Does Improvement of Glycemic Control Cause Acute Charcot Foot in Patients with Diabetes?

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ABSTRACT

Objective Recent studies have suggested that improved glycemic control in patients with diabetes may cause acute Charcot foot. To conduct a narrative review of studies investigating whether improved glycemic control in patients with diabetes causes acute Charcot foot.

Method Publications found by searching PubMed, EMBASE, and Cochrane Library as well as reference lists of identified publications were reviewed.

Results Very few publications were found, primarily consisting of case reports and case studies without control groups, documenting instances where cases of acute Charcot foot had been preceded by improved glycemic control. Recent large multicenter randomized placebo-controlled clinical trials of antihyperglycemic agents in patients with diabetes, where significant improvement of glycemic control occurred, have not reported incidences of acute Charcot foot.

Conclusion There is so far no solid evidence to suggest that improvement of glycemic control in patients with diabetes causes acute Charcot foot.

Introduction

Acute Charcot foot is a rare, but devastating complication of diabetes [1, 2]. It manifests as an acute aseptic inflammation of bones and joints in the foot. If not diagnosed and treated in time, it may lead to the collapse of bones in the foot, which causes deformity, foot ulcers, amputation, and death [1, 3]. These patients have typically had diabetes for years, with poor glycemic control and often several late diabetic complications [3]. Currently, the main pathophysiologic theory is that acute Charcot foot is caused by repeated local microtraumas to the bones and joints in the foot, due to loss of protective sensation caused by neuropathy, which is causing inflammation and increased bone turnover and degradation [3–5].

Good glycemic control is considered key in the prevention and treatment of late diabetic complications, such as acute Charcot foot.

However, recently, it has been suggested, that improved glycemic control in patients with diabetes may cause acute Charcot foot, with references to studies of diabetes patients who have had pancreas-kidney transplants as well as to studies of the receptor activator of nuclear factor κ-B ligand/ osteoprotegerin (RANK-L/ OPG) system [6–9].

This publication aims to perform a narrative review of scientific publications addressing the impact of improved glycemic control on the development of acute Charcot foot.

Materials and Methods

To find publications about improved glycemic control on acute Charcot foot, searches were performed in PubMed and in EMBASE with the search terms: "*intensive insulin treatment*" or "*glycemic control*" or "*glucose control*" or "*glycemic regulation*" combined with ("*AND*") "*Charcot*" or "*neuroarthropathy.*" The Cochrane Library was searched with the search term "*neuroarthropathy.*" Titles and abstracts were read, and if relevant, the publications were read. Relevant publications were also found via the reference lists of the publications suggesting that improved glycemic control in patients with diabetes may cause acute Charcot foot, as well as via reference lists of those publications otherwise identified as relevant.

Results

A total of 31 publications were found in PubMed, of which four publications were relevant. Fifty-two publications were found in EMBASE, of which five were relevant; of these, four were also found in the PubMed search. Thirty-nine publications were found in the Cochrane Library, but none of these were relevant.

Case Reports

Two cases of acute Charcot foot in pregnant women with type 1 diabetes have been reported [10–12]. Both had high hemoglobin A1c (HbA1c) levels and poor diabetes control before pregnancy, which was improved during pregnancy [10]. One of the two cases received glucocorticoids intravenously for 3 days for thyroiditis during the pregnancy and developed several other diabetic complications [10–12].

Cases of acute Charcot foot have been reported after significant weight loss in three patients with diabetes and pre-existing peripheral neuropathy. After the weight loss, the glycemic control improved, and the patients became more mobile [13]. Cases of acute Charcot foot have also been reported in three patients with type 1 diabetes [14] and two patients with type 1 diabetes [15] undergoing double pancreas-kidney transplantation, and the dosing of glucocorticoids was suggested as the main pathogenic factor.

Case Studies

Retrospective studies have shown an increased development of acute Charcot foot in patients with type 1 diabetes after double pancreas-kidney transplantation. Thus, in Belgium, 12 % out of 66 patients developed acute Charcot foot, where the mean pretransplant HbA1c was significantly higher in those who developed acute Charcot foot [16]. In another publication, 9 % out of 100 patients developed acute Charcot foot, and again, the mean pretransplant HbA1c was significantly higher in those who developed acute Charcot foot, whereas the post-transplant HbA1c was similar [17]. Furthermore, the accumulated glucocorticoid doses were higher in those with Charcot foot [17]. In studies from Brazil, 5 % out of 130 patients developed acute Charcot foot. HbA1c levels were not reported, but the total glucocorticoid dose was significantly associated with the development of Charcot foot [18].

