Weighty Matters: Balancing Weight Gain with Cardiovascular Risk among Patients with Type 1 Diabetes on Intensive Insulin Therapy

Running title: Fox; Weighty matters in type 1 diabetes

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Type 1 diabetes, characterized by a deficiency of insulin production due to damaged pancreatic beta cells, is associated with a 10-fold increase in the risk of cardiovascular disease as compared to the general population.\textsuperscript{1,2} Intensive insulin therapy, whether administered by multiple daily injections or continuous infusion via a pump, is the cornerstone of glycemic control in the patient with type 1 diabetes.\textsuperscript{3} Most of what we know regarding the benefits of intensive insulin therapy is derived from the Diabetes Control and Complications Trial (DCCT), a trial of patients with type 1 diabetes who were randomized to either intensive or conventional insulin treatment.

The DCCT enrolled a total of 1441 patients with type 1 diabetes, beginning in 1983, with final close-out in 1993, for a total of 6.5 years of follow-up. Conventional therapy consisted of one or two daily injections of insulin with daily self-monitoring and examinations every 3 months, whereas intensive insulin therapy consisted of at least 3 insulin injections per day or external pump therapy with target blood glucose concentrations of 70 to 120 mg/dl fasting, post-prandial glucose values of $< 180$ mg/dl, and a target hemoglobin A1c goal in the normal range ($< 6.05\%$). The primary trial results showed that intensive therapy achieved a statistically significant lower hemoglobin A1c, evident by the first 3 months of the study, with a close-out A1c of 7.0\% in the intensive therapy arm as compared to 9.0\% in the conventional arm. Importantly, those in the intensive insulin therapy arm experienced delayed progression of nephropathy, retinopathy, and neuropathy.\textsuperscript{4} In the primary trial, the risk of major cardiovascular events trended to significance, although the young age of the participants (mean age 27 years at enrollment) rendered it difficult to detect a statistically significant event reduction. The DCCT has been continued in an observational phase since 1994, with annual follow-up of study participants in the Diabetes Interventions and Complications Study (DCCT/EDIC) of more than 90\% of the cohort through 2005, for a total of 17 years. The DCCT/EDIC demonstrated a
prolonged effect of intensive therapy in association with a reduced risk of incident chronic kidney disease\textsuperscript{5} and a 42\% reduction in the risk of any cardiovascular event (\(p=0.02\)), and a 57\% reduction in the risk of nonfatal myocardial infarction and stroke (\(p=0.02\)).\textsuperscript{6} These results were further supported by two additional measures of subclinical atherosclerosis, carotid intimal media thickness\textsuperscript{7} and coronary artery calcification,\textsuperscript{8} which similarly suggested that intensive insulin therapy was associated with decreased progression and lower levels of these markers. It should be noted that this is in contrast to data from large clinical trials of type 2 diabetes, where there is less compelling evidence to support a role for tight glucose control for the prevention of cardiovascular disease.\textsuperscript{9-11}

So what are the downsides of intensive insulin therapy? The major recognized side-effect and treatment-limiting factor is hypoglycemia,\textsuperscript{12} which was reported to occur during the DCCT at a rate of 2-3 times higher in the intensive compared to conventional arm.\textsuperscript{4} As a result, current practice guidelines suggest that less stringent A1c targets should be used in patients at high risk for hypoglycemia.\textsuperscript{3} Yet there is another important side effect of intensive insulin therapy that is often overlooked in type 1 diabetes: weight gain. Type 1 diabetes is a disease that is not traditionally associated with excess body weight, and in fact the patients in the DCCT/EDIC had mean body weight levels that were close to ideal at the time of randomization. Yet, it is important to remember that patients with type 1 diabetes are susceptible to the obesogenic environment in ways similar to patients without diabetes. It has recently been shown that the prevalence of overweight has increased by 47\% and the prevalence of obesity seven-fold in patients with type 1 diabetes,\textsuperscript{13} and associations between body mass index and mortality are similar to what is observed in the general population.\textsuperscript{14}

In this context, in the present issue of \textit{Circulation}, Purnell and colleagues make use of
new data from the DCCT/EDIC Study, looking up to 6 years post-completion of the DCCT/EDIC. Study participants from either the intensive or conventional insulin therapy arms were stratified by quartile of BMI change during the DCCT trial. “Excess gainers” were those that were in the fourth quartile of BMI change, defined as at least 4.39 kg/m² in the intensive arm and 2.24 kg/m² in the conventional arm. In the intensive arm, excess gainers had higher concomittant increases in hemoglobin A1c (8.2 vs 7.9%, p=0.008) and higher insulin doses at EDIC Year 6 (0.76 vs 0.71 u/kg/day, p=0.02); findings were less clear in the conventional arm. At EDIC Year 6, total and LDL cholesterol, triglycerides, and non-HDL 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 as compared to minimal gainers (48% vs 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 as compared to minimal gainers. Looking at contemporaneous subclinical markers of atherosclerosis, carotid intima medial thickness was higher in excess as compared to minimal gainers, which persisted at EDIC Year 6, even after accounting for concomitant CVD risk factors and original DCCT treatment group. While similar trends were observed for coronary artery calcium, the results were not statistically significant.

These results suggest that patients with type 1 diabetes 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. Further, this is more likely to happen in patients treated with intensive insulin therapy as compared to conventional therapy. Finally, excess weight gain is associated with increased carotid intima medial thickness, a
subclinical measure of atherosclerosis that has been linked to increased cardiovascular events.\(^{16}\)

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. 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, and in the case of patients with type 1 diabetes, 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 pharmacologic agents with cardiovascular benefits that also have cardiometabolic side-effects. The evolving story of increased type 2 diabetes risk among patients on intensive statin treatment can help lend some perspective. A recent meta-analysis of 5 statin trials consisting of 32,752 patients showed that 2749 developed new onset type 2 diabetes, and this risk was higher in patients treated with intensive compared to moderate dose statin therapy, resulting in 2.0/1000 person-years additional cases of diabetes. However, this risk was offset by 6.5/1000 person-years fewer cases of CVD in the intensive treated group, with a number needed to treat of 155 for CVD compared with a number needed to harm of 498 for diabetes.\(^{17}\) Taken together, these data highlight how the benefit of statin therapy exceeds the risk. In a post-hoc analysis of the JUPITER trial, even patients at increased risk for developing diabetes demonstrated a benefit from statin therapy.\(^{18}\) How can we apply this to patients with type 1 diabetes? While we know that patients in DCCT/EDIC treated with intensive insulin had
excess weight gain compared to 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 type 1 diabetes patients are susceptible to weight gain, similar to patients in the general population. These findings point out just how dramatic that weight gain can be, as well as how it may be accompanied by concomitant metabolic abnormalities not typically thought of in conjunction with type 1 diabetes. 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, about the risks of potential weight gain, as well as 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, particularly when insulin analog treatments are available. For example, insulin detemir has been shown to reduce weight gain in patients with type 1 diabetes as compared to NPH insulin by a net difference of approximately 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 sub-groups 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.

Conflict of Interest Disclosures: None.
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