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Diabetic osteoarthropathy care in Sweden – Need for improvement: A national inventory



Linda Wennberg^{a,*}, Paul Lundgren^b, Rimma Axelsson^c, Peter Aspelin^c, Kurt Gerok-Andersson^d, Börje Åkerlund^e

^a Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institute and Department of Radiology, Karolinska University Hospital, Huddinge, Sweden

^b Department of Orthopedics, Södertälje Hospital, Sweden

^c Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institute and FO Medical Physics and Nuclear Medicine, Imaging and Function, Karolinska University Hospital, Huddinge, Sweden

^d Department of Endocrinology, Karolinska University Hospital, Stockholm Huddinge, Sweden

^e Department of Medicine, Unit of Infectious Diseases, Karolinska University Hospital, Stockholm Huddinge, Sweden

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ABSTRACT

Aims: Osteoarthropathy, a rare foot complication in patients with diabetes mellitus, calls for immediate and optimal management to prevent irreversible bone/joint destruction and risk of amputation. Awareness of the condition and adequate guidelines would minimize the consequences and the costs, both for the patient and for the society. We investigated the diabetic osteoarthropathy care in Swedish orthopedic clinics.

Methods: A questionnaire was distributed to 63 Swedish hospitals with emergency department for orthopedic patients. There was a 95% response rate.

Results: Most of the respondents (79%) specified absence of established procedures including guidelines for managing patients with osteoarthropathy. The most common diagnostic method was clinical diagnosis and plain X-ray (95%). MRI or scintigraphy was used by 19% and 10.5% respectively. As treatment method, 84% used a total contact cast, while 38% used orthoses. Treatment duration <3 months was reported in 4%, 3–6 months in 53% and 6–12 months in 28% of the clinics. Four clinics reported treatment duration >12 months and two clinics provided no treatment.

Conclusion: Our national inventory indicates a need for improvement in knowledge as well as guidance and organization at orthopedic clinics regarding optimal care of patients with diabetic osteoarthropathy.

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Introduction

Neuropathic foot arthropathy was first described in patients with tabes dorsalis by Jean-Marie Charcot in 1868 [1]. The association between osteoarthropathy and diabetes mellitus was presented by Jordan [2]. Despite the condition being known for such a long time the diagnostic and treatment options have been limited. However, the reconstruction techniques for unavoidable osteoarthropathy foot deformity have substantially improved during the 20th century [3].

The diagnosis of diabetic osteoarthropathy today is associated with already affected and fractured bones. This will require advanced reconstructive surgery including a long rehabilitation

period with reduced mobility for the patient. Moreover, there will be a risk for amputation if the osteoarthropathy is complicated by chronic ulcers and/or chronic infections [4].

As the current diagnosis is based on plain X-ray findings with a destruction of the foot skeleton (Fig. 1 a-b) the condition, to some extent, has already become too aggravated to heal without sequelae. New diagnostic methods facilitating earlier diagnosis is therefore imperative. More advanced diagnostic tools have been evaluated, with MRI (magnetic resonance imaging) emerging as highly sensitive for the early detection of osteoarthropathy. Unfortunately, due to the similarities with osteomyelitis, the specificity of MRI is unsatisfactory but MRI could probably be a valuable diagnostic alternative [5–7]. Bone scintigraphy is another imaging technique which shows a high sensitivity for bone pathology with increased uptake in patients with osteoarthropathy [8]. Impaired circulation can, however, result in a false-negative result and the uptake of the radionuclide tracers used is not specific for

* Corresponding author at: Karolinska Institute, Department of Clinical Science, Intervention and Technology (CLINTEC), Division of Radiography, Alfred Nobels Allé 10, 141 83 Huddinge, Sweden.

E-mail address: linda.wennberg@ki.se (L. Wennberg).



Fig. 1. Plain anteroposterior X-ray (A-B), on diabetic patient presenting with a hot swollen right foot which was considered as degenerative changes without signs of osteoarthropathy (A). New X-ray 4 month later showed signs consistent with osteoarthropathy (B).

osteoarthropathy [9]. Positron emission tomography (PET) scanning with ^{18}F -FDG has been proposed as a possible diagnostic pathway [10,11]. However, more research is necessary before this technique can be applied in clinical practice.

There have been different pathophysiological models for osteoarthropathy. The original French theory is based on Charcot's studies of ataxia and finds the cause of the condition in lesions in the spinal cord.

