Trends in the relation between hyperglycaemia correction and active Charcot neuroarthropathy: results from the EPICCHAR study

Dured Dardari,1,2 Sophie Schuldiner,3 Carole-Anne Julien,4 Georges Ha Van,5 Jocelyne M’Bemba,6 Muriel Bourgeon,7 Ariane Sultan,8,9 Marc Lepeut,10 Sylvie Grandperret-Vauthier,11 Florence Baudoux,12 Maud François,13 Sylvaine Clavel,14 Jacques Martini,15 Julien Vouillarmet,16 Paul Michon,16 Myriam Moret,17 Arnaud Monnier,18 Venane Chingan-Martino,19 Vincent Rigalleau,20,21 Isabelle Dumont,22 Laurence Kessler,23,24 Ionela Stifii,23 Benjamin Bouillet,25,26 Pierre Bonnin,27 Amal Lemoine,28 Enrique Da Costa Correia,29 Marie Martine Bonello Faraill,30 Marie Muller,31 Marie Cazaubiel,32 Mohammed Zakarya Zemmache,33 Agnes Hartemann34,35

ABSTRACT

Introduction: The pathophysiology of Charcot neuroarthropathy (CN) remains unclear. There are a number of hypotheses but these are not exclusive. In its clinical presentation, this complication intersects with the biology of diabetic-induced neuropathy, such as peripheral hyopervascularization and the appearance of arteriovenous shunt. The EPICCHAR study is as yet an unpublished cohort of people living with diabetes complicated by CN (in active or chronic phase). Based on the findings of the EPICCHAR study, this study aimed to investigate whether a reduction in the rate of hyperglycaemia accompanies the onset of an active phase of CN.

Research design and methods: Hemoglobin A1c (HbA1c) levels were assessed 3 months (M3) and 6 months (M6) before the diagnosis of active CN (M0).

Results: 103 patients living with diabetes and presenting active CN were included between January and December 2019 from the 31 centers participating in this study (30 in France and 1 in Belgium). The mean age of the participants was 60.2±12.2 years; the vast majority were men (71.8%). Mean HbA1c levels was 60.2±12.2 years; the vast majority were men (71.8%) living with type 2 diabetes (75.5%). Mean HbA1c levels significantly declined between M6 (median 7.70; Q1, Q3: 7.00, 8.55) and M3 (median 7.65; Q1, Q3: 6.90, 8.50) (p=0.012), as well as between M6 and M0 (median 7.40; Q1, Q3: 6.50, 8.55) (p=0.014). No significant difference was found between M3 and M0 (p=0.072).

Conclusions: A significant reduction in HbA1c levels seems to accompany the onset of the active phase of CN.

Trial registration number: NCT03744039.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rapid correction of hyperglycaemia has previously been described in the form of treatment-induced neuropathy. However, little is known about the impact of this correction on the development of neuroarthropathy.

WHAT THIS STUDY ADDS

⇒ The significant correction of hyperglycaemia based on the onset of neuroarthropathy seems to be a factor inducing inflammation, which is described as a central element in the mosaic of neuroarthropathy pathophysiology.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This link may help us to understand this complication and reduce its prevalence.

INTRODUCTION

Neuroarthropathy or Charcot neuroarthropathy (CN) consists of acute osteoarticular destruction in the context of neuropathy, most commonly in the foot but also in the knee in some cases. The pathophysiology of this disorder is poorly understood and the knowledge of its causality remains at the theoretical stage. The most common explanation is inflammatory arthropathy, according to which CN occurs as an increased inflammatory response to a lesion inducing increased bone lysis, with the involvement of bone remodelling factors, especially the receptor activator of nuclear factor B ligand (RANKL) and its natural antagonist osteoprotegerin (OPG). Many studies have confirmed abnormalities in the balance of the RANK/OPG system during the development of CN. A recent study examined in a retrospective study...
level in the near period of presentation of CN. We there-
strated a significant drop in hemoglobin A1c (HbA1c)
who have developed an active form of CN and demon-
manner the evolution of glycemic control in patients
onset of the active phase of CN. The primary assessment
of which is to map patients living with Charcot's
Diabetic foot centers in France and Belgium, the main
EPICHAR is a prospective, multicenter, observational
study conducted from January 1 to December 31, 2019.
Thirty-one diabetic foot centers (30 in France and 1 in
BELGIUM) took part in the study. The study population
consisted of all people aged ≥18 years living with diabetes
who were admitted to hospital or consulted for acute
or chronic CN, with or without foot ulcers. Unless the
patient was participating in another interventional study
or refused to participate, no exclusion criteria were used.
No follow-up was required in the protocol. For the active
phase, the diagnosis of CN was retained if the clinical
examination showed a joint with an inflamed appearance
and a temperature that was 3°C higher than the contra-
lateral joint. This was validated by MRI.
In this ancillary evaluation, we analyzed the HbA1c
levels (measured by high-performance liquid chro-
pathophysiology/complications

