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COMMENTARY

Should Prediabetes be Treated Pharmacologically?

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ABSTRACT

Objective: In this commentary I will evaluate whether prediabetes should be treated pharmacologically. To consider this question, certain information concerning prediabetes is relevant. ***Background Information***: (1) Prediabetes is not independently associated with cardiovascular disease; the other factors in the metabolic syndrome increase that risk; (2) various tests and criteria for diagnosing prediabetes are recommended, yielding prevalences varying from 6% to 38% depending on which are used; (3) one-third of patients with prediabetes revert to normal over time; (4) up to two-thirds of patients with prediabetes do not develop diabetes; (5) people with prediabetes have insulin resistance and impaired insulin secretion; (6) although pharmacological treatment of the dysglycemia temporarily lowers it, when the drugs are discontinued, incident diabetes develops similarly as that in those who received placebos; (7) when the drugs are discontinued, there are no changes in insulin resistance or impaired insulin secretion; (8) incident diabetes was similar at 10 years in people remaining on metformin in the Diabetes Prevention Program Outcome Study compared with those who did not receive the drug; (9) no current drugs will directly increase insulin secretion (except sulfonylureas and glinides which have not been used to treat prediabetes because of hypoglycemia concerns); (10) sufficient weight loss to lower insulin resistance by nutritional means is challenging and especially difficult to maintain.
Conclusions: Pharmacological treatment of the dysglycemia of prediabetes is not warranted. On the other hand, the ability of high doses of glucagon-like peptide (GLP)-1 receptor agonists and the combination of a GLP-1 receptor agonist and the glucose-dependent insulinotropic polypeptide (GIP) to lower weight by 15% and 20%, respectively, deserves consideration for the treatment of prediabetes. This amount of weight loss should decrease insulin resistance, allowing endogenous insulin secretion to be more effective and lower the risk for developing diabetes.

Keywords: Cardiovascular disease; GLP-1 Agonists; GIP; Metabolic syndrome; Obesity; Prediabetes

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Key Summary Points
Prediabetes is not independently associated with cardiovascular disease (CVD); other factors in the metabolic syndrome increase that risk.
Two-thirds of people with prediabetes do not develop diabetes.
Pharmacological treatment of the dysglycemia of prediabetes temporarily lowers glycemia but when the drugs are discontinued, development of diabetes is the same as in people who received placebos.
The only effective treatment of prediabetes is significant weight loss, but this is very difficult to achieve, and especially to maintain, by nutritional means.
High doses of glucagon-like peptide (GLP)-1 receptor agonists and combination of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) lower weight by 15% and 20%, respectively, and should be considered for treatment of prediabetes.

Prediabetes is a dysglycemia with glycemic values between normal and those that define diabetes. People with prediabetes are characterized by decreased insulin sensitivity (insulin resistance) and impaired insulin secretion that cannot meet the extra demands on the pancreatic beta cells imposed by the insulin resistance [1, 2]. Prediabetes increases the risk for the subsequent development of diabetes. This risk begins with a fasting plasma glucose (FPG) concentration of 4.6–4.8 mmol/L and increases in a curvilinear manner, with the chances of developing diabetes progressively rising the closer the dysglycemia is to the diagnostic criteria for diabetes [3–5].

The criteria for the diagnosis of prediabetes differs between the American Diabetes Association (ADA) and the international community (Table 1). Moreover, in contrast to the recommendation that the diagnosis of diabetes be confirmed, there is no such recommendation for the diagnosis of prediabetes [6]. This is unfortunate because on a repeat oral glucose tolerance test (OGTT) within 2–6 weeks, approximately half of individuals with Impaired Glucose Tolerance (IGT) have a normal result [7–9]. If the international Impaired Fasting Glucose (IFG) criterion were used to diagnose prediabetes, 32% were normal on repeat testing [10]. OGTTs are rarely used in clinical practice (except in pregnancy) so the diagnosis of prediabetes rests on FPG and glycated hemoglobin (HbA1c) testing. Depending on where one lives and the test used for the diagnosis, there is a marked difference in whether an individual will be diagnosed with prediabetes or not. To illustrate using the largest possible difference, the prevalence of prediabetes in the USA diagnosed by a FPG concentration of 5.6–6.9 mmol/L is 37.5% compared with the international prevalence diagnosed by an HbA1c level of 42–-46 mmol/mol of 5.8% [10].

Finally, the natural history of prediabetes is somewhat reassuring. Approximately two-thirds of people with prediabetes do not develop diabetes. In the placebo arm of the Diabetes Prevention Program Outcome Study (DPPOS), 65% of participants had not developed diabetes 5.7 years after the Diabetes Prevention Program (DPP) had ended [11]. Similarly, 69% of people with prediabetes in the Framingham Offspring Study had not developed diabetes 27 to 30 years later [12]. In people with prediabetes who were older than 60 years enrolled in the Swedish National Study on Aging who were followed for 12 years, 23% died and 13% developed diabetes [13]. Even assuming that all the individuals who died had developed diabetes before doing so (highly unlikely), 64% of those still living would not have developed diabetes. Furthermore, a mean of one-third, with a wide range of 13–69% depending on the diagnostic criteria used to diagnose prediabetes and euglycemia, returned to normal glucose regulation over time [10, 14].