The German theory, as promoted by Volkman and Virchow, focuses on multiple traumas to the joints. The neurovascular theory which could be connected with the French suggests that a neurally initiated vascular reflex leads to activation of osteoclasts and thereby bone resorption and fragility of the bone [2]. However, none of these theories provide a comprehensive explanation for diabetes osteoarthropathy.

Recently the inflammatory role of the condition especially receptor activator of the nuclear factor kappa B ligand (RANKL), NF- κ B and osteoprotegerin (OPG) has been thoroughly discussed [12–14]. With better understanding of the inflammatory mechanisms new therapeutical options seems possible.

The current treatment is focused on an immediate reduction of the bone-altering effects of the inflammatory condition. This usually implies long treatment periods of total off-loading with

casts/orthosis and with non-weight bearing regimes and a considerable risk of low compliance.

Although diabetic osteoarthropathy is a rare foot complication with an estimated incidence of 0, 8–8% [15] the impact for the patient will be a reduced quality of life [16–18] including anxiety and depression [19] and for the society substantial health economical costs [20].

The condition is by our experience overlooked and often missed- and/or late diagnosed and there is in Sweden currently no information available regarding the caregiving of this patient group.

The purpose of this study was to make a national inventory of orthopedic caregivers' organization for the diagnosis and treatment of diabetic osteoarthropathy.

Methods

This descriptive and cross-sectional study was carried out during the spring and early summer of 2014. Based on a registry from the Swedish Association of Local Authorities and Regions (SKL), 73 hospitals with emergency departments for orthopedic patients were identified. Since 14 of the hospitals were so-called "joint

orthopedic clinics” with shared organizational structure, 63 units were chosen to investigate orthopedic caregiver’s organization for diagnosing and managing patients with suspected diabetic osteoarthropathy. The heads of the orthopedic clinics at each hospital were contacted to identify the orthopedic surgeon responsible for the care of patients with foot complications. The orthopedic surgeons were then contacted by e-mail with a description of the project’s purpose.

Data were collected using a structured questionnaire addressed directly to the orthopedic surgeon at each orthopedic clinic, requesting a response within 2 weeks. The questionnaire consisted of 8 questions mainly regarding diagnosis and treatment of patients with diabetic osteoarthropathy.

The respondents were also asked to include the clinic’s current guidelines for diabetic osteoarthropathy management when returning the questionnaire.

The responses received were compiled without identifying individual units because the questionnaires were coded. The data were downloaded into Microsoft Excel, and analyzed and computed in terms of frequencies and percentages using the Statistical Package for Social Sciences (SPSS) Windows version 22.0. The received guidelines were assessed using diabetic (Charcot) foot management directives from the American Academy of Orthopaedic Surgeons (AAOS).

Results

We received answers from 60 clinics representing a 95% response rate (60/63). Three respondents stated that they have never dealt with patients with diabetic osteoarthropathy and therefore the analysis is based on responses from 57 clinics.

The estimated annual number of patients with diabetic osteoarthropathy is presented in Fig. 2.

Two of the responding clinics stated that they did not know whether they had any established guidelines for managing patients with diabetic osteoarthropathy. Most of the respondents, 45 clinics (79%), said they had no guidelines. Ten clinics reported that they had guidelines and seven of those attached them to the questionnaire. Upon evaluating these guidelines, only two could attain the level of management procedures recommended by the AAOS [21].

Diagnosis

Fifty clinics used more than one method for diagnosing osteoarthropathy and the most common diagnostic methods were clinical diagnosis and plain X-ray (Fig. 3).

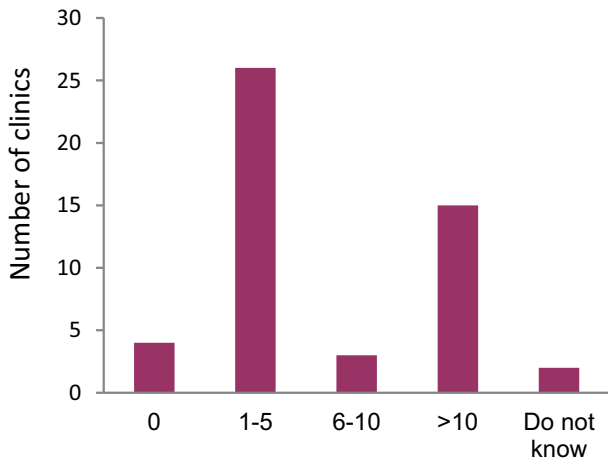


Fig. 2. Estimated number of patients with diabetic osteoarthropathy seen annually.

