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Perspectives in Practice

Is Type 2 Diabetes Associated with Impaired Capacity for Weight Loss?

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Introduction

The impact of type 2 diabetes on weight loss in obese individuals is unclear. Meal-replacement and lifestyle-modification programs are commonly used in the prevention and first-line treatment of obesity and type 2 diabetes. It is important to know whether individuals with type 2 diabetes can have the same expectations when joining a weight-loss program or whether they should consider more powerful weight-management interventions, such as bariatric surgery. Previous studies have attempted to determine the impact of type 2 diabetes and associated pharmacotherapies on weight-loss interventions. Some of these studies have found that patients with type 2 diabetes lose less weight than patients without type 2 diabetes (1–3), while others have found that type 2 diabetes status had no impact (4–7). Relevant to this question, our recent studies of obese patients with type 2 diabetes revealed profound deficits in skeletal muscle oxidative activity and disordered mitochondrial structure (supercomplexes) compared to obese control individuals (8).

Here we examine the impact of type 2 diabetes and associated pharmacotherapy on weight loss; we have studied the largest cohort to date, using prospectively collected data from the Core Program of the Ottawa Hospital Weight Management Clinic. Data were adjusted for factors known to impact weight loss, and the effects of various pharmacotherapy regimens were analyzed. Enrolled patients completed 12 weeks of low-calorie diet (LCD) total meal replacement in a 26-week program to accomplish weight loss in a safe and timely manner. There have been 4173 patients enrolled since the program's inception in 1992 and through 2012 (9). Previous studies from this centre have evaluated genetic and metabolic predictors of weight-loss variability (8,10). We report that type 2 diabetes is associated with a small but significant impairment of weight loss in response to a controlled dietary regimen.

Methods

This study was approved by the Ottawa Hospital Research Ethics Board. Study participants were patients from the Ottawa Hospital Weight Management Clinic who were enrolled in the core program between 1992 and 2012. This program consisted of 12 weeks of calorie restriction to a 900 kcal per day LCD using total meal replacement with Optifast 900 (Nestlé Canada, North York, Ontario) in a 26-week lifestyle-modification course including nutritional counselling and physician supervision (9,10). Patients were weighed weekly, wearing street clothes and without shoes. All consenting patients (N=4173) were initially considered for the study. Individuals deemed nonadherent and those with conditions that affect weight loss were excluded from the study. Adherence criteria were based on weekly attendance at group meetings, reported Optifast 900 use and physician notes about nonadherence. Medical conditions for which individuals were excluded included surgery or pregnancy onset during the study period, severe edematous states and medications known to be associated with weight gain that were taken during the study period. Patients with histories of gestational diabetes or incomplete information concerning diabetes were also excluded. The detailed list of exclusion criteria can be found in the Supplementary Table A1. Patients without type 2 diabetes were compared to patients with impaired fasting glucose (IFG) and to patients with type 2 diabetes. Because medications used in the treatment of type 2 diabetes may also play pivotal roles in weight management, patients with type 2 diabetes were further subdivided in order to study the effect of various pharmacologic regimens. Those who were not taking medications were compared to those taking medications known to cause weight gain and those who were taking weight-neutral medications.

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Among others, insulin, sulfonylureas and meglitinides have been associated with weight gain (11), whereas weight-neutral drugs include metformin, acarbose and dipeptidyl peptidase 4 (DPP-4) inhibitors. Patients taking weight loss-inducing medications, such as glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and lipase inhibitors (orlistat) (11), were too few, given the dates of data collection, and were, therefore, excluded from this study. Although the effects of each drug on weight management are typically studied as monotherapies, it is important to note that clinical situations often require the use of combinations of 2 or more medications in order to produce optimal glycemic control in individual patients. In such cases, patients were assigned to the appropriate group if all drugs being taken had the same effects on weight; if this was not the case, they were removed from the study.

The rate of weight loss (ROWL) was calculated using the slope of the weekly weights during the first 6 weeks on meal replacement because weight loss over this time period is linear. The percentage of weight loss (PWL) was considered at the 26-week time point because weight loss is not linear over 26 weeks. PWL was calculated at 26 weeks using the averages of weight from weeks 22 to 26. This was done in order to avoid missing data points due to a lack of patient follow up and because most patients were weight-stable around this period of time. Results are presented unadjusted and adjusted for age, sex and initial weight, as these factors are known to impact weight loss. In these cases, ROWL and PWL results presented herein are expressed in arbitrary units defined in relation to the aforementioned variables.

Linear regression analysis was conducted to find the significant predictors of weight loss; the null hypothesis tested was that the regression coefficient was equal to 0, and $p<0.05$ was used to reject the null-hypothesis. The chi-square test of independence with the Yates continuity correction was used to compare categorical variables and to investigate whether the proportions of 1 variable were different for differing values of the other variable; the null hypothesis was that the relative proportions of 1 variable are independent of the second variable. An independent-samples t test was used to compare the means of quantitative traits under 2 levels (patients with type 2 diabetes vs. patients without type 2 diabetes or female vs. male), and our null hypothesis was that the difference in means was equal to 0. These analyses were carried out in R (v. 3.0.1).