Metabolic syndrome (MetS) is a cluster of the following risk factors for cardiovascular disease

Table 1 Criteria for the diagnosis of prediabetes

Test	Organization			
	ADA	WHO	DCCPG	NICE
OGTT–2 h	7.8–11.0[a] (IGT)	7.8–11.0[a] (IGT)	7.8–11.0[a] (IGT)	7.8–11.0[a] (IGT)
FPG	5.6–6.9[a] (IFG)	6.1–6.9[a] (IFG)	6.1–6.9[a] (IFG)	6.1–6.9[a] (IFG)
HbA1c	39–46[b]	Not recommended	42–46[b]	42–46[b]

ADA American Diabetes Association (USA), *DCCPG* Diabetes Canada Clinical Practices Guidelines (Canada), *FPG* fasting plasma glucose, *IFG* impaired fasting glucose, *IGT* impaired glucose tolerance, *NICE* National Institute for Health and Care Excellence (Europe), *OGTT* oral glucose tolerance test, *WHO* World Health Organization (International Diabetes Federation)

[a]mmol/L

[b]mmol/mol

(CVD), any three or more of which diagnoses the syndrome:

- Central obesity: waist circumference of > 102 cm for men and > 90 cm for women; for Asians the criteria are > 88 cm for men and > 80 cm for women
- Hypertension: blood pressure > 130/85 mmHg or treatment for hypertension
- Triglycerides: fasting triglyceride level > 1.7 mmol/L
- High-density lipoprotein (HDL) cholesterol: HDL level < 1.0 mmol/L for men and < 1.3 mmol/L for women
- Prediabetes

Although prediabetes is part of the MetS, evidence that it is independently associated with CVD is weak. When the other risk factors in the MetS were taken into account statistically, no significant association was found between prediabetes and incident CVD whether the diagnosis was based on the ADA criteria for prediabetes or the international criteria for prediabetes [15]. Adding the diagnosis of prediabetes by either IFG or HbA1c criteria to the other MetS factors did not improve the prediction of CVD [15]. The presence of prediabetes did not affect the clinical outcomes of patients who experienced an acute coronary syndrome, such as acute pulmonary edema, length of hospital stay, 28-day readmission rates, recurrence or CVD mortality, compared to those with normal HbA1c levels [16]. In individuals with IGT, the risk of CVD mortality was the same whether they returned to normal glucose regulation or not [14].

A large number of studies [15] have tracked incident CVD (but without taking the other risk factors of the MetS into account) for 6–15 years after diagnosing prediabetes by either the lower range of the ADA IFG criteria (5.6–6.0 mmol/L) or the international IFG range (6.1–6.9 mmol/L). The CVD outcomes in these studies, involving 471,769 individuals, were CVD death, coronary artery disease, cerebrovascular disease, and any CVD event. Of the eight studies in which the lower range of the ADA IFG criteria were evaluated, none showed a significant difference in incident CVD compared to persons with a FPG concentration < 5.6 mmol/L. Of the ten studies that evaluated the international range of the IFG criteria, three showed a significant difference in at least one of the CVD outcomes (one was significant in women, not men). Eight studies (with nine cohorts) involving 67,259 individuals tracked incident CVD after the diagnosis of prediabetes was made by HbA1c levels. In the six cohorts in which HbA1c levels < 42 mol/mmol could be evaluated, two showed a significant increase in incident CVD. In the nine cohorts in which the international HbA1c levels were evaluated, five were significant. Although these results show that HbA1c levels may be more specific for an association of prediabetes with CVD, treating the glycemia of

prediabetes should not have much of an overall effect on the CVD risk associated with the MetS.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Given this general background of prediabetes, let us consider whether it should be treated pharmacologically. The well-known Diabetes Prevention Program Research Group studied the effect of an intensive lifestyle intervention or metformin on the development of diabetes in people with prediabetes diagnosed by IGT who also had a FPG > 5.3 mmol/L [17]. Compared to the control group, there was a 58% and 31% decrease in the development of diabetes in those in the lifestyle and metformin groups, respectively, after a mean follow up of 2.8 years. The intensive lifestyle intervention included a 16-lesson curriculum taught monthly on a one-to-one basis over the first 4 months after enrollment with subsequent individual and group sessions to reinforce behavioral changes as well as opportunities and facilities for exercise. Unfortunately, such intensive lifestyle intervention programs are mostly unavailable without research support.

