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The Use of Magnetic Resonance Imaging (MRI) and Other Imaging Modalities in Diagnosing and Monitoring Diabetic Foot

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The aim of this study is to review the diagnostic and monitoring performances of MRI and PET/CT in assessing diabetic foot complications, such as diabetic foot osteomyelitis (DFO) and Charcot neuro-osteoarthropathy (CN). Moreover, the goal is to identify the use of Near Infrared Radiation (NIR) as a clinical translation for screening and monitoring complications with no radiation exposure. Almost all the published materials included in this study were searched in the Scopus database and limited from the year 2000 to 2018 which resulted in 277 papers. Only 47 were utilized. In comparison, modalities have their own clinical strengths and limitations in terms of sensitivity and specificity, demonstration of anatomical details, confirmation of diagnosis and extent of infection, and radiation exposure. Also, NIR as an emerging tool could be a modality of choice in measuring blood glucose concentration within the body.

Keywords : diabetes foot, MRI, PET/CT, NIR, osteomyelitis, charcot foot

1. Introduction

Diabetes Mellitus (DM) or Diabetes is a metabolic, non-infectious, and non-pathogenic disease characterized by a high glucose level in the blood [1]. It is a multi-systemic disease that affects anyone regardless of age, gender, and group [2]. The International Diabetes Federation (IDF) estimated that there are 415 million people suffering from DM globally and this number tremendously increased from the year 2000 which is more than doubled. It is expected that in the year 2040, 10 % of the population worldwide will be affected by constituting to 642 million people [1]. Knowing this increasing number of individuals suffering from DM, the disease is considered common, large, and growing problem all throughout the world that will most likely to rise continuously in the coming years [3].

Looking closely, the disease has two main types such as the Type 1 DM (formerly known as insulin-dependent, juvenile or childhood-onset diabetes) and Type 2 DM (non-insulin dependent or adult-onset diabetes) [4]. Type 1 DM occurs when the pancreas in the body produces not enough amount of insulin due to the destruction of insulin-producing B cells in the islets of Langerhans. It has the highest incidence among individuals with age ranging from birth to 14 (0-14) years and accounts for about 5 to 10 % of patients with DM [5]. The second main type is the Type 2 DM which is a chronic hyperglycemic condition that exists when there is a relative and absolute deficiency of hormone insulin within the body [6]. Majority of people suffering from DM around the world have Type 2 DM and as compared to Type 1 DM, the symptoms are similar but are often less marked or asymptomatic. This is the reason why some cases are undiagnosed until the complication arises. For the past few years, only adults are suffering from Type 2 DM but nowadays, children have begun to develop this as well [4].

Among all the body parts, the foot is considered to be the crossroad of any pathological processes for patients with DM. It involves the entire parts of the lower extremity starting from the skin, soft tissues, muscles, bones and joints to nerves and blood vessels [7]. Variety of clinical derangement detected proved that foot is the

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distinct body part where the manifestations of this condition are really visible [2]. Neuropathy is said to be the main reason why diabetic patients are prone to foot ulcerations characterized by nerve damage in the lower leg and feet due to the high sugar level in the blood for a long period of time. This has early symptoms of pain progressing to numbness and loss of sensation in a more advanced condition that leads to ulceration [8]. Likewise, those individuals who have DM for a longer period of time tend to develop peripheral neuropathy together with the peripheral vascular disease which involves micro-vascular dysfunction that leads to foot complications. The lifetime risk of developing these complications is 25 % and was said to be the highest reason for hospitalization in cases related to DM. In the year 2017, greater than 50 % of the diabetic foot were infected [9]. This involves the soft-tissues and bones of the foot which are considered to be the most common long-term complications [3].

Diabetic foot infection (DFI) arises due to the invasion and multiplication of microorganisms on the host tissues that is dependent on the disease duration and therefore the likelihood of complications [10]. It is regarded as an infra malleolar infection in patients suffering from DM which includes the following, such as paronychia, cellulitis, myositis, abscess, necrotizing fasciitis, septic arthritis, and osteomyelitis [11]. Sadly, an individual suffering from DFI like diabetic foot osteomyelitis (DFO) may have this condition without having any signs and symptoms and this is the reason why it is frequently overlooked [12]. Also, patients who are suffering from DM are the high risk of developing Charcot neuro-osteoarthropathy (CN). In this complication, the foot and the ankle are the most commonly affected areas which can be classified as either acute or chronic. The acute condition involves active inflammation in a localized area while the chronic condition is not characterized by local inflammation but involves destruction, subluxation, dislocation, and deformity of varying degrees of the bones and joints of the foot [3]. In the year 2017, there is an estimated general percentage of point zero eight percent among the diabetic population and can have a range of up to 13 % for those patients who are high risks [13]. One in every six hundred eighty people tends to develop this condition [14].