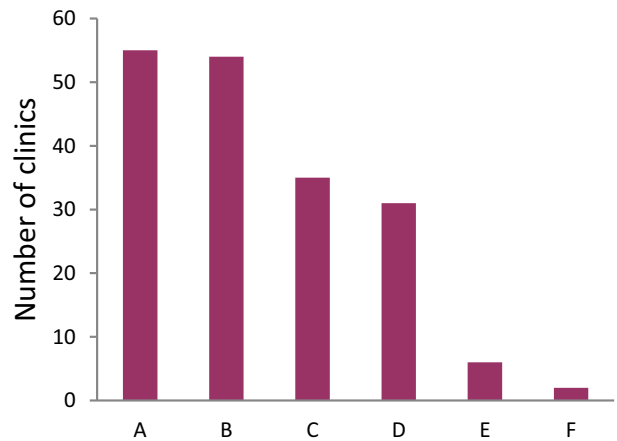


Fig. 3. Methods for diagnosis of diabetic osteoarthropathy. A) Clinical diagnosis. B) Plain X-ray. C) MRI. D) Skin temperature. E) Bone scintigraphy. F) Replied that they did not know.

Table 1

Period of time after suspected diabetic osteoarthropathy until obtained appointment at the clinic.

Obtained appointment after suspicion of diabetic osteoarthropathy	Percentage (%) (n = 57)
Don't know	11 (19.3%)
Within one day	2 (3.5%)
1–5 days	26 (45.6%)
>5 days	18 (31.6%)

Table 2

Treatment methods for diabetic osteoarthropathy.

Treatment	Percentage (%) (n = 57)
Only total contact cast (TCC)	31 (54.4%)
Only orthoses	5 (8.8%)
Only bivalve cast (removable cast)	1 (1.8%)
Total contact cast and orthoses	12 (21%)
Total contact cast and bivalve cast	1 (1.8%)
Bivalve cast and orthoses	1 (1.8%)
Total contact cast, orthoses and bivalve cast	3 (5.2%)
Do not know	3 (5.2%)

The period of time from suspected diabetic osteoarthropathy until the patient obtained an appointment at the clinic is presented in Table 1. Most of the clinics scheduled the patient between 1–5 days or after more than 5 days.

Treatment

As their treatment method, 17 of the clinics stated that they used different casting methods (Table 2), whereof 47 (84%) used a total contact cast and 21 (38%) orthosis. The most frequently used orthosis was the Aircast walker, at 27 institutions (47%). Six clinics (11%) also used individually adapted orthosis and in a few cases additional options were also specified such as the Don Joy Walker (2%), the Walker from Össur (2%) and PTB Orthosis (2%). Ten of the respondent clinics specified an orthosis option even though they had only listed the total contact cast as a treatment method.

Two clinics indicated a treatment duration of less than 3 months, thirty clinics (53%) a treatment duration of 3–6 months and sixteen clinics (28%) a duration of 6–12 months. Only four clinics indicated duration longer than 12 months, while two clinics provided no treatment at all.

The data derived from this study show that 34 of the 57 clinics claim to have access to reconstructive foot surgery for diabetic osteoarthropathy. Eleven referred the patient to the nearest university hospital and nine to the regional hospital. Two clinics stated that they did not know and one referred the patients to other unspecified clinics.

Discussion

To the best of our knowledge, there are currently no official reports at a national level on the prevalence of diabetic osteoarthropathy. However, it is likely that many cases are undiagnosed due to the health care system's lack of recognition of the typical acute manifestation of diabetes osteoarthropathy [15]. Based on the data derived from our study we can only estimate the number of patients managed annually at each orthopedic clinic.

When reviewing the few guidelines provided by participating clinics, the lack of scientific basis for the guidelines became evident. This absence of evidence-based recommendations may partly explain the absence of printed guidelines from the participating clinics. Nevertheless, the AAOS recommendations presented on their website seem widespread and emphasize early diagnosis, treatment with non-weight bearing casts and long periods of treatment [21]. Based on this information, we found that out of seven provided guidelines, only two can be considered acceptable. This observation of non-existing guidelines in Sweden is in accordance with a recently published Danish study [22]. Another recent study from Michigan, USA [23] also indicate the importance of education as well as need for guidelines about Charcot neuroarthropathy for referring providers and more efficient referral processes. It is also noteworthy that even the recommendation from the AAOS is somewhat controversial and, for instance, indicates a much shorter time of treatment than is recommended by others [24].