Based on the response to metformin, some investigators have evaluated whether treating people with prediabetes with other anti-hyperglycemia drugs might delay or even prevent the development of diabetes. Treatment with a thiazolidinedione (TZD) [18–20], an alpha glucosidase inhibitor [21], a basal insulin [22], and a glucagon-like peptide (GLP)-1 receptor agonist [23] did indeed lower the development of diabetes in individuals while they were taking the drug. These drugs simply treated a level of glycemia less than values that fulfilled the criteria for diagnosing diabetes, retarding a possible increase to levels that diagnosed diabetes. However, once the drugs were stopped, the development of diabetes was the same as that in the placebo group. Troglitazone, the first TZD approved, but subsequently taken off of the market because of liver damage that also resulted in a few deaths, was also used in the DPP [18]. It was markedly effective in lowering the development of diabetes while being used, but after discontinuation, the number of new cases of diabetes was the same as in the placebo group (Fig. 1). The same results were seen with the two other TZDs and a basal insulin (Table 2).

These studies are consistent with the experience of the individuals in the DPP who received metformin. At the end of the study, metformin and placebo were discontinued and an OGTT was performed within 1–2 weeks. The number of people newly diagnosed with diabetes based on that OGTT was 64% higher within 1–2 weeks in those who had just stopped metformin (5.4%) compared with the placebo group (3.3%) [27]. Even when the duration of follow-up was taken into account, 50% more people in the metformin group were diagnosed with diabetes than in the placebo group. This difference might have been greater subsequently as metformin was likely still having a tissue effect after only 11 days of being discontinued.

The investigators continued to follow all of the people still enrolled in the DPP at the end of the study. In the DPPOS, those who had received metformin were offered the opportunity to continue it, with 88% of these agreeing to do so. Long-term follow-up at 10 years revealed no difference in diabetes incidence among the lifestyle intervention, metformin, and placebo groups [28]. All of these follow-up results with metformin, TZDs, and basal insulin are consistent with those of studies showing that anti-hyperglycemic drug treatment of

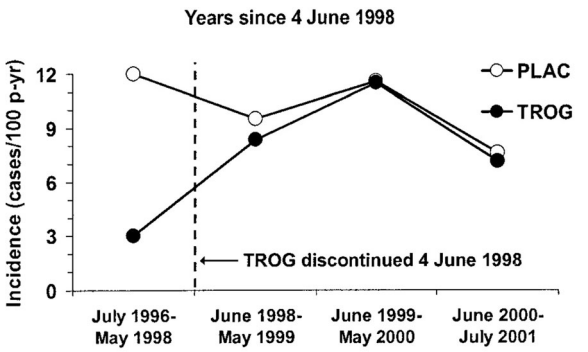

Fig. 1 Effect of troglitazone (*TROG*) on the development of diabetes from prediabetes while in use and after discontinuation. *PLAC* Placebo. Reproduced from New Engl J Med. 2005;346:303–403, Figure 3c [18], with permission of the American Diabetes Association, Inc.

Table 2 Development of diabetes after discontinuing anti-hyperglycemic drugs

Study [Reference]	Drug	Duration after stopping drug	Drug stopped (%)	Placebo stopped (%)
DREAM [21]	Rosiglitazone	2–3 months	10.5	9.8
DREAM [22]	Rosiglitazone	1–2 years	20.7	20.9
ACT NOW [23]	Pioglitazone	1 year	11.2	12.3
ORIGIN [19]	Glargine insulin	3 months	30	35

DREAM Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication, *ACT NOW* Actos Now for Prevention of Diabetes, *ORIGIN* Outcome Reduction With Initial Glargine Intervention

Table 3 Effectiveness of weight loss drugs

Drug (Reference)	Weight loss[a] (%)	Drug (Reference)	Weight loss[a] (%)
Phentermine [33]	9	Liraglutide 3.0 mg [38, 39]	6–8
Orlistat [34]	5	Semaglutide 2.4 mg [40]	15
Naltrexone ER/buproprion ER [35, 36]	6–8	Tirzepatide 10, 15 mg [41]	20–21
Phentermine/topiramate ER [37]	8–10		

[a]Significantly different from placebo at 1 year

people with prediabetes did not alter the pathophysiologic abnormalities of insulin resistance and progressive pancreatic beta cell dysfunction [1, 2]. This explains the lack of a long-term effect when these drugs were discontinued [29]. Thus, treatment of the dysglycemia of prediabetes with anti-hyperglycemia drugs would not seem very helpful.