In studies from the USA, 249 patients with diabetes who have had kidney transplantation and 238 patients who had a pancreas-kidney transplantation were studied [19]. Among those who had a pancreas-kidney transplant, 18 % developed acute Charcot foot, whereas it was 11 % of those who had a kidney transplant. All patients that developed acute Charcot foot had neuropathy. Thus, of those with neuropathy, 31 % who had a pancreas-kidney transplantation developed acute Charcot foot, while it was 20 % of those who had a kidney transplantation. Significantly more patients developed acute Charcot foot after pancreas-kidney transplant compared to kidney transplant ($p < 0.03$). The average HbA1c level was 6.8 % in the pancreas-kidney group and 8.9 % in the kidney group, but HbA1c levels were otherwise not reported. However, it was written in the text that HbA1c was not statistically significantly associated with the development of Charcot foot. More patients with type 1 diabetes than those with type 2 diabetes patients developed Charcot foot ($p < 0.0004$).

In a retrospective study of 173 patients with diabetes and acute Charcot foot from the Copenhagen Wound Healing Center between 1996 and 2015 [3], 26 % had type 1 diabetes, which was higher than the frequency of type 1 diabetes in the general diabetes population. Pre-admission HbA1c levels were not assessed, but the HbA1c at admission was 82 mmol/mol in patients with type 1 diabetes and 67 mmol/mol in patients with type 2 diabetes, which both were significantly higher than HbA1c levels in the general population of patients with diabetes in the Capitol Region of Denmark.

In a retrospective study of 44 patients with diabetes and acute Charcot foot, conducted at three hospital centers in France from 2008–2018, the mean HbA1c was significantly lower at the time of diagnosis of acute Charcot (7.4 % (54 mmol/mol)) compared to 3 (7.8 % (62 mmol/mol)) and 6 (8.3 % 67 mmol/mol)) months before the diagnosis, respectively ($p < 0.001$) [8]. Among these patients, 16 had their anti-hyperglycemic treatment intensified with insulin, four with liraglutide, and six with oral antidiabetics.

In another study of patients with diabetes and acute Charcot foot at 30 diabetic foot centers in France and one in Belgium in 2019, HbA1c was assessed at the time of diagnosis in 103 patients with acute Charcot foot [9]. Results of HbA1c levels 3 and 6 months before the diagnosis were collected retrospectively from medical files. HbA1c results for 75, 50, and 44 patients at the three time points, respectively, were included in the analyses. The mean HbA1c at the time of diagnosis of acute Charcot was 7.5 % (58 mmol/mol), which was significantly lower compared to 6 months (7.8 % (62 mmol/mol, $p < 0.05$)), but not to 3 months (7.7 % (60 mmol/mol)), before the diagnosis [9].

Discussion

The aim of this study was to investigate the scientific evidence whether improved glycemic control may contribute to the development of acute Charcot foot in patients with diabetes.

Very few case reports on the development of acute Charcot foot and glycemic control were found, and they all involved diabetes patients with a priori very high risk of developing late diabetes complications, such as acute Charcot foot. The development of acute

Charcot foot in these patients may have developed randomly, independently of improved glycemic control. Furthermore, case report findings can, at most, be hypothesis-generating.

Patients with diabetes who have a double pancreas-kidney transplantation have a considerable risk of developing acute Charcot foot [16–19], and this risk is higher than in those who only have a kidney transplantation [19]. It has been suggested that this increased risk may be due to the rapid normalization of glycemic control in patients who have undergone a pancreas transplant [7]. However, patients with diabetes who receive kidney and/or pancreas-kidney transplants usually have additional diabetes-related complications as well as considerable comorbidities. Moreover, patients undergoing pancreas-kidney transplants differ from those receiving kidney transplant only, i. e., more patients with type 1 diabetes receive pancreas-kidney transplants, and compared to patients with type 2 diabetes, those with type 1 diabetes are more prone to developing acute Charcot foot [4]. Furthermore, none of the studies reported an association of the development of acute Charcot foot with improved HbA1c, but rather with the doses of glucocorticoids used [18, 19].