The mentioned foot complications associated with DM is considered to be the major reasons for non-traumatic amputations of the lower extremity which is 15 to 45 times higher in comparison to those individuals who are not suffering from DM. This higher prevalence is due to structural deformity of the foot, peripheral neuropathy, and occlusive disease in the arteries within the peripheral region [15]. This affects the economic stability of patients, families, and societies [16]. According to National Health Service (NHS), in their overall budget, five percent accounts for the cost of treatment for DM and 20 to 40 % are being allocated for the treatment of diabetic feet [17]. Therefore, it is undeniably true that the government is allocating more money to effectively manage this condition as compared to education and defense sector of the country that affects its economic development [1].

The progressive characteristics of the disease demands for the importance of early diagnosis [18]. This cannot be underestimated for a missed diagnosis has a high probability of morbidity among patients leading to limb amputation while over diagnosis will contribute to the overspending of resources that will lead to burden among healthcare systems like the unwise use of antibiotics. Indeed, assessing diabetic foot complications in a timely manner is important to have an appropriate decision for the treatment of the disease [19]. It must also be remembered that the important goals of healthcare systems are the early diagnosis, prevention of possible diseases, and therapeutic strategy for each individual. Nowadays, we cannot hide the fact that nuclear medicine and radiology have the potential capacity to provide the increasing demands in diagnosis, disease prevention, understanding disease pathophysiology, and including the possible treatments to be given [12]. Imaging studies play an important role in timely diagnosis [20].

Nowadays, Near Infrared Spectroscopy (NIRS) is currently becoming known as a non-invasive and non-ionizing technique used to image soft tissues in the body using near-infrared (NIR) light ranging from 650 to 1000 nm [21]. It non-invasively explores the hemodynamic concentration in the soft tissues which monitor the oxygen delivery and consumption within the body [22]. Oxygenated and deoxygenated blood is said to have a different NIR light spectrum which allows imaging of the venous blood [13]. This defines NIRS as the optical method that non-invasively measures tissue oxygenation level [23]. This paved way for the measurement of glucose concentration in the body through monitoring of human blood biochemistry [1].

The present study will focus on the diagnosis and monitoring of diabetic foot complications such as DFO and CN using Magnetic Resonance Imaging (MRI) and Positron Emission Tomography/Computed Tomography (PET/CT) imaging modalities from the year 2000 to 2018. Specifically, the study will highlight the strengths and limitations, such as average sensitivity and specificity, superb ability to demonstrate bone and soft tissues in the body, determination of diagnosis and extent of infection, and radiation exposure. For future study, comparative

analysis between the results of Fluorine 18-fluorodeoxy-glucose (18F-FDG) PET/CT and NIRS in diagnosing and monitoring diabetic foot complications will be done.

2. Literature Survey

Almost all published materials included in this study were searched in the Scopus database. The main keywords used were: Diabetes and Foot, supported by MRI or PET or CT or NIR and limited from the year 2000 to 2018 which resulted in 277 published materials. The authors purchased the license to use Scopus database for a complete access but few published papers were rejected for several reasons, such as discussion focused on other topics (treatments, other pathological conditions, and other body parts) not written in the English language. From 277 published materials, only 43 were included in the study. The other 4 papers were accessed from (1) World Health Organization report, (1) SpringerLink and (2) Science Direct database. Total of forty-seven (47) published materials were included.

To show the different performance characteristics of the aforementioned imaging modalities, separate tables for the performance characteristics of MRI and PET/CT in diagnosing DFO and CN were shown. Those clinical research papers with indicated estimator values, such as sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were grouped and separated from the systematic review, meta-analysis, and editorial papers. Clinical research paper results were collated and presented using a table. Moreover, a separate table of previous studies using NIR was presented. For the summary, MRI and PET/CT were compared and the characteristics and usage of NIR based on several studies were shown separately.

As shown in Table 1, over the past 19 years, from the year 2000 to 2018, Scopus database showed an increase in the number of published materials focused on the performance characteristics of different imaging modalities in diabetic foot complications. Specifically, this study summarized the diagnostic and monitoring performances of MRI and PET/CT in DFO and CN.

Table 1. The Number of Published and Selected Papers from the year 2000 to 2018.

Year	Number of Published Papers in Scopus Database	Number of Published Papers Selected in Scopus Database	Other Sources
2000-2004	31	1	1
2005-2009	70	9	1
2010-2014	90	15	1
2015-2020	86	18	1
Total	277	43	4
		47	

3. Diabetic Foot Osteomyelitis (DFO): MRI

DFO is characterized by the infection of the nearby tissues including abscess and sinus tract that affects the cortical part of the bone leading to bone marrow [2]. The infection starts from having a break in the skin within the site of mechanical or thermal trauma or ulceration that leads to invasion and multiplication of microorganisms within the soft-tissue that resulted to inflammatory response [7]. It is said to occur to 20 % of patients with mild to moderate soft tissue infections and 50 to 60 % for severely infected. With the present situation, the complication must be diagnosed to decrease the risk of amputations globally [24]. However, early diagnosis is affected by two (2) important factors. First, it takes several weeks before it is clinically evident in the radiograph and second, the condition may resemble with CN or may co-exist with it [25].

