and bone becomes compromised, resulting in implant migration, pain, and functional impairment [15]. Periprosthetic infections occur when microorganisms colonize the surface of implanted prosthetic joints, leading to infection. These infections can result in substantial morbidity, implant failure, and the need for revision surgery. Surgical options for periprosthetic infections include debridement and implant retention, one- or two-stage revision arthroplasty, resection arthroplasty, or amputation in severe cases [16]. Antimicrobial therapy is a cornerstone of periprosthetic infections management and is typically initiated empirically based on the likely causative organisms, which are often similar to those causing native joint infections. Broad-spectrum antibiotics with activity against Gram-positive cocci, such as Staphylococcus aureus and coagulase-negative staphylococci, are commonly used as initial therapy. Antimicrobial therapy is guided by culture and susceptibility testing of intraoperative specimens obtained during surgical intervention, allowing for targeted therapy tailored to the specific infecting organism and its antimicrobial susceptibility profile [17].

Tetracyclines have various connections to total joint arthroplasties, including their potential use in perioperative infection prophylaxis, treatment of periprosthetic infections and mitigation of complications such as osteolysis and aseptic loosening. The present study is a narrative review focusing on potential association of tetracyclines with joint arthroplasties.

2. Review

2.1. Prophylactic Perioperative Use of Tetracyclines in Joint Arthroplasties

Tetracyclines, including doxycycline and minocycline, are not commonly used as primary perioperative antibiotics in joint arthroplasty procedures. The standard prophylactic antibiotics used in these surgeries typically include agents such as cefazolin or vancomycin, chosen based on factors like the patient’s medical history, allergies, and local antimicrobial resistance patterns. This occurs due to the narrower spectrum of activity of tetracyclines compared to antibiotics like cefazolin or vancomycin and the potential development of resistance to tetracyclines [18].

Animal models have shown that a minocycline/rifampin-impregnated bioreorbable polymer implant coating was effective in reducing the rate of prosthetic joint infections, decreasing inflammation and preventing biofilm formation [19]. A prospective randomized controlled trial has observed that preoperative intravenous administration of doxycycline did not significantly decrease Propionibacterium acnes culture positivity of the skin, dermis, or glenohumeral joint of patients undergoing shoulder arthroplasty [20].

2.2. Adverse Events of Tetracyclines Affecting Joint Arthroplasties

Minocycline-induced black bone disease is a rare side effect associated with long-term use of the antibiotic minocycline. The condition is characterized by a bluish-gray or black discoloration of bone tissue, particularly in weight-bearing bones such as the tibias, femurs and pelvis. This pigmentation occurs due to the deposition of minocycline metabolites in bone tissue, resulting in an alteration of bone color. Minocycline-induced pigmentation usually occurs after several months to years of continuous
therapy with minocycline. The pigmentation is typically irreversible, even after discontinuation of the medication. However, the severity of the pigmentation can vary among individuals. Symptoms of minocycline-induced black bone disease may include bone pain, stiffness, and swelling, although some individuals may not experience any symptoms apart from discoloration [21], [22]. In 2004, McCleskey et al. reported a case of an 81-year-old man who suffered from knee osteoarthritis and was under chronic treatment of rosacea with 100 mg of minocycline daily. During total knee arthroplasty, blue-green to gray pigmentation was noted in the exposed cortical bone of femur and tibia in sites of cartilage erosion [23]. Another similar case of pigmented bone in a 55-year-old woman who was on chronic use of minocycline and sustained a total knee arthroplasty, was reported by Reed et al. in 2012 [22]. Minocycline-induced pigmentation of periartricular bone may be accelerated by inflammation due to rheumatic or pyogenic arthritis [24].

