ANNALS OF TRANSPLANTATION

SHORT COMMUNICATIONS

e-ISSN 2329-0358
© Ann Transplant, 2021; 26: e928449
DOI: 10.12659/AOT.928449

Received: 2020.09.09
Accepted: 2020.10.01
Available online: 2020.12.08
Published: 2021.02.02

Why the Risk of Developing Neuroarthropathy Is Higher After Simultaneous Kidney and Pancreatic Transplantation Compared to Kidney Transplantation Only: The Role of Euglycemia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1,2 Dured Dardari
ABD 3 Randa Dardari

1 Department of Diabetes, Sud Francilien Hospital Center 40 Avenue Serge Dassault, Corbeil-Essonnes, France
2 LEBPS, Univ Evry, IRBA, Université de Paris-Saclay, Evry, France
3 Diabetologist Clinic, Aleppo, Syrian Arab Republic

Corresponding Author: Dured Dardari, e-mail: dured.dardari@gmail.com
Source of support: Self financing

Charcot's neuroarthropathy is a destructive complication of the joint, which is often found in patients living with diabetes. Despite the fact that its description was published almost 100 years ago, its pathophysiology, diagnosis, and treatment remain areas that need to be updated. Its prevalence is low in patients living with diabetes, but this increases in particular situations such as peripheral neuropathy, as well as after simultaneous kidney-pancreas transplantation (SPKT) in patients living with type 1 diabetes. We suggest that the development of neuroarthropathy after SPK in not only due to glucocorticoid therapy, as described, but also to the rapid passage into euglycemia. The reduced prevalence of neuroarthropathy after only kidney transplantation compared to SPK seems to validate our hypothesis.

Keywords: **Arthropathy, Neurogenic • Diabetic Foot • Kidney Transplantation • Pancreas Transplantation**

Abbreviations: **CN** – Charcot neuroarthropathy; **RANKL** – receptor activator of nuclear factor-B; **OPG** – osteoprotegerin; **SPKT** – simultaneous pancreas-kidney transplantation; **KT** – kidney transplantation

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/928449

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Background

Charcot neuroarthropathy (CN) is a rare and devastating disorder presenting with peripheral and/or autonomic neuropathy that affects people with diabetes. It is characterized by painful or painless bone and joint destruction in limbs that have lost sensory innervation [1,2]. The prevalence of CN varies between 0.1% and 0.4% in the diabetic population.

The risk of developing CN is generally not linked to the type of diabetes (I or II), but a study by Petrova did show a greater risk of developing CN in patients with type I diabetes [3]. In a study by Luxma [4], it was observed that this prevalence increases significantly in a population whose diabetes has been followed for 10 years (10.8 vs 27.4 per 10 000), but the incidence remains constant over the period beyond 11 years (average 3.1 per 10 000 cases). The circumstances leading to the appearance of this complication are poorly understood. The theory most often used to explain the appearance of this complication is that of Jeffcoate [5]. Since it is difficult to study the initiation of this serious complication, we wish to focus on the appearance of this complication after double pancreas-kidney transplantation (SPKT), a situation described recently in the literature. Simultaneous pancreas-kidney transplantation (SPKT) is a frequently used therapeutic option for patients with diabetes presenting with end-stage renal disease [6]. Simultaneous pancreas-kidney transplantation (SPKT) is considered the criterion standard treatment for type 1 diabetes patients presenting with end-stage renal failure. SPKT not only restores renal function, but also returns blood sugar levels to a euglycemic state. If studies have shown that there is a marked improvement in the quality of life of patients who have undergone SPKT [7], this evaluation probably did not take into account the deterioration of this benefit in patients who developed CN, a complication in which the lower-limb amputation rate is extremely high [8]. There are several retrospective studies in the literature that indicate a high prevalence of CN development in patients after SPKT. In the study by Rangel et al [9] carried out in 130 patients after SPKT, the prevalence of developing CN was 4.6% during the first year after SPKT; a factor favoring CN according to the authors of this study was corticosteroid therapy due to the impact on bone loss after transplantation. In a study by Matricali et al [10], 8 of 66 patients with SPKT (12%) developed CN within the first year after transplantation. Another retrospective cohort study [11] comparing 478 patients with kidney transplant alone or kidney-pancreas transplant demonstrated that a total of 72 (14.8%) patients developed CN. In the diabetic patients who had a kidney-pancreas transplant, 44 (18.4%) of 238 (P=0.024, 95% CI) developed CN. Of the diabetic patients who had a kidney transplant alone, 28 (11%) of 249 developed CN. Having a kidney-pancreas transplant was statistically significant versus kidney transplant (KT) alone for developing CN. When the 277 diabetic peripheral neuropathy patients were isolated, the incidence of developing CN in the kidney-pancreas group was 31.4% (P=0.037, 95% CI), which was statistically significant compared with the kidney transplant group, with an incidence of 20.4%. In a study by García Barrado et al [12], 9 of 100 patients (9%) developed CN after transplantation, 4 of them within the first year after transplantation (3.2, 3.5, 5.3, and 6.7 months, respectively). In the remaining patients, CN was diagnosed 1.4, 1.9, 2.4, 3.5, and 5.5 years after transplantation (summary statistics of all 9 patients: 1.8±1.8 [1.4, 0.3-5.5] years). It is important to note in the studies cited [9-12] the high prevalence of CN development in the first year after pancreas-kidney transplantation or kidney transplantation alone.

