Symptom or Disease Management: Diagnosis and Management of Hyperglycemia due to Carbohydrate Intolerance. Are We Missing the Target?

BACKGROUND

Overconsumption of low quality carbohydrate and high levels of sugar has been shown to lead to high rates of obesity, insulin resistance, and type 2 diabetes mellitus (T2DM).[1,2] Inflammation and metabolic dysfunction, the two underlying disease mechanisms of diabetes, both stem from metabolic overload, the inability to utilize carbohydrates effectively. Persistent hyperglycemia and insulin resistance lead to obesity and contribute to increased risk of cardiovascular disease and other chronic health conditions.[1,2] However, large well-designed clinical trials have demonstrated that lifestyle interventions, including exercise and appropriate diet, can improve metabolic balance and reduce insulin resistance.[3-5] In these studies, healthy weight management and even modest weight loss were demonstrated to improve glycemic control and enhance health. These findings suggest that avoiding carbohydrate intolerance and progression to insulin resistance and achieving a healthy weight may be the ideal targets for therapy in overweight patients with elevated blood glucose levels.[3,5]

The novel strategy of promoting weight loss targets the underlying cause of metabolic imbalance – obesity – rather than the symptom, which is elevated blood glucose. Targeting hyperglycemia does not address underlying disease mechanisms and may even promote weight gain.[3] In addition, patients who receive pharmacologic therapy for T2DM frequently progress and require ever-increasing doses and/or additional antidiabetes medications, an approach that has been called "treat to failure."[6] Conversely, managing body weight and over-nutrition, the causative factors of weight gain, metabolic overload, and insulin resistance, has the potential to reduce glucose levels and improve clinical outcomes.

Carbohydrate Intolerance – Driver of Metabolic Dysfunction, Obesity and Diabetes

During periods of over-nutrition, excess energy is stored in white adipose tissue (WAT); continuing expansion of WAT may lead to obesity.[7] Obesity alters the cellular physiology of adipocytes, the cells of WAT. In the context of obesity, adipocytes secrete elevated levels of free fatty acids and adipokines, but decreased levels of adiponectin (Figure 1).[2] These pathophysiologic changes have many effects. Elevated free fatty acids contribute to insulin resistance,[1] oxidative stress, inflammation, and impaired arterial flow regulation.[8] Imbalances in adipocytokine signaling between organs important to glucose homeostasis further disrupt metabolic control.[9] The reduced secretion of adiponectin also negatively influences glucose metabolism because adiponectin enhances insulin sensitivity.[2] Finally, adipose tissue produces inflammatory cytokines, most likely derived from resident activated macrophages.[2] Overall, these changes promote aberrant glucose metabolism, which promotes T2DM, as well as thrombosis and atherogenesis in blood vessels, contributing to cardiovascular disease (Figure 1).[2]

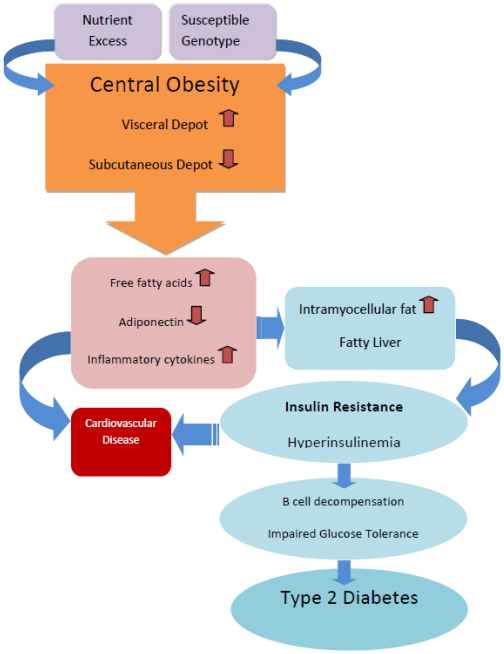

Figure 1. Overview of pathological processes from obesity to T2DM and cardiovascular disease.[1,2]

Targeting Metabolic Balance through Glucose Control Instead of Hyperglycemia?

