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IMPAIRED FASTING GLUCOSE (IFG) or IMPAIRED GLUCOSE TOLERANCE (IGT)

Shall We Treat?

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The Problem

The Type 2 diabetes mellitus (T2DM) epidemic is growing rapidly, with an estimated 285 million people worldwide living with T2DM in 2010. Almost half of those affected are in the 20-60 age-group. It has been estimated that a man diagnosed with diabetes at the age of 40 years will lose on average 11.6 life-years and 18.6 quality adjusted life years (QALY) and women will lose 14.3 life-years and 22.0 QALYs (1). Thus, primary prevention of T2DM and its complications is a major public health issue.

The Opportunity

Impaired fasting glucose (IFG) and Impaired Glucose Tolerance (IGT) are often labeled together as pre-diabetes (Table 1). The natural history and pathophysiology of type 2 diabetes indicate that there exists a prolonged prediabetic phase in most patients. It has been estimated that the majority of individuals (up to 70%) with prediabetes will eventually develop T2DM (2). Particularly high conversion rates (> 10 % per year) have been observed in subjects with a combination of 2 or 3 prediabetic conditions (IGT ± IFG ± Metabolic Syndrome) (2). Hence, family physicians and specialists have a unique opportunity to identify these patients at high risk for developing diabetes and intervene. In addition to a very high rate of conversion to T2DM, an increased risk of cardiovascular disease is already present in prediabetic states. Consequently, early, preventative intervention will yield great benefit.

Table 1

Plasma Glucose (PG) levels for diagnosis of IFG, IGT and diabetes

(adapted from CDA guidelines 2008) Note: CDA does not recommend specific HbA1C criteria for diagnosis of prediabetes.

		FPG (mmol/L)		2-Hour Glucose After 75gm OGTT (mmol/L)
Pre-Diabetes	Impaired Fasting Glucose	6.1-6.9		Not Available
	Isolated IFG	6.1-6.9	And	<7.8
	Isolated Impaired Glucose	<6.1	And	7.8-11.0
	Tolerance			
	Both IFG and IGT	6.1-6.9	And	7.8-11.0
Type 2 DM	Type 2 DM	≥7.0	Or	≥11.1

Case: Mrs. Angela A

Mrs. Angela A is a 42-year-old administrative clerk. She has a history of Gestational diabetes (GDM). She currently takes no medications. She has been unable to lose weight because of her busy schedule. On physical exam, her BMI is 28.1 and waist circumference 102 cm. Blood pressure is 138/84. Her general physical is within normal limits, except for central obesity. Her fasting glucose is elevated at 6.4 mmol/L. 2 hour glucose after a 75 gm OGTT is elevated to 10.1 mmol/L. Two years ago, her FBG was 6.1 mmol/L with a 2-hour value of 9.2 mmol/L. Her fasting lipid panel shows total cholesterol 7.03 mmol/L, triglycerides 4.37 mmol/L, HDL 0.90 mmol/L and a calculated LDL of 4.14 mmol/L. Based on the above results, you diagnose Mrs. A as having IFG/IGT in addition to features of metabolic syndrome.

The Management

There is evidence that lifestyle intervention (combined diet and exercise aimed at weight loss) can improve glucose tolerance and prevent progression from IFG/IGT to type 2 diabetes. This was illustrated by a meta-analysis of eight trials comparing exercise plus diet with standard therapy (RR with intervention compared to control 0.63, 95% CI 0.49-0.79) (3). The lifestyle modification advice is essentially the same as that in diabetes:

- Weight reduction (5-10%), if appropriate
- Reduction in total intake of fat and intake of saturated fat
- Increasing intake of dietary fiber
- Increasing physical activity

Other iatrogenic contributors to IFG/IGT need to be addressed as well. Drugs that adversely affect glucose tolerance should be replaced or minimized, such as thiazide diuretics, corticosteroids and atypical anti-psychotics.

The Evidence

Diabetes Prevention Program (DPP) — in this landmark trial, 3234 obese subjects (average age 51 years) at high risk for diabetes (fasting and 2-hour glucose concentrations between 5.3 to 6.9 mmol/L and 7.8 to 11.1 mmol/L, respectively) were randomly assigned to one of the following groups:

- Intensive lifestyle changes through a behavioral modification program
- Treatment with Metformin (850 mg twice daily)
- Placebo

The Intensive lifestyle group lost an average of 15 pounds (6.8 kg; 7 percent) of weight in the first year, most of which was sustained for the duration of the study. The intensive lifestyle and Metformin interventions reduced the cumulative incidence of diabetes by 58 and 31 percent, respectively, compared with placebo (4).

