Successful treatment of prediabetes in clinical practice using physiological assessment (STOP DIABETES)

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Summary

Background Of the 84 million American adults with prediabetes, over 5 to 7 years, about 28 million progress to type 2 diabetes. We aimed to assess whether a real-world, pathophysiology-based, therapeutic approach could prevent development of type 2 diabetes in high-risk individuals.

Methods We did a retrospective observational study of people at increased risk of type 2 diabetes from a community practice in southern California, USA. Participants had an oral glucose tolerance test and were assigned a risk stratification on the basis of presence and severity of insulin resistance, impaired β-cell function, and glycaemia (ie, 1-h plasma glucose concentration of more than 8·6 mmol/L during an oral glucose tolerance test). Treatment was recommended on the basis of risk: metformin, pioglitazone, glucagon-like peptide-1 (GLP-1) receptor agonist, and lifestyle therapy for participants at high risk of diabetes, and metformin, pioglitazone, and lifestyle therapy for those at intermediate risk. Individuals who refused pharmacological therapy were assigned to lifestyle therapy only. Participants were followed up every 6 months and oral glucose tolerance tests were repeated at 6 months and subsequently every 2 years or sooner. The primary outcome of our analysis was incidence of type 2 diabetes according to the American Diabetes Association criteria, within the study period (2009–16). This study is registered with ClinicalTrials.gov, number NCT03308773.

Findings Between Jan 1, 2009 and Dec 31, 2016, we assessed 1769 people at increased risk of diabetes, of which 747 (42%) were identified at high or intermediate risk and were recommended pharmacological treatment. Of 422 participants analysed, 28 (7%) progressed to type 2 diabetes (seven [5%] of 141 participants who received metformin, pioglitazone, and lifestyle therapy, none [0%] of 81 who received metformin, pioglitazone, GLP-1 receptor agonist, and lifestyle therapy, and 21 [11%] of 200 who received lifestyle therapy only) after mean follow-up of 32·09 months (SEM 1·24). Compared with participants who received lifestyle therapy only, the adjusted hazard ratio for progression to type 2 diabetes was 0·29 (95% CI 0·11–0·78, p=0·0009) in participants who received metformin and pioglitazone, and 0·12 (95% CI 0·02–0·94, p=0·04) in participants who received metformin, pioglitazone, and GLP-1 receptor agonist. Improved β-cell function was the strongest predictor of type 2 diabetes prevention.

Interpretation Progression to type 2 diabetes in people at high risk of diabetes can be markedly reduced with interventions designed to correct underlying pathophysiological disturbances (ie, impaired insulin secretion and resistance) in a real-world setting.

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Introduction

About 84 million American adults, one in three, have prediabetes.[1] Over a period of 5–7 years, a third of these individuals with prediabetes will progress to type 2 diabetes.[2] Prediabetes is characterised by impaired fasting glucose, impaired glucose tolerance, and increased HbA_{1c} concentrations (5·7–6·4%; 39–46 mmol/mol). Although different pathophysiological disturbances are present in individuals with impaired fasting glucose and glucose tolerance,[3,4] their conversion rate to type 2 diabetes is similar.

Prospective epidemiological studies have shown that about 40% of people who progress to type 2 diabetes over 5 years had normal glucose tolerance at baseline, suggesting that many individuals with normal glucose tolerance are also at increased risk of diabetes. In a previous study, we showed that a 1-h plasma glucose concentration of more than 8·6 mmol/L identifies individuals with normal glucose tolerance and at high risk of type 2 diabetes;[5–7] this finding has been confirmed by other studies.[8–10] By measurement of plasma glucose and insulin concentrations during oral glucose tolerance tests, the two core defects responsible for development of type 2 diabetes can also be measured: insulin resistance and β-cell failure.[3,4,6,11] Therefore, to prevent development of type 2 diabetes, interventions that correct the underlying pathophysiological defects should be used.[11–13] Multiple strategies have been used to delay or prevent development of diabetes including lifestyle modification,[14] pharmacotherapy,[15,16] and bariatric or metabolic surgery.[17] Despite success of these therapies in placebo-controlled trials in preventing type 2 diabetes,

Research in context

Evidence before this study

Disturbances in normal physiology precede development of type 2 diabetes by years to decades. This prediabetic period is characterised by insulin resistance, compensatory hyperinsulinaemia, and progressive loss of β-cell response. Physiological heterogeneity exists among patients with prediabetes that influences their risk of progression to type 2 diabetes and microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke, and diastolic dysfunction) complications. We have previously shown that a 1-h plasma glucose concentration more than 8·6 mmol/L during oral glucose tolerance testing identifies patients at increased risk of developing type 2 diabetes. We also have shown that measures of insulin resistance (Matsuda index) and β-cell function (insulin secretion, insulin resistance, or disposition index) from oral glucose tolerance tests are strong predictors of future development of type 2 diabetes in individuals with prediabetes. Multiple randomised controlled trials have shown the benefit of lifestyle modification and pharmacological treatment in the prevention or delay of development of type 2 diabetes. Despite this knowledge, the application of diabetes prevention in clinical practice has been poor and the incidence of diabetes continues to increase. Publications have shown the benefit of real-world data in validating and expanding insights from randomised controlled trials. We searched PubMed between 1983 and 2008, using the terms, "prediabetes", "pathophysiology", "type-2 diabetes prevention", "RTC", and "real world".