Accurate and early diagnosis of DFO remains a challenge and based on the appropriateness criteria of American College of Radiology (ACR), aside from conventional radiography, MRI must be used in the assessment of diabetic patients having diabetic foot symptoms. This modality has proven its capability in identifying and specifying the extent of infection. In addition, its reliability as a preoperative standard examination for diabetic patients suffering from poor wound healing has been confirmed [8]. These recognized diagnostic capabilities of MRI led to several studies reviewing its performance characteristics.

In Table 2, a total of 161 patients have included in the study and all of them had a medical history of DM with lesion or ulcer. Across all studies, T1 weighted spin echo (SE) sequence was used as part of the scanning parameter and all involve the acquisition of images with and without contrast. In addition to the T1 weighted SE sequence, other scanning parameters were also used by the authors. In the study of Ertugrul *et al*., 2006 turbo inversion recovery magnitude (TIRM) was also used for non-contrast imaging having repetition time/echo time (TR/TE) of 5349/71; field of view (FOV): 200; matrix size (M): 256 × 256, and slice thickness (ST): 4 mm [26]. An amount of 0.1 mmol/kg Gadolinium diethylenetriamine-pentaacetic acid (Gd-DTPA) contrast medium was used in T1 SE and F1 fat saturation sequences parameter [26].

The additional pre-contrast scanning parameter used by Schwelger *et al*., 2008 were T2-weighted fat-suppressed

Table 2. Performance Characteristics of MRI in Diagnosing and Monitoring DFO with indicated Estimator Values.

Year	Author	Patient (N) Patient Profile (PP)	Medical History, Criteria for inclusion and Exclusion	Performance	Remarks Advantage	Remarks Disadvantage
2006	Ertugrul *et al.* [26]	N: 31 patients PP: *nothing mentioned*	(+) DM (+) Clinically suspected lesion Size: ≥ 2 cm Depth: ≥ 2 cm Basis: Wagner Classification	Sensitivity: 78 % Specificity: 60 % PPV: 90 % NPV: 37.50 %	It can determine the extent of soft tissue and bone involvement. It is useful for surgical planning	It cannot determine the involved pathogenic organisms and the use of antibiotics for therapy
2008	Schwelger *et al.* [27]	N: 20 patients PP: *nothing mentioned*	(+) DM (+) Chronic foot ulcer > 8 weeks (–) Antibiotic pretreatment (–) Clinical indications of osteomyelitis	Sensitivity: 86 % Specificity: 92 % Accuracy: 90 %	The modality of choice in diagnosing osteomyelitis for providing good anatomical details	The possibility of differentiating infection between bone marrow edema is not always
2012	Rouge & Pierre [2]	N: 110 patients only 85 patients met the inclusion criteria PP: *nothing mentioned*	(+) DM (+) Bone lesion (–) history of foot surgical operation High resolution of radiographic images No artifacts	Sensitivity: 40 % ~ 100 % Specificity: 93 % ~ 100 %	The use of MRI with contrast media can help in determining the osteomyelitis and other entities such as infarct and necrosis	No mentioned disadvantage

Note: For medical history and criteria for inclusion and exclusion, the actual medical terms used in the published papers where adapted

fast- or turbo SE sequence (echo-train length: 8; TR/TE: 2000-4620/75 to 105 (effective); M: 256 × 224 or 256 × 256) and fast SE sequence parameters (echo-train length: 8; TR/TE: 35004800/40-75 (effective); inversion time (TI): 150 ms and M: 256 × 192 or 256 × 224). For contrast imaging, fat-suppressed T1-weighted SE sequence using 0.1 mmol/kg^{-1} Gadopentate-dimeglumine was selected [27]. Lastly, in the study of Rouge & Pierre, 2012 [2] fat saturation short-inversion-time recovery (STIR) was also included in the scanning parameter. The contrast medium used was not mentioned.

On the three studies, the recorded sensitivity ranged from 40 % to 100 %, specificity was 60 % to 100 % and only Ertugrul *et al*., 2006 had recorded PPV (90 %) and NPV (37.50 %). It was concluded that MRI is a good modality of choice in diagnosing osteomyelitis for it has the superb ability to demonstrate the anatomical details and also the extent of its involvement [26]. This was also supported by the study of Lipsky *et al*., 2004 [11] and Markanday, 2014 [25] that MRI can image the infection of bone and soft-tissue however, it's inability to determine the microorganisms, use of antibiotic therapy, and difficulty in differentiating infection and bone marrow were considered disadvantages that affect its specificity.