In contrast to the findings in the entire DPP cohort which favored lifestyle intervention, Metformin and lifestyle intervention were similarly effective in reducing the incidence of diabetes in women with a history of gestational diabetes (GDM) (5). In a preplanned subset analysis of women with a history of GDM and IGT, the incidence of diabetes was reduced by 50 and 53 percent in subjects assigned to Metformin and lifestyle intervention, respectively, compared with placebo. The discrepancy in the two studies is thought to be due, in part, to the higher cumulative incidence of diabetes in women assigned to placebo with GDM versus no GDM (38.4 versus 25.7 percent) and in part due to the inability of women with a history of GDM randomly assigned to intensive lifestyle intervention to sustain physical activity and maintain weight loss. In addition to this high-risk GDM subgroup, Met-

formin was also found to be particularly effective in subjects who were younger and more obese (BMI >35 kg/m2).

The Metformin Argument

In addition to prevention of type 2 DM observed in DPP and other prevention studies, Metformin has been associated with reductions in mortality, cardiovascular disease and cancer incidence in studies involving type 2 DM subjects. Metformin is a relatively inexpensive medication and has no known long-term serious adverse effects. Gastrointestinal intolerance issues with this drug are usually transient and can generally be overcome by slow titration of Metformin dosage or use of the longer-acting Glumetza formulation, which is frequently better tolerated in some patients. As well, Glumetza may be given once-daily leading to potential improvement in patient adherence to the treatment regimen. Metformin and lifestyle interventions can go hand in hand, as there is minimal risk of hypoglycemia with the combination. From an economics perspective too, use of Metformin may save money over time when used in primary prevention of T2DM by:

- delay or prevention of T2DM by reducing progression of beta cell failure,
- better achievement of glycemia goals leading to less complications, and
- delay or prevention of Metformin failure and need for second-line oral hypoglycemic agents in subjects who go on to develop T2DM (6).

Guideline recommendations in most countries (including Canada) have incorporated Metformin as a pharmacotherapy option; though most recommend lifestyle interventions, over prescription medications, as the "therapy" of choice in prevention of type 2 DM. ADA recommends consideration of Metformin for diabetes prevention in high-risk individuals (Table 2).

However, some would argue that preference of lifestyle over Metformin (rather than initiation of both together from the beginning) may engender the "denial" phase in patients with pre-diabetes and early T2DM. Practically speaking, the rationale for Metformin in prevention is strengthened by two facts: 1) once a patient has developed IFG/IGT, they are at a very high risk for T2DM, 2) most patients find it difficult to initiate and maintain weight loss even after repeat counseling. If intensive lifestyle intervention is chosen solely, over pharmacotherapy, patients should be followed annually with a repeat OGTT. In the absence of weight loss or with any worsening of IFG/IGT (even within the non-diabetic range), addition of Metformin may be indicated.

Back to the case: Mrs. Angela A

Reviewing, Mrs. Angela A is a young woman with a history of GDM and metabolic syndrome. She has had a worsening of her IFG + IGT over 2 years and has been unsuccessful at weight loss. Hence, based on the above arguments and results of DPP, Metformin initiation (either as twice-daily Metformin Hydrochloride or as once-daily Glumetza) should be strongly considered to prevent/delay her development of type 2 DM and associated complications.

Table 2

Treatment Recommendation for Individuals with IFG, IGT or both
(adapted from American Diabetes Association Guidelines 2011)

Population	Treatment
IFG or IGT	Lifestyle modification (ie. 5 to 10% weight loss, moderate intensity physical activity – 30 min/day
IFG + IGT + any of the following	Lifestyle modification (as above) and /or Metforim 850mg twice per day
<60 years of age	
BMI > 35 kg/m2	
Family history of diabetes in first degree relative	
Elevated triglycerides	
Reduced HDL cholesterol	
Hypertension	
HbA1c > 6.0%	

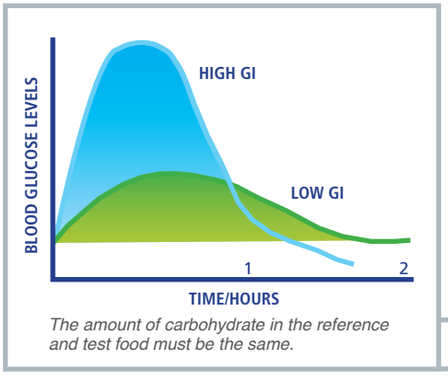
References:

1. *Narayan K M, Boyle J P, et al. Lifetime risk for diabetes mellitus in the United States. JAMA 2003; 290: 1884-1890*
2. *de Vegt F, Dekker J M, et al. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: The Hoorn Study. JAMA 2001; 285: 2109-2113*
3. *Orozco LJ, Buchleitner AM, et al. Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database Syst Rev 2008*
4. *Knowler WC, Barrett-Connor E, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346:393.*
5. *Ratner RE, Christophi CA, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 2008; 93:4774.*

The Glycemic Index – scientific tool or fad diet?