Table 1  Demographic data and diabetes-related complications of participants with active CN

| Age, mean years±IC (S1) (A2) | 60.2±12.2 |
| Men, n (%)                   | 74 (71.8) |
| Body mass index (kg/m²), median (IQR) | 30.12 (25.74–33.14) |
| Missing data, n              | 4        |
| Type of diabetes, n (%)      |          |
| Type 1                       | 22 (21.6) |
| Type 2                       | 77 (75.5) |
| Other                        | 3 (2.9)   |
| Missing data, n              | 1        |
| Diabetes duration, years, n (%) |         |
| >20                          | 41 (40.2) |
| 10–20                        | 43 (42.2) |
| 5–10                         | 10 (9.8)  |
| <5                           | 8 (7.8)   |
| Missing data, n              | 1        |
| Insulin use, n (%)           | 69 (67.6) |
| Missing data, n              | 1        |
| Microangiopathy, n (%)       | 96 (94.1) |
| Missing data, n              | 1        |
| Dialysis, n (%)              | 4 (10.3)  |
| Missing data, n              | 1        |
| GFR (mL/min/1.73 m²), median (IQR) | 64 (46.5–90) |
| Missing data, n              | 1        |
| Macroangiopathy, n (%)       | 30 (31.3) |
| Missing data, n              | 7        |
| DFU history (grade 3 IWGDF), n (%) | 63 (61.8) |
| Missing data, n              | 1        |

HbA1c appears in cases of active CN presented through
the descriptive multicentric study ‘EPICHAR’ handled at
diabetic foot centers in France and Belgium, the main
objective of which is to map patients living with Charcot’s
foot (ie, identification of patients with acute and chronic
Charcot and the diagnostics and therapeutic methods
used).

Study objectives
The primary objective of our study is to investigate if
rapid correction of HbA1c levels is accompanied by
onset of the active phase of CN. The primary assessment
criterion is the comparison of HbA1c levels 6 months
(M6) before the diagnosis of the active phase of CN
(M0). The secondary objective is to determine whether
HbA1c levels rapidly fell between M6 and M3 (3 months)
before the diagnosis of the active phase of CN, as well as
between M3 and M0. The secondary assessment criterion
is the dosage of HbA1c levels between M6 and M3 and
between M3 and M0.

METHODS
EPICHAR is a prospective, multicenter, observational
study conducted from January 1 to December 31, 2019.
Thirty-one diabetic foot centers (30 in France and 1 in
Belgium) took part in the study. The study population
consisted of all people aged ≥18 years living with diabetes
who were admitted to hospital or consulted for acute
or chronic CN, with or without foot ulcers. Unless the
patient was participating in another interventional study
or refused to participate, no exclusion criteria were used.
No follow-up was required in the protocol. For the active
phase, the diagnosis of CN was retained if the clinical
examination showed a joint with an inflamed appearance
and a temperature that was 3°C higher than the contra-
lateral joint. This was validated by MRI.
In this ancillary evaluation, we analyzed the HbA1c
levels (measured by high-performance liquid chro-
nomography) of participants with diabetes and acute
CN who had been referred to one of the participating
diabetic foot centers during the study period. For each
patient living with diabetes who was admitted to one of the
participating centers and presenting with active CN
diagnosis performed by MRI and clinical examination),
HbA1c levels were assessed (M0). The HbA1c values 3
and 6 months before the discovery of CN (respectively,
M3 and M6) were then cross-checked via the patient’s
medical file or by contacting his or her family physician.
Data are presented as median and IQR. To compare
numerical values, statistical analysis was performed with
non-parametric Wilcoxon signed-rank tests. Pairwise
comparisons between time points were performed using the
Bonferroni-Holm method for p value adjustment. The
Benjamini and Hochberg false discovery rate method was
used to adjust for multiple comparisons. Categorical vari-
ables were compared using the Fisher’s exact test. Linear
mixed-effect regression models were applied to inves-
tigate the evolution of repeated glycated hemoglobin
measures and their association with diabetes type. The
fixed-effect variable was diabetes type and the random-
effect was the individual subject. Influence and residual
diagnostics were performed to ascertain whether all the
assumptions of the mixed-effects regression models were
met in the analyses. An unstructured covariance was
chosen. All statistical analyses were performed using the
Statistical Analysis System. This study applied the MIXED
procedure with fixed and random effects in SAS V9.3 to
implement the linear mixed-effects regression models.
RESULTS