To avoid deformity, the early osteoarthropathy diagnosis is of utmost importance for initiation of treatment. If a radiological method should be used, the method must be able to detect the condition in the acute phase before any bone destruction. The data derived from this study show that plain radiography is the most used method even though it will not show the early pathological bone changes [25]. Instead, MRI could possibly be used to visualize subchondral bone marrow edema with or without microfractures [26–28].

Only six clinics stated that they used bone scintigraphy as a diagnostic method even though it has a high sensitivity for detection of diabetic osteoarthropathy. The specificity is, however, considered to be insufficient for the diagnosis of the condition [29]. A hybrid PET/CT technique (positron emission tomography combined with computed tomography) that provides both metabolic and structural information in one imaging session would contribute to the diagnosis of osteoarthropathy [30]. However, this method was not included as an alternative in the questionnaire because it is currently under evaluation and is not considered as a clinical routine in Swedish hospitals.

Another issue that could merit further discussion is the fact that we did not specifically ask for the policy regarding weight bearing/non-weight bearing off-loading. Treatment with casts could possibly indicate non-weight bearing and orthosis a more weight bearing solution. A high number of clinics answered that they use both cast and weight bearing (21%). An explanation for this answer could be that those clinics start with a non-weight-bearing, total contact cast and later change to an orthosis when possible weight bearing is allowed.

Regarding the question of the availability of reconstructive surgery at the home clinic, the reported number is surprisingly high (60%). One explanation for this result could be that surgeons responding to the questionnaire were not aware of the competence needed for this complicated reconstructive surgery. Even though there might be some general foot surgeons at the clinic, this does not necessarily mean that they could perform this kind of advanced surgery. They in turn may actually refer these patients to specific foot surgery departments, without the respondent being aware of it.

A weakness of our study is that the primary care physicians who might be the patient's first health care contact were not part of the inventory. Our findings indicate the need for further assessment of the caregiving of these patients also at the primary care level. However, we believe that as diabetes osteoarthropathy is an orthopedic issue, especially when it comes to reconstructive surgery, it demands the highest and optimal mindset at the orthopedic clinic to reduce the consequences of this rather rare but devastating diabetic foot complication. The knowledge of the orthopedic clinics should then actively and regularly be transferred to the primary care level.

In summary, this inventory clearly indicates a national need for an improvement in knowledge as well as guidance and organization regarding the care of patients with diabetic osteoarthropathy, since only two of 63 clinics presented useful guidelines. We also advocate national inventories of the care of diabetic osteoarthropathy in all developed countries to create a more optimal and equal care for this rare but important foot complication in patients with diabetes. We strongly recommend a multidisciplinary and value based approach [31] to this diabetic foot complication in order to minimize the consequences for the patient and the costs for the society. In addition, we see a need for international consensus discussions in order to improve diagnosis and management of patients with suspected diabetic osteoarthropathy. An improved management will reduce the risk of foot deformity with less need of surgical reconstruction and risk for amputation.

Contribution of authors

L.W. assisted with the study design, collected research data, conducted data analyses and wrote the manuscript. P.L. assisted with design of the questionnaire and data analyses and wrote part of the manuscript. R.A. and P.A. contributed to discussions and reviewed and edited the questionnaire and manuscript. K.G.A. reviewed and edited the manuscript. B.Å. designed the questionnaire, supervised the study and reviewed and edited the manuscript. L.W and P.L are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

No competing interest declared

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Appendix A

1) Approximately how many patients with diabetic osteoarthropathy are handled annually at your clinic?

- 0 1-5 6-10 > 10 Do not know

2) Does the clinic have current guidelines for the management of diabetic osteoarthropathy?

(Please send guidelines together with survey.)

- Yes No Do not know

3) What methodology is used to diagnose diabetic osteoarthropathy at your clinic?

- Clinical diagnosis
 Skin temperature
 Conventional plain radiography
 Bone scintigraphy
 MRI
 Do not know

4) How soon after suspicion of diabetic osteoarthropathy does the patient obtain an appointment at your clinic?

- Within 1 day 1-5 days > 5 days Do not know

5) What treatment do patients with diabetic osteoarthropathy receive at your clinic?

- Total contact cast
 Bivalve cast (removable cast)
 Orthoses
 Do not know

6) If orthoses are used as a treatment, what type?

- Aircast Walker
 Don Joy Walker
 Other.....

7) What is the treatment duration for patients with diabetic osteoarthropathy at your clinic?