Minocycline-induced skin pigmentation refers to a dermatological side effect associated with the use of minocycline. It typically presents as blue-gray or blue-black discoloration of the skin, mucous membranes, or nails [24]. The pigmentation may develop gradually over time with chronic minocycline use and may be localized or diffuse. The affected areas of the skin may exhibit a slate-gray or bluish hue, which can vary in intensity or diffuse. The affected areas of the skin may exhibit a slate-gray or bluish hue, which can vary in intensity or diffuse. The affected areas of the skin may exhibit a slate-gray or bluish hue, which can vary in intensity or diffuse.

Minocycline undergoes oxidation in the skin, leading to the formation of pigmented degradation products that deposit in the skin and mucous membranes. The pigmentation is thought to be dose-dependent and may be more likely to occur with prolonged or high-dose minocycline therapy. Minocycline-induced skin pigmentation is usually benign and does not require treatment unless it causes cosmetic concerns or psychological distress. Discontinuation of minocycline therapy may lead to gradual fading or resolution of the pigmentation over time, although complete clearance may not always occur. A periprosthetic knee infection in a 77-year-old man, by methicillin-resistant coagulase-negative staphylococcus, was treated with chronic suppression with oral minocycline and levofloxacin. Skin pigmentation appeared on the patient’s tongue and over the surgical scar of his knee in six months, and later, it extended to his nails, sclera, face, and extremities [24].

2.3. Use of Tetracyclines for the Treatment of Arthroplasty-Related Infections

A plethora of clinical studies have supported the efficacy of tetracyclines in the treatment of arthroplasty-related infections. These studies have demonstrated reductions in bacterial load, biofilm formation, and inflammatory response in animal models of PJJIs treated with tetracycline-containing regimens. In case a suppressive antibiotic therapy is chosen for the treatment of prosthetic joint infections, doxycycline is the most commonly used antibiotic (61%) [25].

Staphylococci are a common cause of periprosthetic infections. 50% of Staphylococcus aureus biofilm, in case of prosthetic hip and knee infections, can be killed by doxycycline [26]. In 69-year-old man with a methicillin-sensitive Staphylococcus aureus prosthetic hip infection, with a recurrent seroma cavity superficial to fascia lata, injection of 200 mg doxycycline to the cavity, led to a successful seromadesis [27]. The therapeutic combination of minocycline and vancomycin has been used for chronic methicillin-resistant coagulase-negative staphylococcal prosthetic joint infections [28]. Coagulase-negative staphylococci resistance to tetracycline has increased in a little more than a decade [29], [30] and seems to be different between orthopedic centers [31]. Two patients with multidrug-resistant Acinetobacter prosthetic joint infection were reported to be effectively treated by debridement, antibiotics and implant retention. Patients were given high doses of tigecycline followed by standard doses of minocycline for 3 months [32].

Brucella species are bacteria known to cause brucellosis, a zoonotic infection primarily transmitted to humans through direct contact with infected animals or consumption of contaminated animal products such as unpasteurized dairy. While Brucella infections primarily affect organs such as the spleen, liver, and bone marrow, there have been rare cases reported of Brucella causing periprosthetic infections. Two cases of infected total knee arthroplasty by Brucella melitensis were successfully treated with rifampicin and doxycycline without surgery [33], [34]. Cairo et al. reported 3 cases of prosthetic joint infection due to Brucella melitensis, treated with doxycycline in combination with streptomycin or rifampicin [35]. Two other cases of periprosthetic hip infection by Brucella melitensis were managed with a prolonged administration of streptomycin, rifampicin and doxycycline followed by 2-stage revision arthroplasty [36], [37]. Similarly, a periprosthetic hip infection caused by Brucella abortus, was successfully treated with a combination of rifampicin and doxycycline after a 2-stage hip exchange [38]. Walsh et al. reported a case of infected hip arthroplasty by Brucella abortus, 13 years after implantation. Patient was administered intravenous gentamycin, followed by oral doxycycline and rifampicin [39]. Ruiz-Ibán et al. reported 2 cases of periprosthetic hip infections caused by Brucella. The first case was caused by Brucella abortus and was managed with a 2-stage exchange and oral administration of rifampicin and doxycycline. The second case was caused by Brucella melitensis and was conservatively managed with rifampicin, streptomycin and doxycycline [40]. Another case of a 78-year-old man with a prosthetic knee infection by Brucella was successfully treated with a 2-stage revision arthroplasty and an oral 8-week administration of rifampicin and doxycycline [41]. Weil et al. suggested that every prosthetic joint infection by Brucella, in the presence of signs of loosening should be treated with a 2-stage excisional arthroplasty and 3 months of administration of doxycycline and rifampicin [42].