There were 467 people recruited in the EPICHAR study. In brief, 26.55% of the participants were women. The mean age of the population was 61.97 (SD 11.45). Of the patients, 17.13% had type 1 diabetes, 79.66% had type 2 diabetes, and 3% had other types of diabetes. Of the patients, 21.62% had bilateral Charcot foot. Only 103 participants presented an active phase of CN. All individuals with missing HbA1c levels at the three time points were excluded. The demographic characteristics of the participants and their body mass index, diabetes type and duration, and any diabetes-related complications are presented in table 1. The HbA1c levels and values of the patients at M0, M3, and M6, expressed in percentages (DCCT/NGSP), are summarized in table 2.

In the total study sample, the paired Wilcoxon test showed a significant difference between M6 (median 7.70; Q1, Q3: 7.00, 8.55) and M3 (median 7.65; Q1, Q3: 6.90, 8.50) (p=0.012), with mean HbA1c levels significantly falling from 62 mmol/mol (7.8%±1.62) at M6 to 58 mmol/mol (7.45%±1.42) at M0. The paired Wilcoxon test likewise showed a significant difference between M6 and M0 (median 7.40; Q1, Q3: 6.50, 8.50) (p=0.014), with mean HbA1c levels decreasing from 62 mmol/mol (7.8%±1.62) at M6 to 60 mmol/mol (7.67%±1.48) at M3. However, the reduction in HbA1c levels was not significant between M3 and M0 as they decreased only slightly from 60 mmol/mol (7.67%±1.48) at M3 to 58 mmol/mol (7.45%±1.42) (p=0.072) at M0 (table 3 and figure 1).

### Table 2: HbA1c levels and the results for active Charcot neuroarthropathy cases in the EPICHAR study

| Variable       | Type 2 diabetes | Type 1 | Type 2 | Total | P value |
|----------------|-----------------|--------|--------|-------|---------|
| Age            | n               | 22     | 77     | 99    | 0.0014  |
|                | Median          | 54.00  | 63.00  | 61.00 |         |
|                | Q1, Q3          | 44.00, 60.00 | 55.00, 71.00 | 54.00, 68.00 |         |
|                | Min, max        | 30.00, 68.00 | 40.00, 90.00 | 30.00, 90.00 |         |
| HbA1c_t0       | n               | 15     | 60     | 75    | 0.4342  |
|                | Median          | 7.50   | 7.30   | 7.40  |         |
|                | Q1, Q3          | 6.60, 8.70 | 6.40, 8.35 | 6.50, 8.50 |         |
|                | Min, max        | 6.20, 9.70 | 5.00, 12.10 | 5.00, 12.10 |         |
| HbA1c_m_3      | n               | 9      | 41     | 50    |         |
|                | Median          | 7.80   | 7.50   | 7.65  | 0.2943  |
|                | Q1, Q3          | 7.60, 8.40 | 6.90, 8.70 | 6.90, 8.50 |         |
|                | Min, max        | 7.30, 9.10 | 5.20, 11.90 | 5.20, 11.90 |         |
| HbA1c_m_6      | n               | 14     | 30     | 44    |         |
|                | Median          | 8.05   | 7.60   | 7.70  | 0.2461  |
|                | Q1, Q3          | 7.20, 9.40 | 6.80, 8.40 | 7.00, 8.55 |         |
|                | Min, max        | 6.40, 13.00 | 6.00, 12.00 | 6.00, 13.00 |         |

HbA1c, hemoglobin A1c; max, maximum; min, minimum.