- No treatment <3 months 3-6 months 6-12 months > 12 months

8) Is there access to reconstructive foot surgery for foot deformities caused by diabetic osteoarthropathy?

- At our own clinic
 Regional hospital (specify.....)
 University hospital (specify)
 Do not know

Survey questions - Inventory of the management of patients with diabetic osteoarthropathy.

References

- Sanders LJ, Edmonds ME, Jeffcoate WJ. Who was first to diagnose and report neuropathic arthropathy of the foot and ankle: Jean-Martin Charcot or Herbert William Page? *Diabetologia* 2013;56:1873–7. <http://dx.doi.org/10.1007/s00125-013-2961-6>.
- Jordan WR. Neuritic manifestations in diabetes mellitus. *Arch Intern Med* 1936;53:307–66. <http://dx.doi.org/10.1001/archinte.1936.00170060069004>.
- Petrova NL, Edmonds ME. Conservative and pharmacologic treatments for the diabetic charcot foot. *Clin Podiatr Med Surg* 2017;34:15–24. <http://dx.doi.org/10.1016/j.cpm.2016.07.003>.
- Sohn MW, Stuck RM, Pinzur M, Lee TA, Budiman-Mak E. Lower-extremity amputation risk after Charcot arthropathy and diabetic foot ulcer. *Diabetes Care* 2010;33:98–100. <http://dx.doi.org/10.2337/dc09-1497>.
- Höpfner S, Krolak C, Kessler S, Tiling R, Brinkbäumer K, Hahn K, et al. Preoperative imaging of Charcot neuroarthropathy in diabetic patients: comparison of ring PET, hybrid PET, and magnetic resonance imaging. *Foot Ankle Int/Am Orthop Foot Ankle Soc [and] Swiss Foot Ankle Soc* 2004;25:890–5. doi:868990 [pii].
- Abdel Razek AAK, Samir S. Diagnostic performance of diffusion-weighted MR imaging in differentiation of diabetic osteoarthropathy and osteomyelitis in diabetic foot. *Eur J Radiol* 2017;89:221–5. <http://dx.doi.org/10.1016/j.ejrad.2017.02.015>.
- McCarthy E, Morrison WB, Zoga AC. MR imaging of the diabetic foot. *Magn Reson Imaging Clin N Am* 2017;25:183–94. <http://dx.doi.org/10.1016/j.mric.2016.08.005>.
- Pickwell KM, van Kroonenburgh MJ, Weijers RE, van Hirtum PV, Huijberts MS, Schaper NC. F-18 FDG PET/CT scanning in charcot disease: a brief report. *Clin Nucl Med* 2011;36:8–10. <http://dx.doi.org/10.1097/RLU.0b013e3181feeb30>.
- Rogers LC, Frykberg RG, Armstrong DG, Boulton AJM, Edmonds M, Van GH, et al. The Charcot foot in diabetes. *Diabetes Care* 2011;34:2123–9. <http://dx.doi.org/10.2337/dc11-0844>.
- Basu S, Chryssikos T, Houseni M, Scot Malay D, Shah J, Zhuang H, et al. Potential role of FDG PET in the setting of diabetic neuro-osteoarthropathy: can it differentiate uncomplicated Charcot's neuroarthropathy from osteomyelitis and soft-tissue infection? *Nucl Med Commun* 2007;28:465–72. <http://dx.doi.org/10.1097/MNM.0b013e328174447f>.
- Shagos GS, Shanmugasundaram P, Varma AK, Padma S, Sarma M. 18-F flourodeoxy glucose positron emission tomography-computed tomography imaging: a viable alternative to three phase bone scan in evaluating diabetic foot complications? *Indian J Nucl Med* 2015;30:97–103. <http://dx.doi.org/10.4103/0972-3919.152946>.
- Petrova NL, Dew TK, Musto RL, Sherwood RA, Bates M, Moniz CF, et al. Inflammatory and bone turnover markers in a cross-sectional and prospective study of acute Charcot osteoarthropathy. *Diabet Med* 2015;32:267–73. <http://dx.doi.org/10.1111/dme.12590>.