Though hyperglycemia remains the hallmark and the chief measure of metabolic dysfunction in T2DM,[10] recent successes in achieving metabolic control have drawn attention to healthy weight management and appropriate weight loss as a potential therapeutic

target.[3-5,11-13] For example, the Look AHEAD (Action for Health in Diabetes) study of 5,145 obese people with T2DM compared an intensive lifestyle intervention (ILI) with a control group that received diabetes support and education (DSE) only.[5,12] At the end of one year, subjects in the ILI group had lost an average of 8.6% of initial body weight, compared 0.7% in the DSE group. Mean hemoglobin A1C, a measure of hyperglycemia, declined from 7.3% to 6.6% in the ILI group (P<0.001); conversely, A1C fell only slightly in the DSE group, from 7.3% to 7.2%. The ILI group also had reduced systolic and diastolic blood pressure, improved lipid profile, and improved albumin-to-creatinine ratio relative to participants in the DSE group.[5]

Similarly, in the Why WAIT (Weight Achievement and Intensive Treatment) study, a 12-week multidisciplinary program designed for use in routine clinical practice led to significant average weight loss of 18.2 lbs (7.6%) compared to baseline (P<0.001).[3] Why WAIT participants also had a significant reduction in A1C from 7.5% to 6.6% (P<0.001).[3] The profound effects of weight loss on hyperglycemia and disease risk have been observed in other research as well.[3] In 11 long-term studies, mortality risk was reduced by 25% in patients with diabetes who lost between 9 and 13 kg of body weight. Among these patients, improved weight management or loss resulting from better metabolic balance and avoidance of insulin resistance was associated with improved glycemic control.[3]

Overall, preventing or reversing carbohydrate intolerance helps to maintain a healthy weight or achieve appropriate weight loss, possibly reducing the need for antidiabetic medications and improving glycemic control. In this manner, minimizing or avoiding progression of insulin resistance may improve quality of life, especially in those patients who are at risk for diabetes or already obese (Table 1).[3,5,14]

	Targeting A1C	***Targeting Body Weight***
Medications	Progressive increase	May halt completely or reduce
Cost	Progressive increase	Progressive decrease
Weight	Progressive increase	Stable or decrease
A1C	Temporary decrease*	Decreases, a greater proportion of patients achieve and remain on target
Cardiovascular risk	May decrease**	Possible decrease[#]
Quality of life	Suboptimal	Improves
*target may be achieved, then usually progresses and requires increased pharmacologic intervention; **currently controversial; [#]improvement in lipid profile, lowered blood pressure, improvement in markers of inflammation and coagulation		

Table 1. Comparison of targeting A1C versus body weight in obese people.[3]

Success Leaves Clues – Why WAIT, A Model for Lifestyle Management and Glucose Control

The medical nutrition therapy and medical nutrition support available in health management programs like the Why WAIT program foster weight loss and quality of life improvement.[3] The Why WAIT program, developed at the Joslin Diabetes Center, is a multifaceted and comprehensive lifestyle modification program aimed at sustainable weight loss.[3] Why WAIT incorporates an exercise program, a diet plan, group education, diabetes medication adjustment, and patient self-monitoring of blood glucose, diet, and exercise (Figure 2).[3]

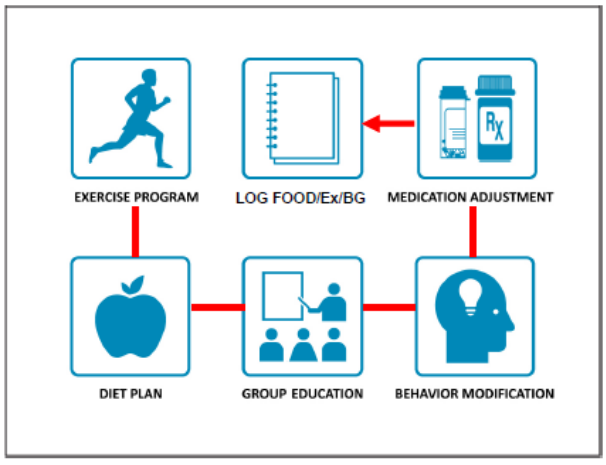

Figure 2. Elements of the multidisciplinary Why WAIT intervention.[3]

