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Abstract

Objective: A serious complication of joint replacement surgery is infection, which results in prolonged invalidity as well as removal and subsequent re-implantation after lengthy antibiotic therapy. In terms of diagnostic imaging, nuclear medicine has presented several tracers and imaging modalities over the years to be used in prosthetic joint infection. The PubMed/MEDLINE literature database was systematically examined for publications on infection, arthroplasty, joint replacement, prosthetic joint, gallium, labeled leukocytes, sulfur colloid, antimicrobial peptides, Fluorine-18-fluorodeoxyglucose (^{18}F-FDG), positron emission tomography/computed tomography (PET-CT), and single-photon emission (SPET-CT). This was determined to be a comprehensive review, not a meta-analysis of prosthetic joint infection and diagnostic imaging in the field of nuclear medicine. Prosthetic joint replacement is more frequently being employed as a way of improving the quality of life in an ever-ageing population. Complications following joint replacement surgery include aseptic or mechanical loosening, as well as polyethylene wear and prosthetic joint infection. The rate of infection is estimated to be between 1%-3%. The therapeutic management of these complications lies in the ability to differentiate between infection and aseptic mechanical loosening. Given that plain radiographs are neither sensitive nor specific to infection and computer tomography, as well as magnetic resonance imaging are limited due to metal-induced artifacts, radionuclide imaging has come to aid in the diagnostic imaging in the failed joint replacement. However, each modality has its advantages and disadvantages, thus there is no gold standard technique of radionuclide imaging. Nevertheless, radiolabelled leukocyte scintigraphy has proven itself to be the gold standard in neutrophil-based infection processes. Several studies have examined the role of PET using radiotracers such as ^{18}F-FDG, gallium-67 and ^{18}F, as well as SPET-CT in diagnosing prosthetic joint infections. Other radiotracers, such as antigranulocyte antibodies and fragments, as well as radiolabeled antibodies and antimicrobial peptide have yet to confirm their role in diagnostic imaging of the failed joint replacement. Nuclear medicine plays a vital role in diagnosing prosthetic joint infections. WBC/bone marrow imaging is the best available diagnostic imaging test. Newer imaging modalities, such as SPET-CT may in the future, play a larger role in diagnosing prosthetic joint infections. The roles of ^{18}F-PET and ^{18}F-FDG-PET have yet to still be determined.

Introduction

Prosthetic joint replacement is being more frequently employed as a way of improving the quality of life in an ever-ageing population, given that life expectancy is steadily increasing [1]. However, as with every surgical procedure, there are certain risks and complications. Common complications following joint replacement surgery are aseptic or mechanical loosening, as well as polyethylene wear [2]. While not often observed, prosthetic joint infection is a serious complication that can result in significant morbidity, decrease in joint function, prolonged invalidity and hospitalization, often leading to explantation and subsequent re-implantation following several weeks of antibiotic therapy [1, 3]. In addition, the financial, clinical and psychological factors of such an infection must be taken into consideration [4]. There is a 1% rate of infection following primary hip implantation and 2% for knee prostheses [5]. Following revision surgery, these numbers increase to about 3% for hip replacements and 5% for knee replacements [5].

Prosthetic joint infections can be grouped into "early" (within three months after surgery), "delayed" (between three months to two years) and "late" (after two years) [6]. The two most common organisms found are Staphylococcus epidermidis (31%) and Staphylococcus aureus (20%) [2]. Whereas Staphylococcus aureus is typically isolated in "early" infections, coagulase-negative Staphylococci, Streptococci, Enterococci and Anaerobes are seen in "late" infections [6]. Some factors that predispose individuals to prosthetic joint infections are higher age, obesity, underlying joint infection (rheumatoid arthritis, psoriasis), poor nutritional status, diabetes mellitus, remote infection and prior joint infection, as well as immune suppression [7, 8].