The level of insulin sensitivity is inherited and varies sixfold among individuals without diabetes [30]. Whatever the inherited level is, obesity lowers it, i.e., increases insulin resistance, elevating the risk for prediabetes and possible subsequent diabetes because of the extra demands on insulin secretion. In addition to this increased risk, obesity also increases the risk for hypertension, CVD, chronic kidney disease, osteoarthritis, non-alcoholic steatohepatitis, and death from several cancers [31]. Comprehensive lifestyle intervention, including hypocaloric diets and increased physical activity accompanied by behavioral support, is the first step in treating obesity. However, achieving even a 5% weight loss is difficult in standard weight loss programs and most of the lost weight starts to be regained after 6 months [32]. For this reason, anti-obesity drugs are often used to supplement weight loss programs. Their effectiveness is summarized in Table 3.

Shortly after starting a meal, a hormone, GLP-1, is released from the small intestine. This hormone stimulates insulin secretion, suppresses glucagon secretion, and delays gastric emptying, all of which aid in reducing the postprandial rise of glucose concentrations. GLP-1 only has a 2-min half-life in the circulation. An effective class of anti-hyperglycemia drugs has been developed by altering the amino acids at the site where the enzyme that destroys GLP-1 acts. This allows GLP-1 to remain in the circulation for hours to days up to a week depending on other additions to the drug preparations. These drugs bind to the GLP-1 receptor, reproducing the actions of endogenous GLP-1. These GLP-1 receptor agonists also suppress hunger and appetite by stimulating the satiety center in the brain, resulting in decreased food intake with resulting weight loss. Randomized

controlled trials involving two GLP-1 receptor agonists, but at higher US Federal Drug Administration (FDA)-approved doses than FDA-approved doses for the treatment of diabetes, have been evaluated for weight loss in obese individuals. Daily injections of liraglutide achieved a 6–8% weight loss [38, 39] and weekly injections of semaglutide achieved a 15% weight loss [40]. In a semaglutide weight loss trial, 42% of the subjects at enrollment had prediabetes which fell to 7% at the end of the study [Results presented at the ADA National Meeting, New Orleans, LA, USA, June 2022]. Unfortunately, as with lifestyle interventions, when semaglutide was discontinued, weight regain occurred [41], suggesting that ongoing treatment might be necessary to maintain the weight loss achieved.

There is another hormone that is quickly released by the small intestine after a meal is begun, namely, glucose-dependent insulinotropic polypeptide (GIP). Not only does this nutrient-stimulated hormone also increase insulin secretion, it also regulates energy balance through cell-surface receptor signaling in the brain and adipose tissue [42]. Therefore, the combination of a GLP-1 receptor agonist that suppresses appetite and GIP that increases the metabolic rate might be more effective for weight loss. Tirzepatide is such a drug, and the weekly injection of its two higher doses achieved a remarkable mean weight loss of just over 20% [43].

In conclusion, should prediabetes be treated pharmacologically? Given the data that: (1) a large number of diagnoses cannot be confirmed on re-testing within 2–6 weeks,(2) approximately one-third of individuals return to euglycemia, depending on the criteria used to diagnose prediabetes and euglycemia, (3) up to two-thirds of individuals diagnosed with prediabetes do not develop diabetes, (4) evidence for an independent association of prediabetes with CVD is weak, and (5) the risk for CVD in individuals diagnosed with prediabetes by IGT is the same whether IGT returns to normal or not (suggesting that the other risk factors of the MetS are responsible), treating the dysglycemia of prediabetes is not warranted.

On the other hand, there are no drugs that will directly improve or stabilize the impaired insulin secretion of prediabetes, with the exceptions of sulfonylureas and glinides, both of which have not been used to treat prediabetes because of the risk of hypoglycemia. The only approach at the current time is to decrease insulin resistance enough so that the available insulin secretion will be more effective. Lifestyle interventions are the current recommendations to achieve this with at least a 5% weight loss, with some experts stating that a 10% weight loss is necessary. Given the inability of lifestyle interventions outside of research studies to produce and maintain enough weight loss to accomplish this, weight loss drugs are currently the only effective option. High doses of GLP-1 receptor agonists with or without GIP lead to much more weight loss than nutrition (hypocaloric diets) and exercise interventions, leading one to believe that unless persistent gastro-intestinal (GI) side effects or cost/insurance issues are present, compliance for the drugs will be better than for ongoing hypocaloric diets and changes in exercise. Persistent GI side effects leading to discontinuation of the drugs occurred in only a small minority (< 10%) in the published studies and tolerance to these drugs, i.e., failure to lose more weight, did not occur until a very significant weight loss (15–20%) had occurred [40, 43].

These drug effects on weight loss are very impressive and will be effective in delaying and possibly preventing the development of diabetes in people with prediabetes. An additional clinical benefit will be their effects on lowering the morbidity of hypertension, CVD, chronic kidney disease, osteoarthritis, non-alcoholic steatohepatitis, and mortality from several cancers associated with obesity [31]. The caveat affecting the use of these drugs, at least in the near future, is their probable continued need to maintain weight loss, insurance coverage, and high costs.

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