In this context, in the present issue of *Circulation*, Purnell and colleagues make use of new data from the DCCT/EDIC Study, looking up to 6 years postcompletion of the DCCT/EDIC.\(^1\) Study participants from either the intensive or conventional insulin therapy arms were stratified by quartile of body mass index change during the DCCT trial. Excess gainers were those who were in the fourth quartile of body mass index change, defined as at least 4.39 kg/m\(^2\) in the intensive arm and 2.24 kg/m\(^2\) in the conventional arm. In the intensive arm, excess gainers had higher concomitant increases in hemoglobin A1c (8.2 versus 7.9%, *P*=0.008) and...
higher insulin doses at EDIC year 6 (0.76 versus 0.71 U/kg per day, \(P=0.02\)); findings were less clear in the conventional arm. At EDIC year 6, total and low-density lipoprotein cholesterol, triglycerides, and non–high-density lipoprotein cholesterol were all higher in the excess gainers, along with both systolic and diastolic blood pressure in the intensive arm; similar associations were not observed in the conventional arm. Notably, the use of lipid-lowering medications was higher in the excess in comparison with minimal gainers (48% versus 32% at EDIC year 6). Finally, components of the metabolic syndrome, including blood pressure and waist circumference criteria, were met far more often in the excess in comparison with minimal gainers. Looking at contemporaneous subclinical markers of atherosclerosis, carotid intima medial thickness was higher in the excess in comparison with minimal gainers, which persisted at EDIC year 6, even after accounting for concomitant cardiovascular disease (CVD) risk factors and original DCCT treatment group. Although similar trends were observed for coronary artery calcium, the results were not statistically significant.

These results suggest that patients with type 1 diabetes mellitus are prone to weight gain such that they begin to develop characteristics of central obesity and the metabolic syndrome, characteristics that are more commonly observed in type 2 diabetes mellitus. In addition, this is more likely to happen in patients treated with intensive insulin therapy in comparison with conventional therapy. Finally, excess weight gain is associated with increased carotid insulin intima medial thickness, a subclinical measure of atherosclerosis that has been linked to increased cardiovascular events.\(^{19}\)

Thus, the big question that we need to consider from these important new findings is their relevance and implications in terms of intensive insulin therapy in patients with type 1 diabetes mellitus. Importantly, how can we reconcile these important new results with what we already know from the existing literature? Existing publications from the DCCT/EDIC Study have already demonstrated that intensive insulin therapy is associated with less retinopathy, neuropathy, nephropathy, chronic kidney disease, and clinical cardiovascular disease including myocardial infarction. So in this context, we must ask whether weight gain matters.

Insulin is a life-saving drug for patients with type 1 and type 2 diabetes mellitus, and, in the case of patients with type 1 diabetes mellitus, there are no alternatives. The relevant question here is whether intensive glucose-lowering goals should be relaxed in the patient with concomitant weight gain. We can learn from some recent examples of pharmacological agents with cardiovascular benefits that also have cardiometabolic side effects. The evolving story of the increased risk of type 2 diabetes mellitus among patients on intensive statin treatment can help lend some perspective. A recent meta-analysis of 5 statin trials consisting of 32752 patients showed that 2749 developed new-onset type 2 diabetes mellitus, and this risk was higher in patients treated with intensive in comparison with moderate-dose statin therapy, resulting in 2.0/1000 person-years additional cases of diabetes mellitus. However, this risk was offset by 6.5/1000 person-years fewer cases of CVD in the intensively treated group, with a number needed to treat of 155 for CVD in comparison with a number needed to harm of 498 for diabetes mellitus.\(^{17}\) Taken together, these data highlight how the benefit of statin therapy exceeds the risk. In a post hoc analysis of the Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, even patients at increased risk for developing diabetes mellitus demonstrated a benefit from statin therapy.\(^{18}\)

How can we apply this to patients with type 1 diabetes mellitus? Although we know that patients in DCCT/EDIC treated with intensive insulin had excess weight gain in comparison with those in the conventional arm, in balance, they had reduced cardiovascular risk, highlighting the sustained benefit from insulin-intensive therapy.

So what can we learn from Purnell et al? First, these findings underscore how patients with type 1 diabetes mellitus are susceptible to weight gain, similar to patients in the general population. These findings point out just how dramatic that weight gain can be, and how it may be accompanied by concomitant metabolic abnormalities, as well, not typically thought of in conjunction with type 1 diabetes mellitus. These findings remind us that surrogate end points such as carotid intima medial thickness or coronary artery calcification should be interpreted with caution. In addition, these data serve as an important reminder that clinicians need to educate all patients, including those with type 1 diabetes mellitus, about the risks of potential weight gain, and provide advice about maintaining a healthy lifestyle that includes physical activity and weight management. These findings also raise important questions about the durability of these findings in a more contemporary era of intensive glucose lowering, in particular, when insulin analog treatments are available. For example, insulin detemir has been shown to reduce weight gain in patients with type 1 diabetes mellitus, in comparison with neutral protamine Hagedorn insulin by a net difference of \(\approx 2.4\) kg after 16 weeks of therapy, highlighting how alternative insulin agents may induce more or less weight gain.\(^{19}\) Whether certain weight change subgroups of the DCCT/EDIC might benefit more or less from intensive insulin therapy with respect to hard cardiovascular outcomes remains to be determined. Moreover, whether intensive insulin therapy using insulin analogs associated with less weight gain would produce more dramatic CVD risk reduction remains an unanswered question. Finally, these findings serve as an important reminder that intensive insulin therapy, when well tolerated, can have major CVD risk reduction in patients with type 1 diabetes mellitus.

Disclosures

None.

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Weighty Matters: Balancing Weight Gain with Cardiovascular Risk among Patients with Type 1 Diabetes Mellitus on Intensive Insulin Therapy
Caroline S. Fox

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