Coxiella burnetii is the bacterium responsible for causing Q fever, a zoonotic disease that typically affects animals but can also infect humans. While Coxiella burnetii infections primarily occur through inhalation of contaminated
aerosols or ingestion of contaminated food, there have been rare cases reported of Coxiella burnetti causing periprosthetic infections. A periprosthetic knee infection by Coxiella burnetti was successfully treated with one-stage exchange arthroplasty followed by oral administration of doxycycline and moxifloxacin [43]. A case of Coxiella burnetti prosthetic joint infection in an immunocompromised woman was effectively managed with a 2-stage hip exchange and oral doxycyclin and hydroxycloroquine [44]. Another 64-year-old woman with an infected knee arthroplasty by Coxiella burnetti was treated with a 2-stage hip exchange and oral doxycyclin and hydroxycloroquine for 24 months [45]. The combination of doxycycline and ciprofloxacin has been used for the management of another periprosthetic knee infection by Coxiella burnetti [46].

Borellia species are a rare cause of prosthetic joint infections. Ali et al. have reported the successful treatment of Borellia burgdorferi prosthetic joint infection after total knee arthroplasty with oral doxycycline for 6 weeks [47]. In the case of 2-stage exchange, the combination of intravenous ceftriaxone and oral doxycyclin was successful in a patient with Lyme-associated prosthetic joint infection [48]. In a 68-year-old woman with a prosthetic knee infection and a positive serum Lyme antibody testing, the combination of doxycycline and ceftriaxone for 4 weeks led to a successful second-stage implantation [49].

Non-tuberculous mycobacteria are a rare cause of prosthetic joint infections. The combination of doxycycline and moxifloxacin has been used successfully for the management of a periprosthetic knee infection caused by Mycobacterium thermoresentibile [50]. A periprosthetic hip infection by Mycobacterium fortuitum was treated with 4 weeks of intravenous cefoxitin and amikacin and later followed by a 5-month course of oral ciprofloxacin and doxycycline, without any additional surgery [51]. Saffo et al. reported a case of 71-year-old female with a prosthetic knee infection by Mycobacterium smegmatis managed with a 2-stage exchange and a postoperative course of oral doxycycline and levofloxacin [52].

After shoulder arthroplasty, doxycycline has been effective in the treatment of periprosthetic shoulder infection, caused by Propionibacterium acnes [53], [54]. A prosthetic shoulder infection by Propionibacterium granulosum has been successfully treated glenosphere and liner exchange followed by continuous local antibiotic perfusion (gentamycin, ceftriaxone and rifampicin) and oral minocycline and cotrimoxazole for 8 weeks [55].

Doxycycline has been used for the chronic suppression of periprosthetic joint infections caused by rare bacteria, such as Francisella tularensis [56], [57] and Streptococcus gordonii [58]. A patient with an infected knee arthroplasty by Streptobacillus moniliformis was successfully treated with surgical debridement, implant retention, intravenous ceftriaxone for 6 weeks and oral doxycycline for another 6 weeks [59]. A periprosthetic knee infection by Pasteurella multocida was successfully managed with a 2-stage exchange and a course of intravenous amoxicillin, ciprofloxacin and doxycycline [60]. Chronic suppression with minocycline after 6 weeks of vancomycin was reported in a case of prosthetic joint infection by Corynebacterium jeikeium [61]. A 64-year-old man with a history of sarcoidosis on corticosteroids and azathioprine suffered from Nocardia nova knee prosthetic joint infection in the setting of disseminated nocardiosis. He was successfully treated by a one-stage complete hardware exchange followed by an adapted antibiotic therapy regimen (meropenem and doxycycline followed by ceftriaxone and doxycycline) [62]. Luo et al. reported a case of a 59-year-old man with a periprosthetic knee infection by Mycoplasma hominis and Ureaplasma urealyticum, successfully managed with a 3-month course of oral doxycycline [63]. Fourman et al. reported a case of a total hip arthroplasty interrupted by intraoperative cardiac arrest. The patient’s wound was packed with sterile sponges and covered with an iodoform dressing. After a successful resuscitation, 6 hours after the incident, the hip arthroplasty was completed. The patient was administered intravenous vancomycin for 2 weeks and oral doxycycline for 12 weeks, with an uneventful healing [64].