The review papers of Palestro, Love & Miller, 2006 [28], Schweitzer *et al.*, 2008 [29], and Pectasides & Kalva, 2011 [30], supported the mentioned advantages. Palestro *et al*., 2006 focused on musculoskeletal infections and documented that MRI sensitivity was 92 %, specificity was 82 %, and NPV was 100 % [28]. The study of Schweitzer *et al*., 2008 focused on several clinical situations were osteomyelitis or diabetic pedal disease was suspected. This study mentioned that the best way to confirm osteomyelitis was with the use of MRI even with no presence of ulcer but still suspected for having infection [29]. In 2013, the study of Fujii, Armstrong & Terashi reviewed 16 medical records from the year 2008 to 2012 focused on cases of DM foot with an ulcer that has undergone surgery. The stated sensitivity was between 90 % to 100 % and 80 % to 100 % specificity. The reported accuracy was considered unclear since it cannot accurately determine DFO with the

Table 3. Performance Characteristics of MRI in Diagnosing and Monitoring DFO without indicated Estimator Values.

Year	Author	Patient (N) / Patient Profile (PP)	Medical History, / Criteria for inclusion and Exclusion	Remarks
2012	Kashiwagi *et al.*, [32]	N: *not specified* PP: 7 to 8 month old Sprague Dawley Rats	(+) Induced Diabetes 65 mg/kg, Sigma Chemical, St. Louis, MO, USA; injected STZ after overnight fasting	Assessing the presence of peripheral tissue perfusion is possible with Dynamic Contrast Evaluation (DCE) technique
2015	Zheng *et al.*, [33]	Total N: 10 participants N: 5 diabetic patients PP: 65 ± 4 years N: 5 healthy volunteers PP: 71 ± 3 years of age	(+) Type I or II DM for 1 to 10 years HbA1c = 7.2 ± 1.8 % (+) Neuropathy (3 patients only) (–) Peripheral Artery Disease Exclusion criteria: (+) Metal implants or pacemaker (+) Lower limb amputation > digits > 400 lbs (*MRI table limitation*)	Diabetes foot evaluation pre and post medical treatment is possible by doing non-contrast MRI perfusion angiosome
2016	Stacy *et al.*, [34]	N: 10 subjects PP: Male	Healthy based on the administered standard medical history questionnaire and International Physical Activity Questionnaire for activity levels involvement a week prior to study (+) 8 hours fasting	Level of blood oxygen in the foot area can be assessed through MRI Blood Oxygen Level Dependent (BOLD) Technique

Note: For medical history or criteria for inclusion, the actual medical terms used in the published papers where adapted

presence of ischemia [31]. This was contradictory to the study of Schwelger *et al.*, 2008 for having an accuracy of 90 % [27]. The authors concluded that the difference between the reported accuracy was due to the different medical history of subjects involved.

In Table 3, aside from healthy and diabetic individuals, the study of Kashiwagi *et al*., 2012 Sprague Dawley rats were employed as subjects [32]. Different MRI imaging techniques in diagnosing DFO were employed, such as the DCE, non-contrast MRI perfusion angiosome, and BOLD.

In 2012, the scanning parameter used in the study of Kashiwagi *et al.*, were T1 weighted SE and gradient echo pulse sequence. The contrast imaging was also done with using 0.1 mmol/kg Gd-DTPA (TR/TE: 15.625/1.5 ms; FOV: 30 × 30 mm^2; M: 128 × 128; flip angle: 20 degrees; averages: 1 and ST: 3 mm) [32]. Meanwhile, Zheng *et al.* in 2015 also did pre-contrast imaging specifically for calf arteries and for side and plantar part of the feet. True fast imaging with steady-state precession (TFSIP) and T1 weighted high-resolution imaging with 3 slices and SE sequence were used respectively. Perfusion imaging was also done in this study using single-shot gradient-echo acquisition for each image [33] and in 2016, Stacy *et al*., used BOLD imaging and T1 weighted SE sequence scanning parameters [34].

4. Diabetic Foot Osteomyelitis (DFO): PET/CT

Nuclear Medicine plays a valued role in diagnosing infection and inflammation and one of the modalities being used is the hybrid PET/CT [18]. This emerged as an alternative tool in diagnosing DFO [20]. This radiographic imaging modality uses 18F-FDG radiotracer which has low physiological uptake in normal organs that resulted to high target to background ratios. In comparison with other conventional radiopharmaceuticals, the cost and dosimetry are said to be favorable and it is considered sensitive for having high NPV although its limiting factor is its specificity. In terms of clinical procedures, a single examination can be completed only within a couple of hours and not days [18]. This modality also offers an option for quantitative and semi-quantitative image analysis [20]. With the mentioned advantages, several papers reviewed the performances characteristics of PET/CT in diagnosing and monitoring DFO.