- [13] La Fontaine J, Lavery L, Jude E. Current concepts of Charcot foot in diabetic patients. *Foot* 2016;26:7–14. <http://dx.doi.org/10.1016/j.foot.2015.11.001>.
- [14] Mabileau G, Petrova NL, Edmonds ME, Sabokbar A. Increased osteoclastic activity in acute Charcot's osteoarthropathy: the role of receptor activator of nuclear factor-kappaB ligand. *Diabetologia* 2008;51:1035–40. <http://dx.doi.org/10.1007/s00125-008-0992-1>.
- [15] Rajbhandari S, Jenkins R, Davies C, Tesfaye S. Charcot neuroarthropathy in diabetes mellitus. *Diabetologia* 2002;45:1085–96. <http://dx.doi.org/10.1007/s00125-002-0885-7>.
- [16] Sochocki MP, Verity S, Atherton PJ, Huntington JL, Sloan JA, Embil JM, et al. Health related quality of life in patients with Charcot arthropathy of the foot and ankle. *Foot Ankle Surg* 2008;14:11–5. <http://dx.doi.org/10.1016/j.fas.2007.07.003>.
- [17] Pakarinen T-K, Laine H-J, Mäenpää H, Mattila P, Lahtela J. Long-term outcome and quality of life in patients with Charcot foot. *Foot Ankle Surg* 2009;15:187–91. <http://dx.doi.org/10.1016/j.fas.2009.02.005>.
- [18] Pinzur MS, Evans A. Health-related quality of life in patients with Charcot foot. *Am J Orthop (Belle Mead NJ)* 2003;32:492–6.
- [19] Chapman Z, Shuttleworth CM, Huber J. High levels of anxiety and depression in diabetic patients with Charcot foot. *J Foot Ankle Res* 2014;7:22. <http://dx.doi.org/10.1186/1757-1146-7-22>.
- [20] Labovitz JM, Shofler DW, Ragothaman KK. The impact of comorbidities on inpatient Charcot neuroarthropathy cost and utilization. *J Diabetes Complications* 2016;30:710–5. <http://dx.doi.org/10.1016/j.jdiacomp.2016.01.004>.
- [21] American academy of orthopaedic surgeons. Diabetic (Charcot) Foot-OrthoInfo - AAOS n.d. <http://orthoinfo.aaos.org/topic.cfm?topic=A00655> (accessed March 22, 2017).
- [22] Jansen RB, Svendsen OL, Kirketerp-Møller K. Clinical management of acute diabetic Charcot foot in Denmark. *Dan Med J* 2016;63.
- [23] Schmidt BM, Wrobel JS, Holmes CM. Physician knowledge of a rare foot condition – influence of diabetic patient population on self-described knowledge and treatment. *Clin Diabetes Endocrinol* 2017;3:2. <http://dx.doi.org/10.1186/s40842-017-0041-4>.
- [24] Game FL, Catlow R, Jones GR, Edmonds ME, Jude EB, Rayman G, et al. Audit of acute charcot's disease in the UK: the CDUK study. *Diabetologia* 2012;55:32–5. <http://dx.doi.org/10.1007/s00125-011-2354-7>.
- [25] Chantelau E. The perils of procrastination: effects of early vs. delayed detection and treatment of incipient Charcot fracture. *Diabet Med* 2005;22:1707–12. <http://dx.doi.org/10.1111/j.1464-5491.2005.01677.x>.
- [26] Chantelau E, Poll LW. Evaluation of the diabetic charcot foot by MR imaging or plain radiography – An observational study. *Exp Clin Endocrinol Diabetes* 2006;114:428–31. <http://dx.doi.org/10.1055/s-2006-924229>.
- [27] Schlossbauer T, Mioc T, Sommerey S, Kessler SB, Reiser MF, Pfeifer K-J. Magnetic resonance imaging in early stage charcot arthropathy: correlation of imaging findings and clinical symptoms. *Eur J Med Res* 2008;13:409–14.
- [28] Ruotolo V, Di Pietro B, Giurato L, Masala S, Meloni M, Schillaci O, et al. A New Natural History of Charcot Foot. *Clin Nucl Med* 2013;38:506–9. <http://dx.doi.org/10.1097/RLU.0b013e318292eeeb>.
- [29] Dissanayake SU, Bowling FL, Jude EB. The diabetic Charcot foot. *Curr Diabetes Rev* 2012;8:191–4.
- [30] Keidar Z, Militianu D, Melamed E, Bar-Shalom R, Israel O. The diabetic foot: initial experience with 18F-FDG PET/CT. *J Nucl Med* 2005;46:444–9.
- [31] Porter ME, Larsson S, Lee TH. Standardizing patient outcomes measurement. *N Engl J Med* 2016;374:504–6. <http://dx.doi.org/10.1056/NEJMp1511701>.