Between the patient's bone and the prosthesis material is a thin layer of reactive fibrous tissue, also known as a membrane [1]. In prosthetic joint infection, either as a result of microbial colonization that occurs at time of implantation or haematogenous seeding leads to inflammatory cells, collagen and blood vessels thicken this membrane [1]. Furthermore, the pathogens attach to the membrane by means of capsular polysaccharide-associated adhesins and a proteinaceous cell wall, subsequently secreting a biofilm that protects them from the host immune response and antibiotics [1]. Therefore, diagnosis and subsequent treatment of joint infections are quite difficult.

It is a known fact that bacteria secrete chemotactic factors, such as histamine and prostaglandins that recruit leukocytes, induce endothelial activation and cause edema. Therefore, the incessant recruitment of leukocytes from the blood to the periprosthetic tissue is typical of acute or sub-acute bacterial infection. Due to active migration into an infected tissue by means of adherence to vascular endothelium followed by migration, autologous radiolabelled white blood cells have a high specificity [9]. A subtype of white blood cells (WBC), neutrophils, are present in the infected joint and are the predominantly labeled circulating cell in labeled leukocyte scintigraphy (LS) with tracers, such as ^{111}In-oxine and ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) [1]. Leukocyte labeling in infection imaging was first introduced in 1976 by McAfee and Thakur [10]. Labeled leukocytes do not accumulate at sites absent of infection or where there is increased bone turnover [1]. Therefore, LS is considered to be a valuable tool in diagnosing prosthetic joint infections [1]. In addition, given that neutrophils are typically absent in aseptic loosened prosthesis, LS should be able to distinguish between an infected prosthesis and an inflamed aseptic prosthesis [5, 11, 12]. However, bone marrow displacement or activation by surgery can result in a secondary uptake of leukocytes around prostheses [1]. Therefore, a combination of LS and bone marrow scintigraphy (BMS) with ^{99m}Tc-sulphur-/nanocolloid has been introduced [1]. Within 48 hours of bacterial seeding, an acidic pH, low oxygen tension, increased intraosseous pressure and vascular insufficiency suppress the uptake of sulfur-/nano colloid [13]. Given that infection stimulates the uptake of leukocytes, but suppresses the uptake of sulfur-/nanocolloid, LS and BMS in infections are spatially incongruent [5]. If however, the uptake of the two radiopharmaceuticals is similar or spatially congruent, the labeled leukocyte activity is attributable to bone marrow uptake [5].

In terms of diagnostic imaging, nuclear medicine has offered various tracers and imaging modalities over the years to be used in diagnosing infected joint replacements. This review will discuss those most widely used.

Preoperative work-up in suspected prosthetic infections

Prosthetic joint infection is defined by major and minor criteria. Major criteria include: a) presence of a sinus tract communicating with the prosthesis or b) two positive periprosthetic cultures with phenotypically identical organisms [14]. Minor criteria include: 1) raised serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein concentration (CRP), 2) raised synovial WBC count change on leucocyte esterase test strip, 3) raised synovial polymorphonuclear neutrophil percentage, 4) positive histological analysis of periprosthetic tissue or 5) a single positive culture [14]. One of the most perplexing diagnostic situations involves a persistent marginally elevated CRP or tenacious pain after surgery [1]. Therefore, diagnosis involves a variety of different factors. Firstly, thorough clinical histories, including medical, surgical and physical examinations deliver excellent initial diagnostic and aid in subsequent diagnostic evaluation [1]. Further diagnostic evaluation of prosthetic joint infection includes hematological tests with inflammation markers (C-reactive protein (CRP), WBC count, ESR and interleukin-6). A study by Glithero et al. (1993) [15] examining CRP values in patients with suspected prosthetic infections reported a sensitivity, specificity and accuracy of 83%, 74%, and 77%, respectively. In a study currently under review, the sensitivity of CRP was 57%, specificity 28%, with an overall accuracy of 33% [16]. A review by Yuan et al. (2014) [17] demonstrated that CRP had good diagnostic accuracy for periprosthetic infections with a sensitivity of 82% and specificity of 77%. Overall, it appears that CRP alone is not very accurate in prosthetic joint infections. In terms of WBC count, a study by Berbari et al. (2010) [18] that demonstrated that WBC count has the lowest diagnostic accuracy for prosthetic joint infections. While this analysis only investigated serum CRP and WBC count, a study by Claassen et al. (2014) [19] that assessed 46 patients with knee arthroplasty and aspiration in 77 cases, demonstrated an increase in WBC count in only 7 cases and normal levels in the remaining patients. In addition, CRP was increased in 33 cases and normal in 44 cases [19]. In a study currently under review, they demonstrated a sensitivity of 0%, specificity of 92% and overall accuracy of 82% [16]. Similar to this study, Claassen et al. (2014) [19] also concluded that CRP and WBC are not accurate in diagnosing ongoing infection.