Glucocorticoids are used for their immunosuppressive effects but they also cause osteoclast activation [20] with increased bone loss, osteoporosis, and increased risk of bone fractures. The acute Charcot foot is characterized by increased inflammation and increased bone turnover. Thus, in theory, long-term use of glucocorticoids may decrease the risk of development of acute Charcot neuroarthropathy (CNO) through its anti-inflammatory effect, whereas its effect on bone turnover may increase the risk. Increasing doses and long-term exposure to glucocorticoids may increase glucose levels in patients with diabetes, consequently increasing the risk of developing acute CNO [18]. Poor glycemic control is associated with high bone turnover [21] and lower collagen quality [22], which increase the likelihood of osteoporosis and bone fractures in patients with diabetes. The effect of glucocorticoid treatment of acute Charcot foot has been investigated in a randomized clinical trial; however, the results did not show a significant effect on the healing of acute Charcot foot [23].

The two French retrospective case studies of diabetes patients with acute Charcot foot [8, 9] only included cases of acute Charcot foot and lacked a control group, such as diabetes patients without acute Charcot foot, for comparison. Furthermore, the improvement of glycemic control in the second study was of borderline significance, warranting caution when interpreting the conclusion based on these two studies. Moreover, the observed effect might be due to bias, as patients newly referred to a diabetes outpatient clinic for improved diabetes care (including improvement of glycemic control) often undergo thorough foot examinations, thus having their otherwise undiagnosed Charcot foot examined and recorded.

The mechanism by which improved glycemic control causes acute Charcot foot is suggested to involve the inhibition of OPG, thereby causing inflammation and bone resorption of the foot [7]. Diabetes patients with an acute Charcot foot exhibit an increase in biomarkers of bone resorption and inflammation, especially in the RANK/RANK-L/OPG system [5, 24]. RANK-L is a key activator of osteoclast maturation and differentiation. Furthermore, RANK-L expression on T cells can modulate T cells and dendritic cells to increase local inflammation. OPG acts as a decoy receptor of RANK-L, inhibiting its activity. A high RANK-L/OPG ratio is a biomarker of increased bone resorption and inflammation [5].

The review mentioned above [7] referred to a study by Xiang [25] stating that the RANK-L antagonist OPG is inhibited by the correction of hyperglycemia - which is not quite true. In the study by Xiang [25], 22 patients with newly diagnosed type 1 diabetes were treated with insulin, with a drop in HbA1c from 11.1 % (98 mmol/mol) at diagnosis to 6.2 % (44 mmol/mol) after 6 months of treatment. The plasma OPG level in the patients decreased from 3.1 ng/L before treatment to 2.6 ng/L after 6 months of treatment ($p < 0.001$) but was still higher than the levels in 28 healthy controls (2.1 ng/L). Elevated levels of OPG have previously been shown in patients with both type 1 and type 2 diabetes and have been associated with hyperglycemia [26, 27]. Thus, it is possible that lowering the average blood glucose by itself lowers the inflammatory stress and thereby lowers OPG – suggesting that OPG may act as a pseudo marker of inflammatory stress overall. However, in the study by Xiang [25], RANK-L was not measured, and a high RANK-L/OPG ratio, rather than OPG alone, was linked to increased bone resorption and inflammation in diabetes patients with acute Charcot foot [5].

To emphasize the role of OPG as a diabetic stress-marker, it is worth noting that increased OPG levels in patients with type 2 diabetes have been associated with asymptomatic coronary artery disease [28, 29], foot ulcers [30], and microvascular complications [31].

Several large, long-term blinded, randomized, placebo-controlled clinical cardiovascular outcome trials with significantly improved glycemic control in the intervention group compared to a control group have been published.

