Glucose Toxicity and Insulin Resistance Disease "Formerly Known as Type 2 Diabetes and Prediabetes"

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BACKGROUND

Too Little, Too Late

At diagnosis, many patients with type 2 diabetes mellitus (T2DM) will have had aberrant glucose metabolism for over a decade.[1,2] During this period the disease may progress unchecked, leading to worsening insulin resistance, β cell dysfunction and other pathophysiologic abnormalities.[3] Indeed, complications associated with T2DM, such as cardiovascular disease,[4] microalbuminuria,[5] and retinopathy,[6] have been observed in people with impaired glucose metabolism who did not meet the threshold for diagnosis of T2DM (Table 1). Even prediabetes is characterized by maximal or near-maximal insulin resistance and significant loss of β-cell function.[1]

Criteria for the diagnosis of diabetes and prediabetes[7]	
Diabetes	A1C ≥6.5%
	FPG≥126 mg/dL
	2-hour OGTT ≥200 mg/dL
	Hyperglycemic crisis*
Prediabetes	A1C from 5.7% to 6.4%
	FPG 100 mg/dL to 125 mg/dL (impaired fasting glucose)
	2-hour OGTT 140 mg/dL to 199 mg/dL (impaired glucose tolerance)
A1C, glycosylated hemoglobin A1c; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; in patients in hyperglycemic crisis, a random plasma glucose value ≥200 mg/dL is considered diagnostic.	

Table 1. Criteria for the diagnosis of diabetes and prediabetes.[7]

A Shift of Perception

More than a decade ago, the focus of T2DM research shifted towards understanding the timing and cell biology of disease progression.[1,2] From this research, two main discoveries have the potential to change the therapeutic approach to T2DM. First, T2DM is a disease of progressive decline in β cell function that eventually leads to β cell failure. This decline begins more than a decade prior to diabetes diagnosis (Figure 1).[1,2] Second, the rate of β cell failure determines the rate of diabetes progression and severity,[1] and preservation of β cell function, especially in the early stages, prevents disease progression.[8] These findings suggest that the optimal approach should include early initiation of therapy before significant loss of β cell function by using therapies that potentially preserve β cell function. It has recently been argued that guideline-recommended pharmacologic therapy is a "treat-to-fail" approach that is ineffective for advanced T2DM.[3] Another approach is to employ non-pharmacologic interventions, such as medical nutrition therapy and lifestyle modifications, to reverse glucose intolerance at earlier disease stages before significant pathology has occurred.[9]

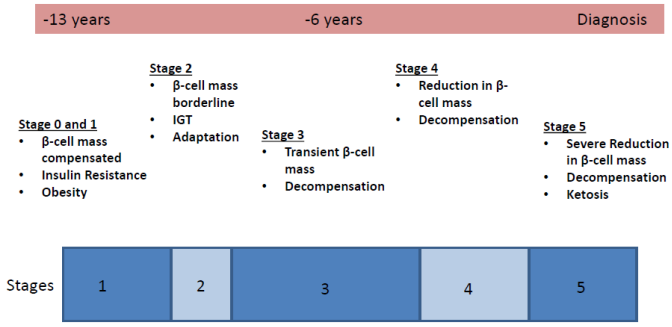

Figure 1. Progression of T2DM.[2,10]

Insulin Resistance Drives Disease Progression

Glucose metabolism is precisely regulated in healthy individuals. Fasting glucose typically remains between 70-100 mg/dl (3.9 and 5.6 mmol/L), and postprandial increases in blood glucose levels rarely exceed 55 mg/dl (3 mmol/L) above baseline.[1] Under normal physiological conditions, small increases in blood glucose stimulate insulin secretion, and insulin enhances glucose uptake by muscles and liver cells.

Inactivity and central obesity promote insulin resistance, in which glucose uptake by muscles and liver may be reduced by 85% to 90%,[11] contributing to increased blood glucose levels, also known as hyperglycemia.[10] Impaired glucose tolerance (IGT) is a condition of hyperglycemia that is associated with insulin resistance.[1]

During the early stages of insulin resistance, pancreatic β-cells respond to hyperglycemia by increasing insulin secretion.[12] At that stage, hyperinsulinemia is associated with euglycemia. However this compensatory increase in insulin secretion falls as the β-cell population becomes depleted. These processes ultimately lead to chronic hyperglycemia.