A normal CRP or ESR cannot completely rule out a low-grade infection, given that false negative results can occur following long-term antibiotic treatment or in patients with delayed-onset infection [18]. Therefore, additional diagnostic examinations, such as joint aspiration with a WBC count and differential, gram stain and culture, as well as numerous imaging modalities may be required [1, 18].

Well-established tracers in infection

[67]Gallium-citrate

Gallium-67 (^{67}Ga) is an analog of iron that can bind to circulating transferrin in its ionic form and thus uses transferrin receptors to enter cells and become highly stable [20, 21]. Roughly 90% of ^{67}Ga-citrate is transferrin-bound and found in the plasma [22]. It is believed that ^{67}Ga-citrate can seep through the vascular endothelium and attach to lactoferrin, which is released by leukocytes or siderophores expelled by the infectious microorganisms at infection foci [23]. Given that the siderophores have a high affinity for ^{67}Ga, they readily bind and are transported into the microorganism, to later be

phagocytized by macrophages [24]. [67]Ga is normally distributed within the liver, bone marrow, bone, soft tissues, gastrointestinal- and genitourinary tracts [21, 24]. In the past, ^{67}Ga has been used for accessing prosthetic joint infection. The reported accuracy lies between 50% [25] and 95% [26]. Gomez-Luzuriaga et al. (1988) [27] demonstrated a sensitivity, specificity and accuracy of 70%, 90% and 80%, respectively. Mountford et al. (1986) [28] and McKillop et al. (1984) [29] also reported the accuracy of gallium scintigraphy in prosthetic joint infection to be 80%. Conversely, Kraemer et al. (1993) [30] exhibited a low sensitivity of 38% but a high specificity of 100% and overall accuracy of 81%. In addition, Aliabadi et al. (1989) [31] demonstrated a sensitivity of 37% and specificity of 100%. Merkel et al. (1986) [32] presented a study showing 66% sensitivity, 81% specificity and 77% accuracy in ^{67}Ga diagnostic testing of infection in the painful prostheses. Similar results have been seen in ^{67}Ga testing in animals. Merkel et al. (1984) [33] reported a sensitivity, specificity and accuracy of 61%, 71% and 67%, respectively in loose and infected canine arthroplasty. While diagnostic testing with ^{67}Ga in prosthetic joint infections has been carried out at one time, its accuracy was not acceptable when trying to determine an infected prosthetic joint from an inflamed one. It is now typically limited to diagnosing chronic osteomyelitis, fever of unknown origin (FUO) and lung infections.

[111]In-oxine

[111]In-oxine is characterized by its ability to diffuse through the cell membrane and detach itself from the lipophilic complex, thus leading to an irreversible binding to the nuclear and other intracellular components [21, 34]. Some advantages of using ^{111}In-oxine include a 67h half-life with a constant distribution limited to the bone marrow, liver and spleen, which is a great benefit, especially in infections of the prosthetic joint and musculoskeletal system [22]. Disadvantages include not being able to use this radiotracer in inflammatory bowel diseases, as well as a 24h-interval requirement between injection and imaging [22]. The sensitivity of indium-111 LS lies within 38%-100%, specificity between 15%-100% and accuracy 60%-96% [15, 35-37]. However, in combination with technetium-99m sulfur colloid, it is possible to increase sensitivity, specificity and accuracy. Mulamba et al. (1983) [38] demonstrated a sensitivity, specificity and accuracy of 92%, 100% and 96%, respectively. Furthermore, Palestro et al. (1991) [39] exhibited a sensitivity of 86%, specificity of 97% and accuracy of 95% in 41 patients with knee prostheses suspected of being infected. In addition, Palestro et al. (1990) [40] reported a sensitivity, specificity and accuracy of 100%, 97% and 98%, respectively in 92 cemented total-hip arthroplasties. Finally, a study by Joseph et al. (2001) [41] in 58 patients before reoperation of total knee or hip arthroplasty demonstrated a sensitivity of 46%, specificity of 100% and overall accuracy of 88%. Typical indications of using ^{111}In-oxine include diagnostic imaging for prosthetic joint infections, chronic osteomyelitis and in certain cases of fever of unknown origin/occult fever [23].