### Table 3: Pairwise comparison of HbA1c levels for all diabetes types and for each group

| Diabetes type | Time 1       | Time 2       | Mean difference | SE   | P value | Adjusted p value |
|---------------|--------------|--------------|-----------------|------|---------|------------------|
| All           | HbA1c_t0     | HbA1c_m_3    | −0.228          | 0.134| 0.072   | 0.072            |
| All           | HbA1c_m_3    | HbA1c_m_6    | −0.627          | 0.234| 0.012   | 0.021            |
| All           | HbA1c_t0     | HbA1c_m_6    | −0.608          | 0.232| 0.014   | 0.021            |
| Type 1        | HbA1c_t0     | HbA1c_m_3    | −0.325          | 0.384| 0.844   | –                |
| Type 1        | HbA1c_m_3    | HbA1c_m_6    | −0.786          | 0.552| 0.297   | –                |
| Type 2        | HbA1c_t0     | HbA1c_m_6    | −0.667          | 0.485| 0.210   | –                |
| Type 2        | HbA1c_t0     | HbA1c_m_3    | −0.206          | 0.143| 0.065   | 0.065            |
| Type 2        | HbA1c_m_3    | HbA1c_m_6    | −0.578          | 0.262| 0.029   | 0.060            |
| Type 2        | HbA1c_t0     | HbA1c_m_6    | −0.579          | 0.258| 0.04    | 0.060            |

HbA1c, hemoglobin A1c.
We studied the evolution of HbA1c levels according to diabetes type (mixed model). A similar trend in the evolution of HbA1c was found (figure 2). There was a significant main effect of time between M6 and M0 and between M6 and M3. However, there were no significant main effects for diabetes type. It is important to note that the results of HbA1c adjusted and confounded for age, body mass index, and duration of diabetes did not impact the significance of the reduction in HbA1c (table 4).

**DISCUSSION**

CN generally evolves in two phases: (1) acute and (2) chronic. The typical clinical picture of active CN is a red swollen joint with a temperature difference greater than 2°C compared with the unaffected joint. These symptoms may go unnoticed because the pain may be absent or disproportionate depending on the presence or absence of lesions on the foot. The pathogenic mechanisms of CN have been subject to a long-running debate with several diverging theories. The inflammatory arthropathy theory described by Jeffcoate is the most common theory to explain the development of active CN. A new series of experiments were recently carried out to assess the evolution of bone modelling factors in the appearance of CN by associating RANKL and OPG. However, this explanation does not address the link between the appearance of the active phase of CN and the rapid correction of HbA1c levels. The latter element is increasingly present in the pathophysiology of CN, with several cases showing the onset of active CN after the rapid correction of HbA1c levels, as in the context of a double pancreatic kidney transplant or significant weight loss after bariatric surgery.

![Figure 1](image1.png) Mean hemoglobin A1c (HbA1c) levels (mmol/mol) and their evolution at month 6 (M6), month 3 (M3), and month 0 (M0).

![Figure 2](image2.png) Mean hemoglobin A1c (HbA1c) levels (mmol/mol) and their evolution at month 6 (M6), month 3 (M3), and month 0 (M0) according to diabetes type.