Glucose Toxicity and β Cell Preservation

The functional state of pancreatic β cells defines disease stage and reversibility.[1,8] Repeated and/or prolonged

exposure to higher-than-physiologic concentrations of blood glucose causes desensitization of β cells, a temporary physiologic state in which cells are refractory to further stimulation by glucose. Chronic exposure to hyperglycemia may cause β cell exhaustion in which cells become unable to secrete insulin due to depletion of intracellular stores.[13] Both desensitization and exhaustion of β cells are reversible states. If this hyperglycemic situation continues it may lead to irreversible cessation of insulin production and ultimately to β cell death. The relationship between hyperglycemia and β cell dysfunction and death supports the rationale for initiation of β cell-preserving interventions as soon as abnormalities in glucose homeostasis are detected.[13-15]

The Value of Early Therapy

Several clinical trials have demonstrated a reduced risk of progression to T2DM with lifestyle intervention in patients with IGT.[9,16-18] For instance, the landmark Diabetes Prevention Program (DPP) compared lifestyle intervention versus metformin therapy and placebo, in 3234 individuals diagnosed with IGT.[9] The lifestyle intervention group had a 58% reduction in conversion to type 2 diabetes compared to the placebo group.[9] The patients who received monotherapy with metformin had a 31% reduction in incidence of diabetes compared to patients who received placebo. In other words, lifestyle interventions were more effective than metformin for reducing progression of IGT to T2DM.[9]

Managing Insulin Response with Dietary Protein

Two findings guided researchers to explore the value of high-protein diet as a method for reducing hyperglycemia in patients with T2DM.[19] First, in non-diabetic people, ingestion of 50 g of lean beef did not increase blood glucose levels; in people with diabetes, ingesting lean beef resulted in a *decreased* level of blood glucose. Second, when protein (lean beef) and glucose were ingested together, the resultant blood glucose level was lower compared to an identical amount of glucose consumed without protein.[19] In one study among subjects with T2DM, investigators evaluated the impact of reducing dietary carbohydrate by 15% (from 55% to 40% of total calories) and increasing dietary protein from 15% to 30% of total calories. The results showed a significant (38%) decrease in postprandial blood glucose and an increase in 24-hour insulin response.[19] A1C also decreased significantly from 8.1% to 7.3% over 5 weeks. (Figure 2).[19] In other studies, low carbohydrate and higher protein diets improved glycemic control in healthy people,[20] obese individuals,[21,22] and patients with T2DM.[23-26] In fact, a high protein diet has the potential to provide a greater decrease in A1C than would be expected from pharmacologic therapy with metformin or pioglitazone alone.[19]

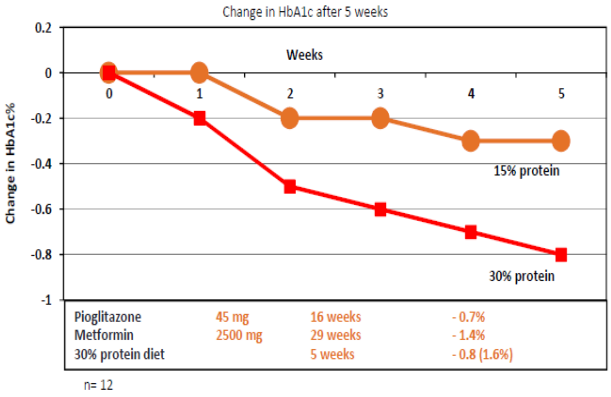

Figure 2. Change in A1C after 5 weeks of high- and moderate-protein diets.[27]

Other Benefits of High Protein Diets

High protein diets provide many benefits to patients with obesity and insulin resistance. Predominant among these effects is the potential for weight loss.[28-30] This effect was demonstrated by a study that compared three diets in overweight women (BMI >27kg/m^2) with insulin resistance: high carbohydrate, high fat, and high protein.[28] Though all three diets resulted in weight loss, participants on the high-protein diet lost significantly more weight (Figure 3).[28] The high-protein group also had a significant decrease in mean LDL cholesterol levels.[28] Another study comparing a standard protein diet with a high-protein diet in obese women with hyperinsulinemia revealed greater weight loss in the high protein group (-4.1% of body weight versus -2.9%).[29]

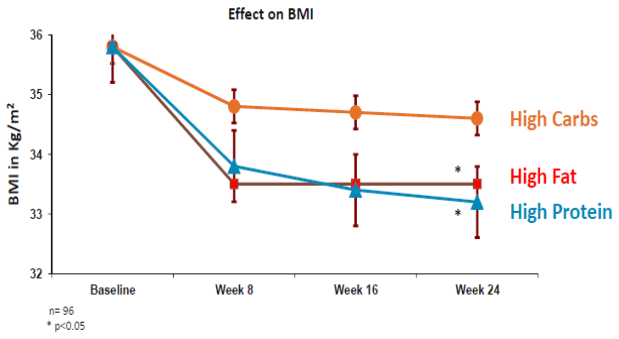

Figure 3. Effect on BMI of three diets: high carbohydrate, high fat, and high protein.[28]