In the LEADER trial [32], 9340 patients with type 2 diabetes and high cardiovascular risk were randomized to liraglutide or placebo. The HbA1c was nearly 8.4 % (68 mmol/mol) at baseline and decreased to around 7.9 % (52 mmol/mol) and 7.5 % (58 mmol/mol) with liraglutide after 3 months and 54 months, respectively, whereas it decreased to nearly 8.0 % (64 mmol/mol) and 7.7 % (61 mmol/mol) after 3 months and 54 months in the placebo group. There was no difference in the incidence of foot ulcers between the liraglutide and the placebo group (3.9 % vs 4.2 %, $p = 0.38$). However, the number of amputations in patients with foot ulcers was lower in those treated with liraglutide compared to placebo (25 % vs 35 %, $p = 0.04$) [33].

In the SUSTAIN-6 trial [34], 3297 patients with type 2 diabetes and cardiovascular disease were randomized to either semaglutide or placebo. HbA1c decreased from nearly 8.7 % (72 mmol/mol) at baseline to nearly 7.0 % (53 mmol/mol) after 4 months and 7.5 % (59 mmol/mol) after 24 months in those receiving semaglutide, versus 8.3 % (67 mmol/mol) after 16 and 104 weeks in the placebo group. There was an increase in incidence of retinopathy in those receiving semaglutide compared to placebo (1.5 vs 0.9 per 100-person year, respectively, $p = 0.02$), but no increase was reported in nervous system disorders, musculoskeletal nor connective tissue disorders.

In a recent trial [35], 478 patients with type 2 diabetes were randomized to different doses of tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, or placebo. The baseline HbA1c was 7.9 % (63 mmol/mol), which decreased to around 5.9 % (41 mmol/mol) after 6 months. Nota-

bly, no cases of neuropathy or acute Charcot foot were reported despite rapid corrections of glycemic control [35].

In another recent study [36], 281 patients with type 2 diabetes were randomized to different doses of retatrutide, a triple GIP, GLP-1, and glucagon receptor agonist, or placebo. The baseline HbA1c was approximately 8.3 % (67 mmol/mol), which decreased from 7.8 % to 6.2 % (62 to 44 mmol/mol) after 6 months of treatment with the lowest to the highest dose of retatrutide. Despite rapid corrections of glycemic control, no cases of neuropathy nor acute Charcot foot were reported [36].

A recent review on incretins [37] concluded that the effect of GLP-1 receptor agonists on peripheral neuropathy remains unclear due to little trial evidence. One trial showed a reduced risk of peripheral neuropathy with a DPP-4 inhibitor (which inhibits the elimination of endogenous GLP-1); however, acute Charcot foot was not mentioned in that review.

A review of sodium-glucose co-transporter 2 inhibitors [38], which improve glycemic control in patients with diabetes, found a positive effect of these inhibitors on neuropathy, but there was no mention of acute Charcot foot.

At last, in a recent study involving 492 patients with type 2 diabetes [39], patients were randomized either to insulin degludec or insulin glargine U100. The baseline HbA1c was approximately 8.5 % (69 mmol/mol), which decreased to around 6.9 % (52 mmol/mol) after 6 months of insulin treatment. However, despite rapid improvement in glycemic control, neither cases of neuropathy nor acute Charcot foot were reported [39].

In addition to acute Charcot foot, rare cases of acute painful neuropathy, called insulin neuritis, have also been observed after initiation of insulin therapy with rapid glycemic control [40]. Cases of painful neuropathy have also been seen with other anti-hyperglycemic treatments, and the condition is called treatment-induced neuropathy of diabetes (TIND) [40]. However, as with acute Charcot foot, no adverse events of painful neuropathy were reported in the studies mentioned above.

In contrast to the limited number of studies on improved glycemic control and development of acute Charcot foot, there are several publications on the development of retinopathy. The use of "*retinopathy*" instead of "*Charcot*" in our search term could identify 1920 publications. It is evidence-based knowledge that rapid reduction in blood glucose may worsen retinopathy early on after improved glycemic control but decrease retinopathy later [41]. Improved glycemic control is recommended, together with screening and treatment of retinopathies, to manage the condition effectively and prevent further complications [42].

In conclusion, there is so far no solid evidence that improving glycemic control in patients with diabetes causes acute Charcot foot. Optimizing glycemic control remains a good clinical practice to prevent long-term diabetic complications and their worsening.

Contributors' Statement

OLS wrote the manuscript and RJB contributed with discussions and reviewed and edited the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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