In Table 4, a total of 228 patients were included in the study. In 2010, in the study of Nawaz *et al*., 18 cm axial and 56 cm trans-axial FOV was used having 86 cm diameter. The documented energy resolution at full width half maximum was 17 % and the reconstructed spatial resolution was 4.8 [35]. Meanwhile, Kagna, Srour, Melamed, Militianu & Keidar, 2012 used the following

Table 4. Performance Characteristics of PET/CT in Diagnosing and Monitoring DFO with indicated Estimator Values.

Year	Author	Patient (N)	Medical History,	Performance	Remarks
		Patient Profile (PP)	Criteria for Inclusion and Exclusion		
2010	Nawaz *et al*., [35]	N: 110 patients	< 200 mg/dl serum glucose level Not MRI contraindicated	Sensitivity: 81 % Specificity: 93 % PPV: 78 % NPV: 94 % Accuracy: 90 %	In comparison with MRI, it has higher specificity and NPV and considered as a highly specific imaging modality in diagnosing osteomyelitis. MRI has limitations of having low specificity and contraindications.
2012	Kagna *et al*., [36]	Total N: 39 patients PP: 29 male, 10 female 28 to 71 years of age	(+) Type 2 DM: 38 patients for 4 to 25 years (+) Type 1 DM: 1 patient for 4 to 25 years (+) Use of insulin: 28 patients (+) Antibiotic therapy Criteria for having infected foot: (+) non-healing wounds (+) necrotic ulcers (+) cellulitis (+) severe pain with or without systemic fever	Patient-based: Sensitivity: 100 % Specificity: 92 % PPV: 87 % NPV: 100 % Accuracy: 95 % Lesion-based: Sensitivity: 100 % Specificity: 93 % PPV: 90 % NPV: 100 % Accuracy: 96 %	The high sensitivity of this modality is important in the diagnosis and further management of this condition. Also, the reported high NPV showed this as an excellent tool for excluding infection with a high degree of certainty.
2015	Shagos *et al.*, [19]	Total N: 79 patients Group I: 36 patients Group II: 43 patients PP: 58 males, 21 females 40 to > 70 years of age	Inclusion criteria: (+) Type 1 DM (+) Type 2 DM (+) pain (+) edema (±) bony deformity (±) ulcer (±) bony deformity Suspected for CN/cellulitis, DFO Exclusion criteria: < 6 weeks foot surgery from the day of study	Specificity: 71 % NPV: 71 %	Compared to Three Phase Bone Scanning, it has higher specificity and NPV which showed its importance in therapeutic decision making.

Note: For medical history and criteria for inclusion and exclusion, the actual medical terms used in the published papers where adapted

scanning parameters: CT scan technical factors used: 140 Kv and 90 mA; the number of slices: 4 slices at 0.8 seconds (sec) per rotation; pitch: 0.75:1 and ST: 5.0 mm with a dedicated full-ring PET scanner [36]. Lastly, Shagos, Shanmugasundaram, Varma, Padma & Sarma, 2015 used low dose CT correlation for a single bed position and images were acquired for two (2) minutes (min) duration [19]. As stated, the radioactive tracer for each study were not exceeding 10 mCi, 5 to 15 mCi, and 5 mCi respectively [35, 36, 19]. In terms of visual qualitative criterion, the patients were said to be positive for DFO when FDG uptake was increased focally with a clearer intensity compared to adjacent structures physiological uptake and it is localized in the bony structures [35, 36, 19].

The reported sensitivity for Table 3 ranged from 81 % to 100 %, specificities were almost the same, such as 92 % and 93 %, PPV of 78 % to 90 %, NPV of 71 % to 94 % and accuracy of 90 % to 96 %. The studies of Nawaz *et al*., 2010 [35], Kagna *et al*., 2012 [36], and Shagos *et al.*, 2015 [19] pointed out that PET/CT has high NPV in diagnosing osteomyelitis. This modality is said to be highly specific, excellent in excluding infection and important in therapeutic decision making. Moreover, this was supported by the review paper of Sheleg & Keidar, 2018 focusing on chronic limb osteomyelitis which stated that PET/CT can discern bone and soft-tissue involvement because of high target background ratio and high spatial resolution [37]. Also, in the systematic review and

meta-analysis written by Lauri *et al*., 2017 that focused on DFI and the comparison of four imaging modalities commonly used in diagnosing this condition (MRI, 111In-oxine–WBC SPECT/CT, ^{99m}Tc-HMPAO–WBC SPECT/CT, and 18FFDG–PET/CT), 18F-FDG–PET/CT and 99mTcHMPAO–WBC have the highest specificity of 92 %, followed by MRI and 111In-oxine–WBC SPECT/CT having 75 %. The sensitivity of all the three modalities was almost similar to MRI having 93 % (111Inoxine–WBC scans, 92 %; 99mTc-HMPAO–WBC scans, 91 %; and 18F-FDG–PET/CT, 89 %) [9].