[99m]Tc-hexamethylpropyleneamine oxine (HMPAO)

Labeling of leukocytes with ^{99m}Tc-HMPAO was first introduced in 1986 by Peters et al (1999) [42]. The ^{99m}Tc-HMPAO complex is able to enter the cell, transform to a hydrophilic state and then becomes trapped in the cell [23]. Some advantages of using this tracer include low radiation burden, continuous availability, cheapness and ideal γ-ray energy [43]. It also has a higher proton flux, which permits the imagining of body parts such as feet [23]. Given its low radiation, this tracer can easily be used in children. However, this tracer is less stable than ^{111}In-oxine, eluting from cells up to 7%/h, which requires imaging to occur within 2-4h after injection of the tracer [23, 43, 44]. ^{99m}Tc-HMPAO accumulated in the gastrointestinal tract, bone marrow, spleen, liver and kidneys [23]. It is commonly used in the imaging of bone/joint infection, irritable bowel disease and soft tissue infection.

Leukocyte labeling with ^{111}In-oxine or ^{99m}Tc-HMPAO

The reported accuracy of WBC-labeling combined with bone marrow imaging ranges from 86-98% of patients [39-41, 45-54]. One of the earliest studies with 30 patients examining labeled leukocytes with bone marrow imaging and hip arthroplasty by Mulamba et al. (1983) [38] observed a 92% sensitivity and 100% specificity for diagnosing hip infections. Another study of labeled leukocytes and bone marrow scans in 72 patients with hip arthroplasty by Palestro et al. (1990) [40] demonstrated 100% sensitivity and 97% specificity in diagnosing infection. A review examining 59 patients with failed hip- and knee arthroplasties by Love at al. (2004) [53] reported the sensitivity, specificity and accuracy of combined leukocyte/bone marrow scanning to be 100%, 91%, and 95%, respectively. In addition, a study by El Espera et al. (2004) [52] determined 80% sensitivity, 94% specificity and 91% accuracy in 60 patients with knee or hip arthroplasty that received combined leukocyte/bone marrow scanning. While most studies show that combined leukocyte-and bone marrow scanning is highly specific, the sensitivity of this method can vary. A study by Pill et al. (2006) [55] reported only 50% sensitivity in combined leukocyte/bone marrow scan. Furthermore, while Joseph et al. (2001) [41] reported 100% specificity in their patient population of 58 patients with total knee or hip arthroplasty, they observed only 46% sensitivity for combined leukocyte/bone marrow imaging.

It has been argued that poor sensitivity can be attributed to chronicity of an infection, as well as non-specific inflammation [29, 56-58]. While chronic infections are typically characterized by less distinct neutrophil recruitment and edema [59], a study by Datz et al. (1986) [11] that examined the labeled leukocytes in acute and chronic infections found no significant statistical difference in sensitivity. In non-specific inflammation, neutrophils are generally absent [60]. Given that LS is most sensitive in imaging neutrophil-dominate responses [60], aseptic inflammation may lead to false negative results and a decrease in sensitivity [61]. While it was once discussed that false negative results could be due to prior antibiotic treatment, several studies have shown this not to be the case [62, 63]. However, one must keep in consideration that both the activity and uptake can vary, as well as the normal distribution of WBC in the bone marrow [64]. For example, one would expect to see fewer WBC migrating to the joints of chronic infection. Furthermore, uptake depends on the number of WBC that migrate to the site of infection [64].

