In the Name of God

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Should Prediabetes be Treated Pharmacologically?

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Prediabetes is a dysglycemia with glycemic values between normal and definite diabetes.

prediabetes are characterized by decreased insulin sensitivity (insulin resistance) and impaired insulin secretion.

This risk begins with a fasting plasma glucose (FPG) concentration of 4.6–4.8 mmol/L (82-86mg/dl) 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

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 .

The prevalence of prediabetes in the USA diagnosed by a FPG 5.6–6.9 mmol/L (100-125mg/dl) is 37.5% compared with the international prevalence diagnosed by an HbA1c level of 42–- 46 mmol/mol (6-6.4%) is 5.8%

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

140-199mg/dl
110-125mg/dl
6%-6.4%

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. Similarly, 69% of people with prediabetes in the Framingham Study had not developed diabetes 27 to 30 years later.

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.

Even assuming that all the individuals who died had developed diabetes (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, returned to **normal glucose** regulation over time.

Metabolic syndrome (MetS) is a cluster of the following risk factors for cardiovascular disease(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- 150mg/dl]
- **High-density lipoprotein** (HDL) cholesterol: HDL level <1.0 mmol/L- 38.6 mg/dl for men and <1.3 mmol/L- 50 mg/dl 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, no significant association between prediabetes and incident CVD (diagnosis was based on the ADA criteria or the international criteria).

Adding the diagnosis of prediabetes to the other MetS factors did not improve the prediction of CVD.

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.

In individuals with IGT, the risk of CVD mortality was the same whether they returned to normal glucose regulation or not.

A large number of studies have tracked incident CVD (but without taking the other risk factors of the MetS) for 6–15 years after diagnosing prediabetes by either the lower range of the ADA IFG criteria (5.6–6.0 mmol/L, 100_108 mg/dl) or the international IFG range (6.1–6.9 mmol/ L, 110_125mg/dl).

The CVD outcomes in these studies, involving 471,769 individuals, were CVD death, coronary artery disease, cerebrovascular disease, and any CVD event.

lower range of the ADA IFG criteria were evaluated in 8 studies, none showed a significant difference in incident CVD compared to persons with a FPG concentration <5.6 mmol/L (100 mg/dl).

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, 6%) 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.

The well-known Diabetes Prevention Program Research Group studied the effect of intensive lifestyle or metformin on the development of diabetes in people with prediabetes diagnosed by IGT who also had a FPG [5.3 mmol/L] (95 mg/dl).

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

Some investigators have evaluated whether treating people with prediabetes with other anti-hyperglycemia drugs.

Treatment with a thiazolidinedione (TZD), an alpha glucosidase inhibitor, a basal insulin, and a glucagon-like peptide (GLP)-1 receptor agonist 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.

- 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. 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.
- The same results were seen with the two other TZDs and a basal insulin

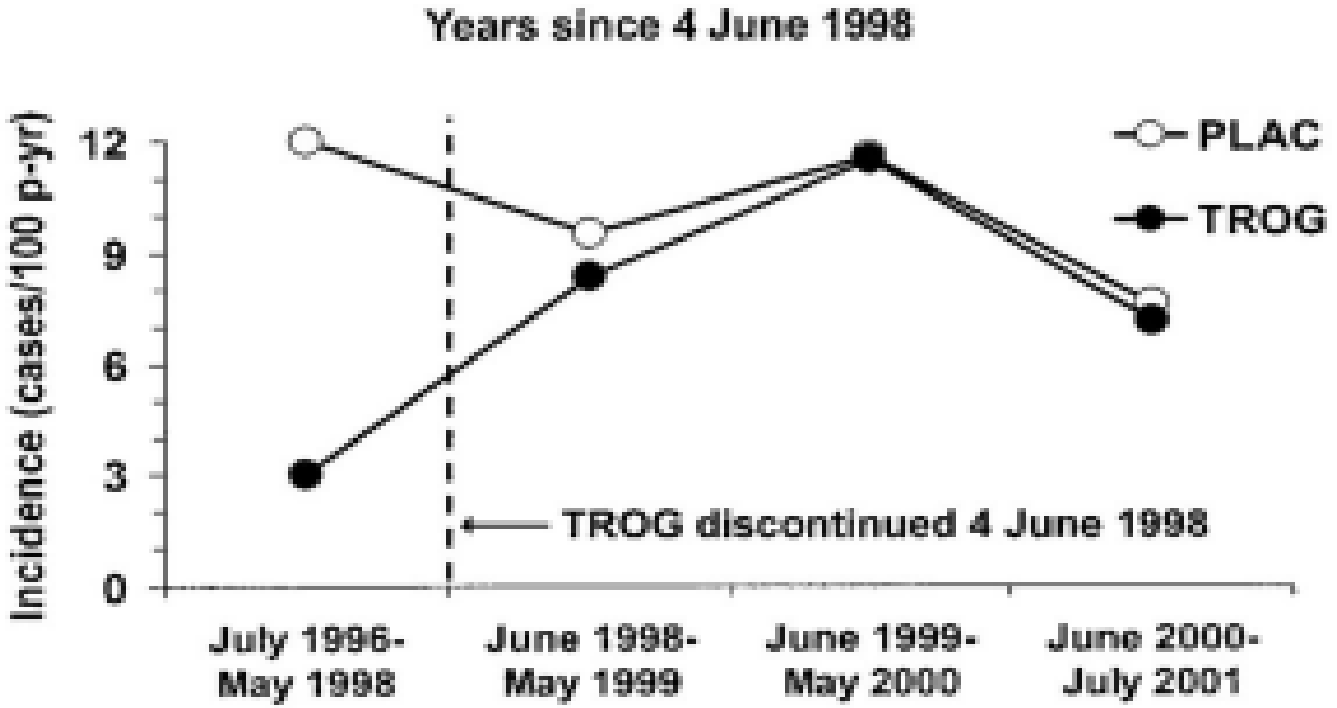

Fig. 1 Effect of troglitazone (*TROG*) on the development of diabetes from prediabetes while in use and after discontinuation. *PLAC* Placebo. Reproduced from New Engl J Med. 2005;346:303–403, Figure 3c [18], with permission of the American Diabetes Association, Inc.

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

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%).

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.

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 prediabetes did not alter the pathophysiologic abnormalities of insulin resistance and progressive pancreatic beta cell dysfunction.

This explains the lack of a long-term effect when these drugs were discontinued. 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.

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.

- Comprehensive lifestyle intervention, including hypocaloric diets and increased physical activity accompanied by behavioral support, is the first step in treating obesity.

- 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. For this reason, anti-obesity drugs are often used to supplement weight loss programs.

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

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.

Two GLP-1 receptor agonists, but at higher US (FDA)-approved doses for the treatment of diabetes, have been evaluated for weight loss.

Daily injections of liraglutide achieved a 6–8% weight loss and weekly injections of semaglutide achieved a 15% weight loss. In a semaglutide weight loss trial, 42% of the subjects at enrollment had prediabetes which fell to 7% at the end of the study.

Unfortunately, as with lifestyle interventions, when semaglutide was discontinued, weight regain occurred, 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.

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%.

Should prediabetes be treated pharmacologically? Given the data that:

(1) a large number of diagnoses cannot be confirmed on re-testing (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 with prediabetes do not develop diabetes,

(4) evidence for an independent association of prediabetes with CVD is weak,

(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, 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, 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 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.

- 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.

The caveat affecting the use of these drugs, is their probable continued need to maintain weight loss, insurance coverage, and high costs.

Summary:

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.

THANKS FOR YOUR ATTENTION