In the published paper written in 2010, Glaudemans & Signore mentioned that PET/CT has an important role in the assessment of chronic osteomyelitis, however, using this modality together with other conventional methods for diagnosing uncomplicated acute cases may have a limited value and solid evidence-based criteria for FDG to be used in infections should be provided [38]. Indeed, in 2011, Israel & Keidar reported in their study that FDG is recommended to use for chronic osteomyelitis. At the same time, this is less expensive compared to other radiotracers. The sensitivity was 95 % and specificity ranged from 75 % to 99 % [39]. Moreover, in the editorial paper written by Papanas, Zissimopoulos & Maltezos, 2013, it was stated that accumulation of radiotracer in the infected site allows diagnosis and differentiation of this condition from CN foot because it has high resolution, allows visualization of small bones, and image analysis has an option of quantitative or semi-quantitative. However, an inconsistency regarding the result of 18F-FDG in the diabetic foot was also mentioned [20].

5. Charcot neuro-osteoarthropathy (CN): MRI

It was in 1868 when Jean Marie Charcot made the first description of CN associated with tabes dorsalis in the foot and ankle. CN of the foot and ankle was said to be less misunderstood including its evaluation and management until W.R. Jordan established the relationship between neuro-osteoarthropathy and DM [13]. This condition is characterized by the increase in glucose concentration in the blood damaging the nerves in the lower leg and feet. Early symptoms involve pain progressing to numbness and loss of sensation leading to ulceration resulting in amputations of toes, thumbs or feet [10]. Clinically, this condition cannot be easily differentiated from infection for the affected foot appears as warm with a swollen foot and ankle [13]. Acute active stage and the chronic inactive stage are the (2) two phases of CN [14]. Comparing the two, acute CN as stated can be clinically described as less swollen, red and hot, and may only be painful when acted upon by weight [40]. In comparison with contralateral foot, the temperature is 2 degrees Celsius hotter and can be high as 10 degrees Celsius as measured by infrared skin thermometer. Meanwhile, for chronic CN, it is usually less than 2 degrees, might have the presence of edema and it is no longer warm and red [14]. The condition occurs when acted upon by continued weight of the body through walking and inflammation causing fractures in bones and joints [40]. The general estimated prevalence in 2017 was less than one percent, however, for patients who are at high risks it can range up to 13 % [13]. Even though CN is considered a rare complication, this condition still causes a reduction in quality of life among patients causing anxiety and depression. The increasing health economic costs became the societal concern as well [41]. Accordingly, many works of literature have been written regarding the use of MRI in diagnosing osteomyelitis and little attention has been given to follow-up CN cases. Managing this condition is still considered a challenge among physicians [42].

In Table 5, the study of Zampa *et al*., 2011 acquired pre-contrast and contrast imaging. In contrast imaging, fast SE T1 weighted and fast inversion recovery sequences were the scanning parameters used for axial and sagittal planes. Moreover, for abnormal bone marrow signal inten-

Table 5. Performance Characteristics of MRI in Diagnosing and Monitoring CN.

Year	Author	Patient (N)	Medical History,	Remarks
		Patient Profile (PP)	Criteria for Inclusion and Exclusion	
2011	Zampa *et al*., [42]	N: 40 patients PP: 22 male, 18 female Age: 53.8 ± 13	(+) Type 1 DM: 17 patients (+) Type 2: 23 patients (+) Unilateral Acute Charcot foot for ≥ 5 years (+) Peripheral Neuropathy (+) Lesion	The modality is non-invasive and the procedure can be well tolerated by patients. In the early stages of this condition, sensitivity is particularly high for bone marrow and soft-tissue abnormality diagnosis and most especially when dynamic MRI is performed

Note: For medical history and criteria for inclusion and exclusion, the actual medical terms used in the published papers where adapted

sities dynamic MRI was applied using the fast spoiled gradient echo (TR/TE: 80-90/2.1 ms; flip angle: 75 degrees; ST: 7-8 mm; M: 320-256 × 160; acquisition time: 10 to 12 sec). An amount of 0.1 mmol/kg Gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) was used and the sequence was repeated for contrast imaging. Also, the study described the use of MRI as non-invasive and can be well tolerated by the patients [42] which was contradictory to the review paper written by Sheleg & Keidar, 2018. MRI is the modality of choice due to its high reported accuracy but this modality has limitations, such as low tolerability of the procedure, patient motion artifacts, contraindicated to patients with metal implants and for individuals who are claustrophobic, not available in many locations, and high cost. More over, their study also mentioned that MRI has difficulty in differentiating foot infection and CN. This is most likely for patients who have cases of infection superimposed on chronic changes, who have a history of recent surgical procedure or presence of osteosynthesis material at the region of interest [37].