Despite the high accuracy of this technique, LS does have its disadvantages, which have to be considered

before performing this test. Firstly, the procedure is labor intensive. Given that two to three technologists are involved in the labeling and imaging processes, it can be estimated that a total of 8-10 hours is required from them for this technique, over two days. Furthermore, this technique is routinely available in only a few hospitals worldwide. In addition, it involves contact with blood products, which requires strict protocols, such as the use of a laminar flow hood [51, 53, 60, 65]. The indications for the combination imaging LS/BMS include prosthetic joint infection, musculoskeletal infections, and neuropathic joint [64]. Leukocyte scintigraphy has also been implemented in patients with fever of unknown origin, postoperative infections, as well as systemic infections [64].

^{18}F-deoxyglucose (FDG)

The first studies investigating the role of ^{18}F-FDG in infection imaging were first introduced in 2006 [66-68]. Cells with increased glucose requirements, such as inflammatory cells and tumor cells readily take up ^{18}F-FDG [43]. Given that deoxyglucose cannot leave the cell after it has been taken up, it can be used in the imaging of the above-mentioned cells [69, 70]. Some of the advantages of this tracer include easy preparation and imaging [43]. On the other hand, disadvantages include a short half-time of 110 minutes, as well as a low labeling efficiency when compared to ^{111}In-oxine and ^{99m}Tc-HMPAO [59]. Given the negative aspects of the tracer, two to three times more activity must be used in the labeling process, which ultimately results in a higher activity being injected into the patient [71]. In addition, given its short half-life, late images required in prosthetic joint infection imaging are not possible [59]. Physiological uptake of ^{18}F-FDG is seen in the brain, heart, kidneys and bladder [59]. Infection imaging with ^{18}F-FDG has shown high sensitivity, but low specificity, mainly due to the fact that imaging is based on increased metabolic activity [72, 73]. Thus, its role in diagnosing osteomyelitis and infected prosthetic joints is limited. One major drawback with ^{18}F-FDG in infection imaging are the artifacts adjacent to prostheses [74]. In addition, healing tissues up to 6 months following surgery, bone fractures, varicose veins and atherosclerotic lesions can all demonstrate non-specific ^{18}F-FDG uptake [75, 76]. As shown in a recent study by Aydin et al. (2015) [77] ^{18}F-FDG uptake was confined to the proximal segment of the prosthesis in 62 asymptomatic patients who underwent total hip replacement, whereby the femoral segment showed no uptake. Thus, a positive ^{18}F-FDG-scan in infection must be interpreted with caution given the various reasons that can produce false positive results [78]. Several studies have investigated ^{18}F-FDG in infection imaging. Zhuang et al. (2001) [79] demonstrated 89.5% increase in ^{18}F-FDG uptake along hip arthroplasties and 77.8% in knee arthroplasties. Chacko et al. (2002) [80] exhibited 92% sensitivity and 97% specificity in infection of hip arthroplasty. In both of these studies, intensity was not able to differentiate between aseptic inflammation versus infection. As seen in a study by Delank et al. (2006) [81] they were able to demonstrate that ^{18}F-FDG-PET was able to positively diagnose evidence of loosening in 76.4% of patients and detect periprosthetic inflammation in 100% of septic cases. However, only 45.5% of cases were positive for increased abrasion and aseptic inflammation, thus, ^{18}F-FDG-PET was not able to deduce the difference between abrasion-induced versus inflammation due to bacteria [81]. Similar results were seen in a study by Garcia-Barrecheguren et al. (2007) [82] who reported a low sensitivity (64%) and specificity (67%) of ^{18}F-FDG-PET in hip replacement infections. In regards to accuracy, Cremerius et al. (2003) [83] and Gravius et al. (2010) [84] reported roughly 89% accurate in infection of hip arthroplasties, while Manthey et al. (2002) reported 96% accuracy [85]. On the other hand, Stumpe et al. (2004) [86] demonstrated an accuracy of only 69%, with bone scintigraphy being more accurate (80%) than ^{18}F-FDG-PET in their study. Pill et al. (2006) [55] exhibited 95% sensitivity and 93% specificity in infected hip replacements, versus 50% sensitivity and 95.1% specificity of WBC/marrow imaging in a subgroup of these patients. Regardless of the different criteria on how to interpret ^{18}F-FDG uptake in infection, it has been exhibited in several studies that ^{18}F-FDG-PET is less accurate when compared to labeled WBC/bone marrow imaging in diagnosing prosthetic joint infection [53, 87, 88]. In a meta-analysis, the overall sensitivity and specificity of ^{18}F-FDG-PET in prosthetic joint infection was 82% and 87%, respectively [89]. Thus, its role in diagnosing prosthetic joint infection still needs to be determined. However, it has been shown to be important in diagnosing spondylodiscitis [79, 90, 91].

