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Cardiovascular risk in relation to weight gain: The risks of intensive insulin therapy in type 1 diabetes

The seminal Diabetes Control and Complications Trial-Epidemiologic Diabetes Intervention and Complications Trial (DCCT-EDIC) demonstrated a significant delay in the development/progression of renal disease, retinal disease and neuropathy with intensive glucose control in patients with T1D. However, the initial DCCT study did not demonstrate any statistically significant impact on major cardiovascular events. The subsequent follow-up of these patients in the DCCT-EDIC study, for a total of 17 years, revealed the prolonged effect of intensive therapy in reducing risk of renal disease but also a 42% reduction in the risk of any cardiovascular event (P=0.02) and a 57% reduction in the risk of non-fatal myocardial infarction (P=0.02; Nathan et al, 2005). Parallel studies revealed reduced development and progression of surrogate measures of atherosclerosis.

So were these positive features evident in all patients with T1D receiving intensive insulin therapy? There were, of course, the downsides of intensive insulin therapy in the form of hypoglycaemia but also, less well considered, weight gain.

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A recent publication (Purnell et al, 2013) evaluates these data, examined over 6 years after completion of the DCCT-EDIC study. The weight gain effects of intensively treated patients were of course identified in the original DCCT-EDIC study where 25% of the intensively treated patients gained weight such that BMI increased from a mean of 24 kg/m² to 31 kg/m². This initial analysis had demonstrated that those patients who had gained weight achieved similar glycaemic control but at higher levels of insulin, also higher mean weight circumference, increased levels of low density lipoprotein cholesterol (LDL), triglycerides and lower high density lipoprotein (HDL) cholesterol. Current analyses demonstrate that as the excess weight gain increased the BMI by up to 4.39 kg/m² in the intensive arm compared with 2.24 kg/m² in the conventional arm. The excess gain is associated with higher concomitant increases in HbA_{1c} and high insulin doses at the EDIC year 6 point. These excess weight gainers also all revealed higher total and LDL cholesterol as well as non-HDL cholesterol, together with increases in systolic and diastolic blood pressure in the intensively treated patients. Similar changes were not observed in those who gained weight in the conventional arm. Components of the metabolic syndrome including blood pressure and weight circumference were seen far more in those who had excess weight gain. Sub-clinical markers for atherosclerosis including carotid intimal thickness and coronary artery calcium scores increased with the excess weight gain in the intensive treated arm compared with minimal weight gainers, even correcting for other cardiovascular risk factors.

Given the original findings of the DCCT-EDIC study in relation to cardiovascular disease, and the more recent results of these analyses, should intensive glycaemic targets for T1D patients be adapted in relation to weight gain during attempts at intensive therapy? All these findings suggest that patients with T1D can gain weight during intensive therapy and some dramatically so, and this is associated with concomitant metabolic and demographic abnormalities. Thus, whilst intensive therapy, when appropriately undertaken, can have major cardiovascular risk reduction in the long-term in patients with T1D, should these targets be modified according to level of weight gain?

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Nathan DM, Cleary PA, Backlund et al; Diabetes Control and Complications Trial–Epidemiologic Diabetes Intervention and Complications Trial [DCCT-EDIC] Study Research Group (2005) Intensive diabetes treatment and cardiovascular disease in patients with Type I Diabetes. *N Engl J Med* **353**: 2643–53

Purnell JQ, Hokanson JE, Cleary PA et al (2013) The effect of excess weight gain with intensive diabetes mellitus treatment on cardiovascular disease risk factors and atherosclerosis in Type I Diabetes. *Circulation* **127**: 180–7