Dietary protein content has also been demonstrated to contribute to maintenance of weight loss. This relationship was illustrated in a study of 773 obese

adults (median BMI 34 kg/m^2) who had lost weight during a previous dietary intervention.[31] Participants were randomized to one of four diet groups: low protein, low glycemic index (LPLGI); low protein, high glycemic index (LPHGI); high protein, low glycemic index (HPLGI); or high protein, high glycemic index (PHHGI). All four experimental diets and the control, had a fat content of 30%. While both low glycemic index groups maintained weight loss better than the high glycemic index groups, the HPLGI group was the only group that sustained weight loss over the 26 weeks of the study (Figure 4).[31] In addition, significantly fewer participants in the high protein groups dropped out of the study compared with low protein and control groups (26.4% and 25.6% versus 37.4%, P=0.02, P=0.01. respectively), which the authors interpreted as a satiety effect.[31]

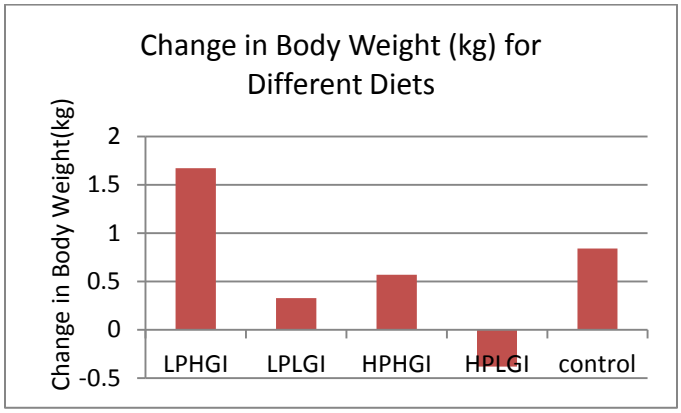

Figure 4. Change in body weight for 4 different diets and control subjects.[31]

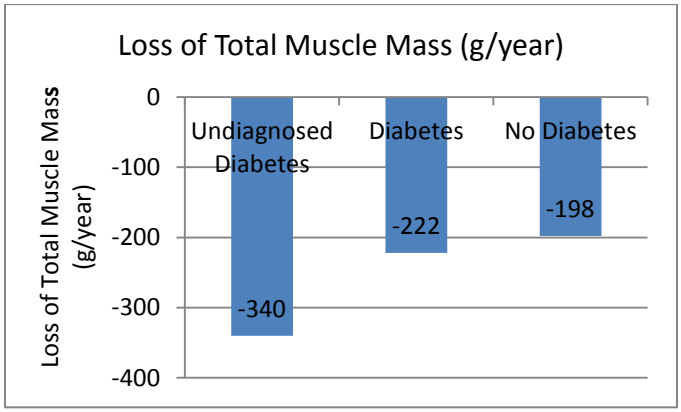

Figure 5. Loss of muscle mass, gram/year, in people with and without diabetes and with undiagnosed diabetes.

Protein - Getting It Right

Patients with diabetes are at risk for muscle mass loss (Figure 5).[32] Though the mechanism of muscle loss is not completely understood, protein metabolism is known to be reduced in T2DM and insulin resistance.[32] Patients above age 40 with undiagnosed or poorly controlled diabetes lose >400 gm of their lean muscle mass per year in comparison to ~300 gm of muscle mass loss in none-diabetic individuals. Sufficient protein intake is important in providing a sense of fullness, maintaining weight reduction, and minimizing loss of lean body mass. Guidelines recommend protein intake of at least 1.2 gm/kg of adjusted body weight per day for overweight patients with type 2 diabetes or insulin resistance.[33]

It is preferable to calculate protein intake in grams per kilogram of body weight rather than calculating it as percentage of total caloric intake. The reason is that diets that are calorie restricted may provide a significantly smaller amount of protein if protein is calculated as a ratio of total energy intake and may result in protein malnutrition and significant loss of lean muscle mass. (Table 2) Patients with diabetes or insulin resistance should not reduce protein intake to less than 1 gm/kg of body weight. [34] Now, it is known that protein restriction does not prevent the decline in glomerular filtration rate or prevent proteinuria in patients with diabetes.[35]

Protein Intake Category	***Grams per kilogram body weight***	
Very Low	<0.6	• Dietary protein is sometimes calculated as a percent of total energy consumed in a diet • This is not the preferred approach when providing guidance to patients • Dietary protein should be prescribed as grams per kilogram of body weight and should remain unchanged under conditions of caloric restriction because people with diabetes are susceptible to muscle protein loss
Low	0.6-0.8	
Moderately Low	0.8-1	
Average	1-1.5	
Moderately High	1.5-2	
High	>2	

Table 2. Recommended protein intake for patients with T2DM.[34]

Conclusions

Insulin resistance is the primary pathophysiologic defect leading to T2DM. Early recognition and intervention have the potential to prevent progression of diabetes and the development of diabetes-related complications. Lifestyle interventions have the potential to improve glycemic control and slow disease progression. Protein is an especially important dietary component for patients who are obese, have diabetes, or are at risk for diabetes. A higher level of dietary protein has been shown to improve blood glucose, increase insulin secretion, and reduce A1C in patients with T2DM. In combination with a diet of low glycemic index carbohydrates, increased protein consumption enhances weight reduction and reduces fat mass.

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