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Early intensive glycaemic control decreases the long-term risk of diabetic foot ulcer in subjects with type 1 diabetes

Aim: The aim of the study was to evaluate the effects of intensive versus conventional glycaemic control during the Diabetes Control and Complications Trial (DCCT) on the subsequent risk of diabetic foot ulcers (DFU) and lower-extremity amputations (LEA) in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the observational follow-up of DCCT.
Methods: In the DCCT study a total of 1441 subjects with type 1 diabetes (T1D) were enrolled and allocated to intensive (n=711) compared to conventional (n=730) treatment for a duration of an average 6.5 years (range 3–9 years). After that, 96% (n=1408) of the surviving cohort were enrolled in the EDIC observational study. DFU occurrence was not recorded during the DCCT study, but data on DFU were collected during the EDIC study. Data on LEA have been collected from follow-up year 12 of EDIC study (2005).
Results: Intensive versus conventional glycaemic control was associated with a significant risk reduction for all DFUs (hazard ratio 0.77 [95% CI 0.60, 0.97]) and a similar magnitude but non-significant risk reduction for first-recorded DFUs (0.78 [0.59, 1.03]) and first LEAs (0.70 [0.36, 1.36]). In adjusted Cox models, clinical neuropathy, lower sural nerve conduction velocity, and cardiovascular autonomic neuropathy were associated with higher DFU risk; estimated glomerular filtration rate <60 mL/min/1.73 m2, albuminuria, and macular edema with higher LEA risk; and any retinopathy and greater time-weighted mean DCCT/EDIC HbA1c with a higher risk of both outcomes ($P < 0.05$).
Conclusions: Early intensive glycaemic control decreases long-term DFU risk, a relevant risk factor for the development of LEA.

Comments. For the first time, this study showed a reduction in DFU risk associated with intensive glycaemic control in subjects with T1D. Interestingly, Kaplan-Meier curve showed a higher risk of DFU in the former conventional treatment group compared to the intensive group around eleven years in the EDIC study follow up, almost seventeen years from the start of DCCT study. This evidence seems to suggest that the phenomenon of so-called “metabolic memory” could be applied also to the risk of developing DFU. The relevance of sustained hyperglycaemia in the development of DFU is also supported by the association of DCCT closeout HbA1c and DCCT mean HbA1c with a higher risk of DFU in the EDIC study. Further, time-weighted mean DCCT/EDIC HbA1c resulted also as a risk factor for both DFU and LEA after adjusting for age, sex, and diabetes duration at DCCT closeout. Unfortunately, a low number of LEA events have been recorded until now, and for this reason, limited conclusions can be drawn. The other risk factors associated with DFU (clinical neuropathy, lower sural nerve conduction velocity, cardiovascular autonomic neuropathy) and LEA (estimated glomerular filtration rate <60 mL/min/1.73 m2, albuminuria, macular edema and retinopathy) suggest the relevance of microvascular damage and how it is paramount for health care providers tackle down hyperglycaemia early to prevent the development of these complications.

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Reference. Boyko EJ, Zelnick LR, Braffett BH, Pop-Busui R, Cowie CC, Lorenzi GM, Gubitosi-Klug R, Zinman B, de Boer IH. Risk of Foot Ulcer and Lower-Extremity Amputation Among Participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. Diabetes Care. 2022 Feb 1;45(2):357-364. doi: 10.2337/dc21-1816.
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