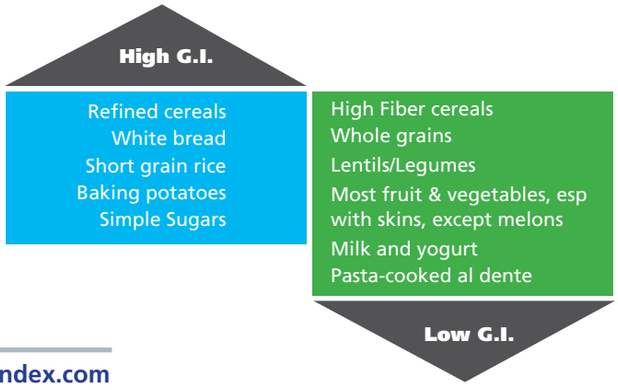
Both really. The glycemic index (GI) was actually developed with significant Canadian scientific contribution through the team of David Jenkins et al at our own St. Michael's Hospital in Toronto. It was developed in recognition of observations that some highly-favoured diets, such as the Mediterranean diet, do incorporate carbohydrate (CHO), but that their CHO were less likely to cause post-prandial hyperglycemia, even in patients with diabetes. On other words, some carb's are 'better' than others.

The glycemic index was developed to quantify 'better or worse'. It is based on the premise that one slice of white bread has a GI of 1. Over the past decade, many carb's have been scored relative to one slice of white bread, producing a GI for each one. Low glycemic index carbohydrates tend to include high fibre content, such as whole grains. Their slower rate of digestion results in more limited and delayed increases in blood glucose levels.



The amount of carbohydrate in the reference and test food must be the same.

www.glycemicindex.com



The more processed and refined a carbohydrate, generally the higher the GI. For example, we consider oatmeal to be a healthy, low GI carb and it is – as long as it's prepared in its traditional form: steel cut whole grains that require 45 minutes to cook. Popular processed oatmeal preparations that can be cooked in 5 minutes or micro-waved in 1 minute – have a very high GI because the pre-cooking in the processing method has denatured the complex CHO's, leaving a product no better than white bread.

Cooking method can also change the GI of a food. For example, slightly undercooked pasta (al dente) has a lower GI than well-cooked pasta. Baked potatoes actually have a lower GI than mashed. Raw vegetables have a lower GI than cooked.

Finally, macronutrient combinations can alter a food's GI. Adding fat tends to delay CHO digestion, effectively raising its GI. Adding almond butter to toast is an effective way of raising its GI and nutritive value. In the potatoe example above, french fries actually have a lower GI than mashed potatoes.

	DAY 1	DAY 2
breakfast	• ½ cup steel cut oatmeal • 1 cup mixed berries • ¾ cup low fat yogurt	• 2 pieces of sourdough/stone ground whole grain bread • 1-2 Tbsp peanut butter • 1 cup low fat milk
snack	• ¼ cup almonds	• 3/4 cup low fat yogurt
lunch	• 1 cup Mixed bean salad with tomatoes, lemon juice and balsamic vinaigrette dressing • 1 cup broccoli salad • 1 cup low fat milk	• Tuna pasta salad • 1 cup pasta, cooked el dente • 2 cups mixed vegetables • 1/2 cup tuna • Light mayonnaise • Lemon juice • 1 cup low fat milk
snack	• 1 medium apple	• 3/4 cup low fat yogurt
dinner	• 4-5 ounce chicken breast • 3/4 cup Quinoa salad • Large spinach salad with raspberry vinaigrette dressing • 1 cup low fat milk	• 2/3 cup basmati or Doongara rice • 4-5 ounce pork chop • Mushroom salad with balsamic vinaigrette • Mixed green salad with low fat dressing • 1 cup fruit salad

◀ Here is a sample of a two day low glycemic index diet.

It happens to be that lower GI diet foods, or food combinations, tend to also be more filling, making them appealing to people who are actively trying to reduce their food portion sizes while avoiding excessive hunger. Recent popular diet books and TV shows have referenced the GI concept, and one diet is named after it. This is one popular diet phenomenon that we can actually endorse.

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Dear Colleagues

Type 2 Diabetes is a rapidly growing epidemic in both developed and developing nations. It will be an increasing challenge to health care providers as the Canadian population ages. In our August issue of Clinical Practice Update Dr. Harpreet Bajaj discusses the entity known as "Pre-Diabetes", exploring the addition of metformin when lifestyle measures fail to achieve the desired goals of weight reduction and euglycemia. Metformin is well supported by current evidence to delay or prevent Type 2 Diabetes. Glumetza, a longer acting formulation of metformin, may be more tolerated by patients, and as a once a day dose claim better adherence. From our own LMC patient database, a retrospective analysis showed a trend toward lower HbA1c levels in patients taking Glumetza vs meformin.

Also in this edition, Tanya Levin, a registered dietician at LMC Bayview, gives some helpful insights on the Low Glycemic Index Diet, which we recommend for our pre-diabetic and diabetic patients.

Sincerely,

Samantha Sandler MD, FRCPC

Editor,
Clinical Practice Update