2.4. Use of Tetracyclines for the Prevention of Aseptic Loosening

The use of doxycycline in the prevention of osteolysis and aseptic loosening is an area of interest and ongoing research in orthopedic surgery, particularly in the context of total joint arthroplasties. Doxycycline has been investigated for its potential anti-inflammatory and anti-osteoclastic effects in the context of osteolysis and aseptic loosening [65]. Studies have suggested that doxycycline may inhibit the activity of matrix metalloproteinases, enzymes involved in the degradation of extracellular matrix proteins, including collagen and proteoglycans. By inhibiting matrix metalloproteinases activity, doxycycline may help mitigate the inflammatory response and tissue destruction associated with wear particle-induced osteolysis and aseptic loosening [66].

Preclinical studies using animal models of osteolysis and aseptic loosening have shown promising results with doxycycline treatment, including reductions in bone resorption, inflammatory cytokine levels, and osteoclast activity. A murine osteolysis model suggests that through the down-regulation of RANK/RANKL, tetracycline significantly inhibits debris-induced inflammatory osteolysis [67]. In an animal study by Zhang et al. doxycycline treatment effectively suppressed in vitro osteoclastogenesis, affected the fate of mature osteoclasts, and inhibited mature osteoclasts, causing bone resorption. In vivo data suggested that doxycycline strongly attenuates bone cement- or polyethylene-induced osteolysis and osteoclastogenesis. Researchers suggested that doxycycline may be useful in the treatment or prevention of osteolysis and aseptic loosening after joint arthroplasty [65]. An in vitro study by Ong et al. used radiolabelled mouse calvariae cultured with human interface membrane cells from aseptically loosened hips. Researchers found that doxycycline can inhibit osteolysis at the interface membrane of aseptically loosened hips, suggesting a preventive measure for aseptic loosening of total joint replacements [66]. On the other hand, Santavirta et al. observed that doxycycline and tetracycline could inhibit MMP activity in reactive periprosthetic tissue [68].
2.5. **Use of Tetracyclines for the Prevention of Postoperative Pain, Delirium and Cognitive Dysfunction**

A prospective, double-blind, placebo-controlled trial, by Takazawa et al. included 202 patients undergoing total knee arthroplasty under general anesthesia. They were randomly assigned to receive 100 mg of oral minocycline (n = 100) or placebo (n = 102) twice daily from the day before surgery until the seventh postoperative day. Cogni-tive function was evaluated preoperatively, and 1 week and 3 months postoperatively. Researchers found no signifi-cant differences between the 2 groups, in postoperative pain, postoperative delirium and postoperative cognitive dysfunction [69].

2.6. **Tetracycline Labeling in Bones**

Tetracycline labeling in bones refers to a technique used in medical and research settings to study bone formation and turnover. This technique involves the administration of tetracycline antibiotics, followed by examination of bone specimens under a microscope to visualize the deposition of tetracycline within bone tissue. Tetracycline labeling takes advantage of the ability of tetracycline antibiotics to bind to calcium in bone tissue. When tetracycline is administered systemically, it becomes incorporated into the newly formed bone matrix during the process of bone mineralization. By administering tetracycline at specific time intervals and then examining bone specimens, the sequence and rate of bone formation can be tracked and the bone turnover dynamics can be assessed.