Future outlook

Recently published papers assessing future directions in leukocyte labeling include using monoclonal antibodies, SPET-CT as an adjunct to scintigraphy, as well as ^{18}F-FDG PET. The use of monoclonal antibodies such as Sulesomab for infection diagnostics has also been recently discussed and reported sensitivity and specificity lie between 75% to 93% and 65% to 86%, respectively [92-94]. Its role in infection diagnostics has, however, yet to be determined. On the other hand, the additional role of SPET-CT is a promising direction in infection diagnostics. In a study by Graute et al. (2010) [95] they were able to increase sensitivity from 66% to 89% and specificity from 60% to 73% by combining planar images with SPET-CT. Furthermore, a recently published study by Kim et al. (2014) [96], which assessed adding SPET-CT to ^{99m}Tc-HMPAO-labeled leukocytes, demonstrated an increase in sensitivity from 82% to 93.3%, specificity 88% to 93.3%, PPV from 89% to 94.3% and NPV 80.5% to 92.1% and diagnostic accuracy from 84.8% to 93.3%. Additionally, a study by Bar-Shalom et al. (2006) [97] demonstrated the additional role of SPET/CT in patients with ^{111}In-WBC, as it is able to provide exact localization, as well as the extent of the infection, thus improving diagnosis. In addition, Filippi et al. (2006) [98] demonstrated 100% accuracy when using SPET/CT with ^{99m}Tc-exametazime labeled leukocytes in patients with suspected musculoskeletal infection, compared to 64% when using solely scintigraphy. Horger et al. (2003) [99] exhibited 97% accuracy when using ^{99m}Tc-labeled anti-granulocyte antibody and SPET/CT in the diagnosis of bone infection versus 59% accuracy of scintigraphy alone. It is believed, in accordance with other studies that the CT component increases the sensitivity by precisely localizing the anatomical site of infection [98]. Lastly, the role of ^{18}F-FDG PET has showed great potential for infection diagnostics and for studying bone metabolism. A study by Sterner et al. (2007) [100] was able to

demonstrate that the sensitivity, specificity and accuracy of ^{18}F-FDG PET, 100%, 56%, and 71%, respectively, were higher when compared to radiographs with 43%, 86%, and 64%, respectively, when assessing for aseptic loosening in 14 patients with painful knee arthroplasties. Kobayashi et al. (2011) [101] exhibited sensitivity 95%, specificity 88% and overall accuracy 91% of ^{18}F-PET in 49 patients following total hip arthroplasty with significant differences shown between the maximum standardized uptake value (SUVmax) values for aseptic and septic loosening. Several studies by Ullmark et al. (2012, 2013) [102, 103] demonstrated the promising role of ^{18}F-FDG PET in analyzing bone formation. While SPET-CT increases sensitivity through the CT component, an increase in sensitivity leads to a decrease in specificity. In conclusion, until the roles of SPET-CT and ^{18}F-FDG PET in diagnostic infection imaging can be determined, the combination of LS with bone marrow imaging is an accurate technique in diagnosing prosthetic infections.

Conclusion

Nuclear medicine plays a vital role in diagnosing prosthetic joint infections. This review has shown that currently, WBC/bone marrow imaging is the best available diagnostic imaging test. Newer imaging modalities, such as SPET-CT may in the future, play a bigger role in diagnosing prosthetic joint infections, especially given that it can provide us with important additional information, such as exact anatomical location. The roles of ^{18}F-FDG PET and ^{18}F-FDG PET/CT have yet to be determined.

The authors declare that they have no conflicts of interest.

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