Why WAIT Exercise Plan

Obese individuals may have physical and psychological obstacles that make exercising difficult. For this reason, it is important to determine exercise capacity and

identify any physical limitations before designing an exercise program. In the Why WAIT study, each participant received an exercise program tailored to their individual needs by an exercise physiologist.[3]

Exercise plans were designed with an intensity level above the participants current exercise capacity and below a level that might provoke clinical symptoms. Each exercise plan incorporated aerobic exercise (cross and interval training), resistance exercise (circuit and superset training), and stretching. Strength training improves glucose sensitivity,[16] prevents bone mineral loss,[17] and offers a choice to people for whom aerobic exercise is difficult.[18]

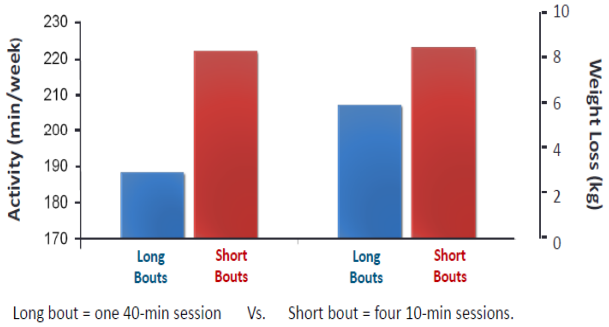

Figure 3. Effect of exercise session length on weight loss and participant engagement.[3]

The structure and staging of exercise influence adoption of the program by patients.[18] For instance, exercising in sessions of 10 minutes compared to 40 minutes improved participant adherence and led to increased weight loss (Figure 3).[19] Incorporating flexibility into the exercise regimen and providing the option of exercising at home also promoted adherence.[20] The Why WAIT program combined a weekly 60-minute exercise session with an individualized plan that participants completed at home (Table 2). Participants started with modest goals and increased over the initial 12 weeks of the program. A variety of exercises was provided to prevent boredom and keep people engaged in the program.[3]

Session Number	Frequency	Duration	Type of Exercise
1-4	4 days/week	20-40 min	AEX+STCH+CST+ CT
5-8	5 days/week	40-45 min	AEX+CT+IT+STCH +Y+CSE
9-12	6 days/week	50-60 min	AEX+CT+IT+STCH +Y+CSE+SS
AEX, aerobic; CT, circuit training; IT, interval training; STCH, stretching; Y, yoga; CSE, core stability; CST, cross training; SS, superset training.			

Table 2. Why WAIT exercise program.[3]

The Why WAIT Diet

The structured dietary plan of the Why WAIT program was developed according to Joslin Diabetes Center nutrition guidelines for obese people and tailored to individual participants by a registered dietician (Table 3).[21] The plan used nutritionally complete meal replacement products for breakfast and lunch, and prescribed dinner menus and snack ideas.[3] Total caloric intake was restricted to 1500 calories and 1800 calories, for women and men respectively, while adhering to a macronutrient profile of 40:30:30, carbohydrate:protein:fat.[3] Carbohydrates were enriched for low glycemic index and high fiber foods, which aid in blood sugar stability.

Natural foods (Dinner Menus and Snacks)	↓	Reduced total macronutrient calories 40:30:30 Carbohydrate:Protein:Fats
+	↓	Reduced glycemic index
Meal Replacements (Breakfast and Lunch)	↑	Increased protein intake 1-1.5 g/kg body weight Increased fiber Increased MUFA*
	↓	Decreased saturated fat from meat Decreased sodium

Table 3. Elements of the Why WAIT diet.[3]

The Value of Medical Nutrition & Medical Food

Medical nutrition foods and meal replacements have been an integral part of programs that fostered healthy weight and weight loss in obese, carbohydrate intolerant people.[3,22] Medical foods as meal replacements deliver the target calories for a meal with the correct macronutrient mix and often with micronutrient supplementation.[23] Medical foods help redirect patients' focus away from habitual unhealthy food choices, breaking the pattern of eating the wrong foods.[23] In the Look AHEAD study, use of meal replacements was one of the top three parameters that influenced weight loss and decreased A1C.[12] Medical food use was directly correlated to the amount of weight lost (Figure 4).[12] Dietary programs that include meal replacements are one of the only methods shown to achieve significant weight loss in obese people.[24]