6. Charcot neuro-osteoarthropathy (CN): PET/CT

In a condition like CN, the risk of false positive from the increased marrow turnover is one of the biggest challenges considered in nuclear medicine imaging specificity [13]. PET/CT using 18F-FDG is currently one of the modalities being used.

In Table 6, the study of Basu *et al*., 2007 was similar to the typically limited imaging which was completed in less than 30 min. The determination of abnormally increased uptake was based upon the conventional method of visual assessment that involves the unilateral Charcot's foot evaluation such as the asymmetry and symmetry. Moreover, this study showed that FDG PET is important in diagnosing CN and this has higher specificity and accuracy as compared with MRI [43]. On the other hand, in the study written by Peterson, Widnall, Evans, Jackson & Platt, 2017 it was mentioned that this can be used in determining this diabetes complication, however, several studies presented different sensitivities and specificities [17]. The authors of this study believed that different medical history and number of patients might be a factor for having different performances.

7. Near-Infrared Spectroscopy (NIRS) for Screening Diabetic Foot

NIRS is considered as an emerging tool that non-invasively uses non-ionizing radiation specifically NIR light with a wavelength of 650 to 1000 nm to image tissues in the body that focuses on oxygenated and deoxygenated hemoglobin concentration [21]. The regional Oxygen saturation in the specific part of the body can be measured through the changes in the absorption spectrum of the hemoglobin. It is the modified Lambert-Beer law that describes how the changes in the concentration of the dissolved chromophores in the blood affect the NIR light absorption [23].

Table 7 shows the results of different studies that used NIR to measure the oxygenated and deoxygenated hemoglobin concentration in the body. The results showed

Table 6. Performance Characteristics of PET/CT in Diagnosing and Monitoring CN.

Year	Author	Patient (N) / Patient Profile (PP)	Medical History, / Criteria for Inclusion and Exclusion	Remarks
2007	Basu *et al.*, [43]	Total N: 63 patients divided into 4 groups: N: 17 patients (Group A) PP: 11 male, 6 female Mean Age: 59.4+/–8.6 years N: 21 patients (Group B) PP: 16 male, 5 female Mean Age: 63+/–10 years N: 20 patients (Group C) PP: 12 male, 8 female Mean Age: 54+/–19 years N: 5 patients (Group D) PP: 3 male, 2 female Mean Age: 61.2+/–13.9 years	Group A (+) Charcot Neuroarthropathy Group B (+) Uncomplicated Diabetic Foot Group C (–) DM with normal lower extremities Group D (+) Osteomyelitis secondary to complicated Diabetic foot	FDG PET has a valuable role in differentiating CN foot from DFO is with or without the presence of an ulcer. It was noted that when Charcot Neuro-osteoarthropathy were compared with normal and uncomplicated joints, there was a low degree diffuse uptake in the joint. FDG PET Sensitivity: 100 % Accuracy: 93.8 % MRI Sensitivity: 76.9 % Accuracy: 75 %

Note: For medical history and criteria for inclusion and exclusion, the actual medical terms used in the published papers where adapted

Table 7. Blood Oxygen Level Measurement using Near Infrared Spectroscopy (NIRS).

Year	Author	Patient (N) / Patient Profile (PP)	Medical History, / Criteria for Inclusion and Exclusion	Result
2009	Papazoglou *et al*., [44]	N: 11 patients 65 years of age	(+) DM for at least 6 months (+) The chronic wound in the ankle or foot Size: 1 cm^2 × 1 cm^2	Diffuse Photon Density Wave and NIR used a wavelength of 685 to 830 nm and were able to distinguish non-healing and healing ulcer. This indicates that NIR could be of use in determining the wound healing potential.
2010	Neidrauer *et al*., [45]	N: 16 patients 30 to 65 years of age	(+) DM for at least 6 months (+) Wound Size: 1 cm^2 (+) excision of infected bone (+) pre-antibiotic treatment	Measured the hemoglobin level through the linear rate of change which can be used to differentiate the healing and non-healing diabetic foot ulcers.
2015	Godavarty *et al.*, [21]	N: 4 subjects PP: 56 to 75 years of age	(+) DM (+) Healing and non-healing foot ulcer only in one foot	The contrast profile determined the healing and non -healing diabetic foot ulcer since NIR light absorption corresponds to oxygenated and deoxygenated hemoglobin concentration in the blood
2017	Chen *et al.*, [46]	N: *not mentioned* PP: Patients treated in tertiary wound care center for DFU between January 2015 to August 2015	(+) DFU Exclusion Criteria: Unable to coordinate (+) Smoking within 24 hours prior to the examination With the history of amputation, bypass surgery, and venous ulcer	NIRS allowed monitoring of the lower extremity non-invasively, continuously, accurately, conveniently, and remotely. Also, it was proven that performing the exercise can increase the oxygenation in the peripheral tissues of the lower limb.
2017	Arabi *et al*., [1]	Total N: 10 patients N: 5 diabetic patients N: 5 controlled participants PP: *Nothing mentioned*	(+) DM	The pixel intensity in the NIR images showed that in diabetic patients thermoregulatory compression and expansion of blood vessels in the foot are more affected compared to healthy individuals with smooth contractions.
2018	Manfredini *et al*., [22]	N: 80 patients PP: 63 males	(+) Peripheral Artery Disease: 80 patients (+) Co-existing DM: 41 patients	NIRS technique measured the hemodynamic Oxygen level during the study. It can also monitor the oxygenation in the tissue level aside from the skin in the foot. It can also be used in outpatient under the normal condition which does not need any of the following such as calibration, warm-up procedures, disposable and supplies, and specifically trained personnel.
2018	Arabi *et al*., [47]	Total N: 10 patients N: 5 diabetic patients (S1-S5) N: 5 healthy patients (C1-C5)	(+) DM: 5 patients	The pixel intensity matrix of NIR images after subjecting the feet to cold stress showed that it is possible to develop an automatic screening system to diagnose early diabetic foot