**Table 4** HbA1c values adjusted for selected confounders

|                          | Estimate | SE   | Inferior | Superior | P value |
|--------------------------|----------|------|----------|----------|---------|
| Intercept                | 11.2374  | 1.3134| 8.6223   | 13.8525  | <0.0001 |
| HbA1c (temporality)      |          |      |          |          |         |
| M3                       | 0.1876   | 0.1683| −0.1469  | 0.5222   | 0.268   |
| M6                       | 0.6137   | 0.1789| 0.2581   | 0.9692   | 0.0009  |
| M0 (ref)                 |          |      |          |          |         |
| Diabetes type            |          |      |          |          |         |
| 1                        | −0.3871  | 0.4516| −1.2878  | 0.5136   | 0.3942  |
| 2 (ref)                  |          |      |          |          |         |
| Age                      | −0.05798 | 0.01355| −0.08496| −0.031   | <0.0001 |
| Sex                      |          |      |          |          |         |
| Female                   | −0.09947 | 0.3303| −0.7583  | 0.5594   | 0.7642  |
| Male (ref)               |          |      |          |          |         |
| BMI                      |          |      |          |          |         |
| ≥20                      | −0.01083 | 0.02981| −0.07028| 0.04862  | 0.7174  |
| 10–20                    | 0.5098   | 0.4354| −0.3579  | 1.3776   | 0.2454  |
| <10                      | 0.4165   | 0.4161| −0.4129  | 1.246    | 0.3202  |

BMI, body mass index; HbA1c, hemoglobin A1c; M3, month 3; M6, month 6; ref, reference.
Our study included 103 people with acute CN. This represents a large sample size for a rare disorder, as its frequency varies between 0.1% and 0.4% of people with diabetes.\textsuperscript{10} Nevertheless, aggressive antidiabetic therapy and rapid glycemic control may result in diabetic neuropathy, also known as treatment-induced neuropathy of diabetes (TIND).\textsuperscript{11} It is noteworthy that in the clinical presentation of active CN and TIND, a common symptom is hypervascularization in the extremities.

Taking the above elements into account, we may legitimately consider that the rapid and significant correction of HbA1c levels may accompany the onset of the active phase of CN. An interesting evaluation\textsuperscript{12} demonstrated that the RANKL antagonist OPG is inhibited by hyperglycemia correction, which may explain the elevated levels of RANKL observed during the active phase of CN.\textsuperscript{3} Indeed, high RANKL levels will be linked to the inhibition of its antagonist following decrease in HbA1c levels. It is important to mention that osteoblasts,\textsuperscript{2} the cell described as the main actor in the pathophysiology of CN, has insulin receptors on its membranes. We may therefore suppose that the sensitivity of these cells to insulin changes in the event of a significant reduction in HbA1c levels. Therefore, the rapid correction of hyperglycemia seems to be the inflammation-inducing factor, which is described by Jeffcoate\textsuperscript{2} as a core component in the mosaic of the CN pathophysiology.

In conclusion, the link between the onset of active CN and a significant reduction in HbA1c levels is once again brought to light in this paper. This description can help to understand the physiopathology of CN and potentially to implement monitoring measures, screening, and support for patients living with neuropathy-complicated diabetes who intend to rapidly correct their HbA1c levels.
Pathophysiology/complications

of receptor activator of nuclear factor-kappaB ligand. *Diabetologia* 2008;51:1035–40.

4 Dardari D, Van GH, 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:e0233168.

5 Edmonds ME. Progress in care of the diabetic foot. *Lancet* 1999;354:270–2.

6 Chantelau EA, Grützner G. Is the Eichenholtz classification still valid for the diabetic Charcot foot? *Swiss Med Wkly* 2014;144:w13948.

7 Petrova NL, Edmonds ME. Acute Charcot neuro-osteoarthropathy. *Diabetes Metab Res Rev* 2016;32 Suppl 1:281–6.

8 Rangel Érika B, Sá JR, Gomes SA, et al. Charcot neuroarthropathy after simultaneous pancreas-kidney transplant. *Transplantation* 2012;94:642–5.

9 Murchison R, Goody C, Dhathariya K. The development of a Charcot foot after significant weight loss in people with diabetes: three cautionary tales. *J Am Podiatr Med Assoc* 2014;104:522–5.

10 Sinha S, Munichoodappa CS, Kozak GP. Neuro-arthropathy (Charcot joints) in diabetes mellitus (clinical study of 101 cases). *Medicine* 1972;51:191–210.

11 Gibbons CH. Treatment-Induced neuropathy of diabetes. *Curr Diab Rep* 2017;17:127.

12 Xiang G-da, Sun H-ling, Zhao L-shuang, et al. [Changes of osteoprotegerin before and after insulin therapy in type 1 diabetic patients]. *Zhonghua Yi Xue Za Zhi* 2007;87:199–206.