Discussion

Charcot neuroarthropathy is a rare and devastating disorder that affects people with diabetes and peripheral and/or autonomic neuropathy [1]. A late diagnosis can have serious consequences, including amputation. The physiopathology of this disorder is poorly understood. In the studies mentioned above, intensive corticosteroids therapy prescribed after transplantation (SPKT as well after KT) was the main factor responsible for the appearance of CN. This was due to the action of glucocorticoids on bone structure and bone remodeling factor, especially the receptor activator of nuclear factor kappa-B ligand (RANKL) [13], but this information does not explain why there is a higher prevalence of CN after SPKT than after KT.

Also, there is no description of the impact of this corticosteroid therapy on the action on estroprogestin, which is the natural antagonist of RANKL. However, the rapid regulation of hyperglycemia found after pancreas transplantation can reduce the value of RANKL antagonist osteoprotegerin (OPG) [14]. Recently, we published a study showing that the rapid regulation of chronic hyperglycemia is associated with development of CN [15]. Therefore, the presence of euglycemia induces the elevated rate of the CN after SPKT transplantation.

To strengthen this hypothesis, we can take into account the evolution of the HbA1c rate in the García Barrado et al study [12]. Patients living with diabetes who undergo pancreas-kidney transplantation have a 2-fold higher risk of developing CN (the glucocorticoids act on RANKL and rapid regulation of glycemia, and have their own action on osteoprogesterin).

The link between the transition to rapid euglycemia and neurological complications in people living with diabetes has already been described [16,17], but this link has never been described in the onset of neuroarthropathy.

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Conclusions

Rapid correction of hyperglycemia appears to be the cause of the higher prevalence of the onset of CN after SPKT versus KT. This information is useful in order to sensitize the clinician and to set up follow-up and diagnostic consultations in specialized CN units for post-pancreas-kidney transplant patients during the first year after transplant. The diagnosis of CN is often complicated and can lead to the development of ulcers requiring amputation.

Conflict of Interest

None.

References:

1. Rajbhandari SM, Jenkins RC, Davies C, et al. Charcot neuroarthropathy in diabetes mellitus. Diabetologia, 2002;45:1085-96
2. Sinha SB, Munichoodappa CS, Kozak GP. Neuroarthropathy (Charcot joints) in diabetes mellitus: A clinical study of 101 cases. Medicine (Baltimore), 1972;51:191-210
3. Petrova NL, Edmonds ME. Acute Charcot neuro-osteoarthropathy. Diabetes Metab Res Rev, 2016;32:281-86
4. Lomax GA, Jones GR. The natural history of Charcot arthropathy in a stable diabetic population – 11-year review. Diabetes, 2007;56(Suppl. 1):A68
5. Jeffcoate WJ. Theories concerning the pathogenesis of the acute Charcot foot suggest future therapy. Curr Diab Rep, 2005;5:430-35
6. Atkinson MA, Eisenbarth GS. Type 1 diabetes: New perspectives on disease pathogenesis and treatment. Lancet, 2001;358:221-29
7. Hanlon M, Cooper M, Abrams P. Quality of life after pancreas transplantation: Time to look again. Curr Opin Organ Transplant, 2019;24(4):451-55
8. Nilsen FA, Molund M, Hvaal KH. High incidence of recurrent ulceration and major amputations associated with Charcot foot. Foot Ankle Surg, 2018;57(2):301-4
9. Rangel ÉB, Sá J, Gomes SA, et al. Charcot neuroarthropathy after simultaneous pancreas-kidney transplant. Transplant J, 2012;94(6):642-45
10. Matricali GA, Bammens B, Kuypers D, et al. High rate of Charcot foot attacks early after simultaneous pancreas-kidney transplantation. Transplantation, 2007;83(2):245-46
11. Anthony M, Cravey KS, Atway SA. Development of Charcot neuroarthropathy in diabetic patients who received kidney or kidney-pancreas transplants. J Foot Ankle Surg, 2019;58(3):475-79
12. García Barrado F, Kuypers DR, Matricali GA. Charcot neuroarthropathy after simultaneous pancreas-kidney transplantation: Risk factors, prevalence, and outcome. Clin Transplant, 2015;29(8):712-19
13. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: Pathophysiology and therapy. Osteoporosis Int, 2007;18(10):1319-28
14. Xiang GD1, Sun HL, Zhao LS, et al. [Changes of osteoprotegerin before and after insulin therapy in type 1 diabetic patients.] Zhonghua Yi Xue Za Zhi, 2007;87(18):1234–37 [in Chinese]
15. Dardari D, Ha Van G, M'Bemba J, et al. Rapid glycemic regulation in poorly controlled patients living with diabetes, a new associated factor in the pathophysiology of Charcot's acute neuroarthropathy. PLoS One, 2020;15(5):e0233168
16. Gibbons CH. Treatment-induced neuropathy of diabetes. Curr Diab Rep, 2017;17:127
17. Gibbons CH, Freeman R. Treatment-induced neuropathy of diabetes: An acute, iatrogenic complication of diabetes. Brain, 2015;138:43-52

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]