Note: For medical history and criteria for inclusion and exclusion, the actual medical terms used in the published papers where adapted

that NIR was able to determine the wound healing potential through the contrast profiles, the linear rate of change of hemoglobin, the importance of exercise in improving the oxygenation in the lower extremity through the analyzed pixel intensity acquired using NIR. In addition, it was seen that thermoregulatory compression

and expansion of the blood vessels within the foot area contracted smoothly for healthy individuals in comparison with patients suffering from DM. In the study of Manfredini *et al*., it was pointed out that NIR can be used under the normal out-patient condition without doing any warm-up procedure, no supplies and disposables needed, no special training required to operate the device and can be remotely used [22].

8. Summary

The literature review from the year 2000-2018 showed the comparison of both imaging modalities in terms of the average sensitivities and specificities, demonstration of anatomical details, confirmation of the diagnosis and extent of infection and radiation exposure. Also, the characteristics and usage of NIR were determined based on previous studies.

In Table 8, data showed that PET/CT has higher sensitivity and specificity compared to MRI in diagnosing and monitoring DFO. However, PET/CT has the risks of radiation exposure among patients. Both imaging modalities have the ability in demonstrating superb anatomical details most especially in determining the diagnosis and extent of infection. In the study, no table was provided for the comparison of two imaging modalities in diagnosing and monitoring CN for the reason that different performance characteristics were reported within the papers searched. Also, only a few papers focused on this condition and one of the factors considered by the authors that might be attributed to this is for CN being considered as a rare complication which was supported by the Wennberg *et al*., [41]. In the year 2017, Womack mentioned that the general prevalence within the entire diabetic population was only point zero eight percent and can increase up to 13 % for those who are high risks [13].

Meanwhile, based on the results of several studies, NIRS being the newly emerging tool have proven its characteristics and use in determining the oxygenated and deoxygenated hemoglobin concentration in the body (see Table 9) and this could be of use to the increasing number of people suffering from DM. NIRS will allow diagnosis and monitoring at low cost with no radiation exposure. Furthermore, this clinical translation screening and monitoring tool will lessen the travel time going to the hospital and inconvenience on the part of the patient. With all these mentioned advantages, a high quality of life among DM patients will be provided while helping the economic healthcare sector.

Table 8. Comparison of MRI and PET/CT in Diagnosing and Monitoring DFO.

Diabetic Foot Osteomyelitis		
Performance Characteristics	MRI	PET/CT
Average Sensitivity	87 % [9, 26, 27, 28, 30]	93 % [9, 35, 36]
Average Specificity	77 % [9, 26, 27, 28, 30]	93 % [9, 35, 36]
Ability to demonstrate anatomical details	Yes [11, 25, 26, 27, 28]	Yes [20]
Ability to confirm the diagnosis and extent of infection	Yes [26, 29, 30]	Yes [37]
Radiation exposure	None [28]	Yes

Table 9. Characteristics and Usage of NIR based on several studies.

Near Infrared Radiation Studies
1. Non-ionizing [21]
2. Non-invasive [21, 46]
3. Easy to use due to the following reasons:
3.1 No need for calibration [22]
3.2 No need for warm-up procedure [22]
3.3 No need for disposables and supplies [22]
3.4 No need for specifically trained personnel [22]
3.5 Portable[22]
4. Can determine the following:
4.1 Wound Healing Potential [21, 44, 45]
4.2 Compression and expansion of blood vessels [1]
4.3 Oxygenated and deoxygenated hemoglobin concentration in the blood [22, 46]

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