Many different types of medical food formula and meal replacements are available with formats including bars, beverages, and soups, or even complete meals. Micronutrients in meal replacements may prevent

deficiencies that are frequently observed in people on a calorie-restricted diet.[24]

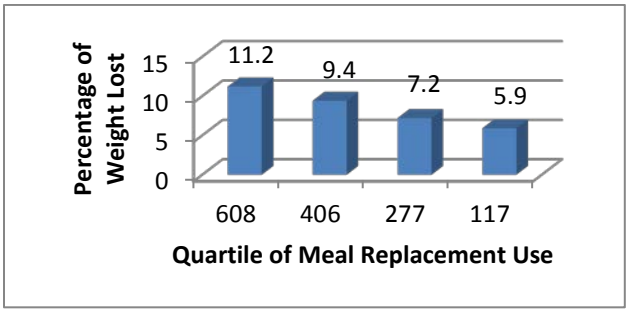

Figure 4. Percent of weight lost according to number of meal replacements used by participants in the Look AHEAD trial.[12]

Patient Support and Education

Obstacles to weight loss and maintenance of weight loss must be identified and addressed directly.[20] Self-efficacy and social support are essential for people trying to lose weight. There are many possible approaches to improve self-efficacy and support. The Why WAIT program used a structured program of cognitive behavioral support and didactic education (Table 4). In addition, monthly support groups focused on problem solving related to maintenance of weight loss.[3] At the end of the program, participants also met one-on-one with an advisor to support weight maintenance going forward.[3] Patient self-monitoring engenders awareness of dietary patterns and continuing engagement in the program.[3]

Patient Support and Education Methods

• Cognitive behavioral support sessions
  • Led by clinical psychologist
  • Weekly during first 12 weeks
  • Self-monitoring of eating and exercise
  • Behavior goal setting
  • Stimulus control techniques
  • Cognitive restructuring
  • Assertive communication skills
  • Stress management
  • Relapse prevention

• Didactic education with certified diabetologist
  • Weekly during first 12 weeks
  • Written materials
  • Topics related to weight management and diabetes

• End of study support session with provider

Table 4. Elements of the Why WAIT cognitive behavioral support.[3]

Anti-diabetic Medication Adjustment

Antidiabetes medications differ in modes of action and effects on body weight. Reducing the dose of and/or replacing medications that promote weight gain is one way to support weight loss in obese people with T2DM.[3] Adjustments to anti-diabetic medication and improvement in diet may result in reduced need for anti-diabetic medications. For this reason, frequent and accurate blood glucose monitoring is essential for titration of medication dose and to identify risk for hypoglycemia.[3]

Diabetes medications associated with weight gain	Sulfonylureas	glyburide glipizide glimepiride
	Glinides	nateglinide repaglinide
	Thiazolidinediones	pioglitazone rosiglitazone
Weight neutral diabetes medication	Dipeptidyl peptidase IV inhibitor (DPP-4 inhibitor)	sitagliptin
Diabetes medications associated with weight loss	Metformin	metformin
	Amylin analogue	pramlintide
	GLP-1 receptor agonist	exenatide

Table 6. Effect upon body weight of different anti-diabetic medications.[3]

Conclusions

Patients who are carbohydrate intolerant, often defined as obese and prediabetic, have aberrant glucose metabolism and insulin resistance and frequently progress to a diagnosis of T2DM. Many studies have demonstrated that managing carbohydrate intolerance and reducing hyperglycemia by promoting weight loss and healthy weight status improves glycemic control. Therefore, reducing caloric intake and improving nutrition can improve glycemic control and reduce insulin resistance and the progression to T2DM. However, improving nutrition and changing dietary habits to reduce body weight is a challenging goal for any at-risk patient.

Medical nutrition therapy programs that employ medical nutrition foods in the context of multifaceted health management support healthy weight and optimal metabolic control. The Why Wait Program of the Joslin Diabetes Center was an evidence-based program that fostered weight loss and reduction in A1C in patients with hyperglycemia. The Why WAIT strategy included reduced use of antidiabetes medications that promote weight gain, use of medical foods as meal replacements to provide appropriate nutrients and retrain patients' eating patterns, a specific diet and exercise regime, and psychological and social support. Medical foods and meal replacements help people improve glycemic control because they provide balanced nutrition and help change unhealthy eating patterns.

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