Diagnosis of type 2 diabetes and IFG was based on the guidelines published by the Canadian Diabetes Association (12,13), and the status of each patient was confirmed by the treating physician at the Weight Management Clinic. Type 2 diabetes was diagnosed using the following criteria: fasting plasma glucose levels of 7.0 mmol/L or higher; or glycated hemoglobin levels 6.5% or higher; or 2-hour plasma glucose levels in a 75 gram oral glucose tolerance test of 11.1 mmol/L or above; or random plasma glucose levels of 11.1 mmol/L or above. IFG included patients who had fasting plasma glucose levels of 6.1 mmol/L or above or 6.9 mmol/L or below at week 1 of the program and those who had previously documented histories of IFG or type 2 diabetes.

Results

A total of 2231 patients remained after the filters were applied. Of these, 1667 (74.7%) were female, and 339 (15.2%) had type 2 diabetes. Table 1 outlines the baseline characteristics of all the groups of study participants. Sex, age and initial weight are well known to affect weight loss; therefore, data were adjusted for 1) sex and age and 2) sex, age and initial weight of individual patients. Without these adjustments, there were significant differences in the ages, weights, body mass indexes and glycated hemoglobin levels in patients without type 2 diabetes, those with IFG and those with type 2 diabetes ($p<0.01$ for all).

After 6 weeks on the meal-replacement program, the adjusted ROWL was similar in the 3 groups (Table 1). However, at 26 weeks, the PWL was clearly lower in individuals with type 2 diabetes. This is evident in the unadjusted data (0.191±0.06 for patients without type 2 diabetes, 0.192±0.06 for patients with IFG, 0.180±0.06 for patients with type 2 diabetes; $p<0.05$) as well as the data adjusted for sex and age (0.203±0.31 for patients without type 2 diabetes, 0.200±0.31 for patients with IFG, 0.125±0.33 for patients with type 2 diabetes; $p<0.01$) and, most significant after data adjustment for sex, age and initial weight (0.205±0.31 for patients without type 2 diabetes, 0.195±0.31 for patients with IFG, 0.118±0.33 for patients with type 2 diabetes; $p<0.01$) (Table 1).

Joint contributions of baseline characteristics to the ROWL and PWL were further queried by fitting a linear model. Sex, initial weight and age were all highly associated with ROWL at 6 weeks (Table 2). Specifically, ROWL was higher in males compared to females ($p<0.01$); initial weight was positively associated with ROWL at 6 weeks ($p<0.01$); and age was negatively associated with ROWL ($p<0.01$). However, after 26 weeks in the treatment program, sex, initial weight and type 2 diabetes were associated with PWL (Table 2). Specifically, PWL was higher in males compared to females ($p<0.01$), and initial body weight was positively associated with PWL ($p<0.01$). Patients without type 2 diabetes had lost more weight at 26 weeks than those with type 2 diabetes ($p<0.01$).

Some medications for type 2 diabetes are known to cause weight gain, so we further analyzed the effects of medications. For this purpose, patients with type 2 diabetes were segregated into 3 groups based on their medication status: 1, no medications; 2, medications known to cause weight gain; and 3, medications not known to cause weight gain. As in the above-described analyses, unadjusted and adjusted ROWL at 6 weeks and PWL at 26 weeks were examined. As reported in Table 1, B, no differences were observed in the adjusted ROWL at 6 weeks or the PWL at 26 weeks in all 3 groups.

Discussion

We demonstrated that, compared to individuals with IFG or without type 2 diabetes, individuals with type 2 diabetes lose less weight in a standardized clinical meal-replacement and lifestyle-modification program 26 weeks after starting a standardized weight-loss program.

The strengths of this study include the analysis of weight loss in patients with IFG and type 2 diabetes in the largest cohort of patients studied to date. It is the first study to examine rates of weight loss at 6 weeks and percent of weight loss at 26 weeks, adjusted for factors known to impact weight loss, and to examine differences among patients taking various pharmacotherapy regimens.

Previous to this current work, Leslie et al had published a systematic review of the question, in which they combined data from 5 studies to demonstrate that weight loss is unchanged between patients with and without type 2 diabetes (14). Among the relevant works in the field, Li et al had published the largest study to directly compare weight loss in groups with and without diabetes (6). By analyzing data retrospectively, they concluded that patients with type 2 diabetes lose weight as effectively as patients without diabetes and those with prediabetes at 1, 3, 6 and 12 months after the initiation of a meal-replacement program. Their model for calculating the rate of weight loss (kg/week) did not, however, account for various medication regimens. Furthermore, the same rigorous criteria for removing patients on the basis of adherence and concomitant morbidities were not applied. In the current work, 6-week and 26-week values were collected in a prospective manner, and patients were excluded for poor adherence and weight-affecting