Tetracycline antibiotics are typically administered orally or intravenously at predetermined intervals. The timing and duration of tetracycline administration depend on the specific research protocol or clinical question being addressed. Multiple doses of tetracycline may be given over several days or weeks to allow for adequate labeling of bone tissue [70]–[72]. After tetracycline administration, bone specimens are obtained through biopsy or autopsy procedures. Thin sections of bone tissue are prepared and stained using fluorescent dyes or viewed under ultraviolet light to visualize the presence of tetracycline within the bone matrix. Tetracycline labeling appears as fluorescent bands or lines within the bone tissue, corresponding to areas of active mineralization where tetracycline was deposited during bone formation [70]. The spacing and intensity of tetracycline labeling bands provide information about the rate and pattern of bone formation. The intensity of labeling can also indicate the extent of mineralization and the activity of osteoblasts, the cells responsible for bone formation. By comparing tetracycline labeling patterns between different bone specimens or over time, researchers can assess changes in bone metabolism associated with various conditions or interventions [73].

Tetracycline labeling in bones has been used in various clinical and research settings to study bone diseases such as osteoporosis, osteomalacia, and Paget’s disease. It has also been utilized to evaluate the effects of osteoporosis medications, such as teriparatide, on bone formation and turnover [71], [74], [75]. Tetracycline labeling can provide valuable insights into implant incorporation and aseptic loosening of prosthetic joints [72], [76], [77].

Tetracycline data has shown that bone viability was not compromised at initial or final reaming levels before hip revision arthroplasty [70]. In femoral head fractures, the apical part of the femoral head has the most extensive vascular damage [78]. The mechanical stability of cemented femoral surface replacement prostheses depends mainly on the original bone present at the time of primary operation [76]. Moreover, it has been shown that 99mTc-Sn-pyrophosphate scintigraphy is an excellent method for the assessment of bone vitality in the femoral head [79]. In the case of the preoperative existence of bone marrow lesions in the femoral heads, increased bone turnover, vascularity and angiogenesis are observed [80]. In bilateral non-cemented total hip arthroplasty, tetracycline labeling indicated active bone turnover in the femoral cortex and regions of ingrowth [71]. Tetracycline treatment showed that in excised femoral heads, new bone tissue contributes to hyperplasia of the osteoarthritic femoral head [73], [75]. New bone formation and ingrowth in bilateral total knee arthroplasty are not inhibited by the administration of celecoxib [81]. However, there are no signs of doxycycline interference with calcium deposition in the trabecular bone from a patient with total hip arthroplasty [82]. Tetracycline labeling has shown that hydroxyapatite-coating showed 90% integration versus 53% of titanium-coated implants [77].

3. **Conclusions**

Tetracyclines have several potential uses in the context of arthroplasties, although they are not commonly used as prophylactic antibiotics during surgery due to concerns about their efficacy against the typical pathogens associated with surgical site infections. However, in the case of prosthetic joint infections, tetracyclines may be considered as part of the antibiotic regimen. While tetracyclines are not typically considered first-line agents for prosthetic joint infections, they may be used as alternative agents in cases where the infecting organism is susceptible and other antibiotics are contraindicated or ineffective. After successful treatment of a prosthetic joint infection, some patients may require long-term antibiotic suppression therapy to prevent the recurrence of infection. Tetracyclines, such as doxycycline, may be one option for long-term oral antibiotic therapy in these cases. Minocycline-induced black bone disease and skin pigmentation are adverse events that should be taken into consideration, in terms of joint arthroplasties. The use of doxycycline in the prevention of osteolysis and aseptic loosening is an area of interest and ongoing research in orthopedic surgery, particularly in the context of total joint arthroplasties. Tetracycline labeling in bones can provide valuable insights into implant incorporation and aseptic loosening of prosthetic joints.

**Conflict of Interest**

Authors declare that they do not have any conflict of interest.