Added value of this study

This retrospective observational study of real-world data from clinical practice assesses the prevention or delay of type 2 diabetes using a personalised medicine approach on the basis of the pathophysiology of disease in high-risk individuals. By measuring the glycaemic response during oral glucose tolerance testing (1-h glucose concentration more than 8·6 mmol/L), insulin sensitivity, and β-cell function, the underlying pathophysiology and severity of the pathophysiological abnormality can be characterised. With this information, a personalised restorative pharmacological plan can be implemented in a real-world setting. Our results show the effectiveness of a patient-tailored, low-dose pharmacological regimen designed to improve insulin sensitivity and β-cell function in the prevention or delay of type 2 diabetes. Additionally, patients identified with prediabetes by assessment of fasting plasma glucose or HbA_{1c} concentrations, but who have a glucose concentration of less than 8·6 mmol/L and normal insulin sensitivity and β-cell response were at low risk of developing type 2 diabetes. Importantly, characterisation of the severity of glycaemic response, insulin sensitivity, and β-cell response allows ongoing reassessment and collaboration between the physician and patient that is characteristic of real-world practice. Lastly, this study shows, for the first time, that this approach can be achieved in a real-world setting without external support.

Implications of all the available evidence

Our study suggests that clinicians might want to reconsider their approach to prediabetes on the basis of the pathophysiology of the disease in individual patients and should not simply rely on fasting plasma glucose and HbA_{1c} concentrations. Our results highlight the heterogeneity of the population with prediabetes and the effectiveness of early intervention based on a personalised medicine approach. The results require confirmation in other populations and in patients with different social and economic determinants of health. Treatment considerations should be weighed against risks of pharmacological agents and personalised based on patient comorbidities. Cost of pharmacological agents vary substantially in the USA and worldwide. However, regimens using inexpensive agents (metformin and pioglitazone) provide substantial benefit and expensive agents are nearing generic availability.

no previous study has examined their application in clinical practice.

Our study shows the feasibility of diabetes prevention in people at increased risk of type 2 diabetes in a private practice setting, using pathophysiological measures derived from oral glucose tolerance tests. We aimed to assess a personalised medicine approach based on pathophysiology to prevent diabetes in a high-risk population.

See Online for appendix

Methods

Study design and participants

1769 people at increased risk of diabetes were assessed on the basis of customary assessment used by an internal medicine and endocrinology community practice in southern California, USA, between 2009 and 2016. This retrospective observational study of real-world data from clinical practice reflects an assessment of this approach. This approach to management of participants used five steps: first, participants were identified at high or intermediate risk of future diabetes on the basis of well established risk factors (appendix); second, oral glucose tolerance tests were done by measuring plasma glucose (hexokinase reaction; Beckman Synchron CX-9, Brea, CA), insulin, and C-peptide (Siemens ADVIA Centaur/XP assay; Siemens Medical Solutions, Tarrytown, NY, USA) concentrations; third, presence and severity of insulin resistance, β-cell dysfunction, and glycaemia were determined; fourth, participants were stratified by risk (high, intermediate, low) on the basis of severity of pathophysiological disturbances; and fifth, pharmacological therapy was recommended on the basis of severity of these measures. All participants were in good health based on medical history, physical examination,

screening laboratory studies, and electrocardiogram results. Inclusion criteria for our analysis were intermediate and high risk of developing type 2 diabetes, age 18–100 years, and good general health. Exclusion criteria for our analysis included presence of type 1 or type 2 diabetes, use of drugs known to affect glucose tolerance, and major organ disease.

This study is registered with ClinicalTrials.gov (number NCT03308773) and was approved by Providence Health and Services Oregon Institutional Review Board. A waiver of consent was granted by the Institutional Review Board for this retrospective study.

Risk stratification and treatment

From oral glucose tolerance tests with measurement of plasma glucose, insulin, and C-peptide concentrations, we measured glycaemic response, insulin sensitivity, and β-cell response. Severity of abnormalities in each of these three physiological responses was identified as mild, moderate, or severe. People with a severe defect in two of three physiological responses (glycaemic response, insulin sensitivity, or insulin secretion) and those with a severe defect in one of three responses plus an intermediate defect in both other responses were considered to have the highest risk and were offered metformin, pioglitazone, a glucagon-like peptide 1 (GLP-1) receptor agonist, and lifestyle therapy. After excluding people at low risk of type 2 diabetes, all others were considered to have intermediate risk and were offered pioglitazone, metformin, and lifestyle therapy. Participants at moderate or high risk of diabetes who declined pharmacotherapy were assigned to lifestyle therapy only. Lifestyle intervention consisted of counselling consistent with Diabetes Prevention Program guidelines.[14] Risks and benefits of and alternatives to off-label use of pharmacological agents were discussed. The lowest dose of medication deemed likely to have a physiological effect was used to minimise side-effects and improve compliance. Metformin (850 mg/day) and pioglitazone (15 mg/day) doses were unmodified throughout the study. The GLP-1 receptor agonist used was based on insurance coverage: exenatide, 10 µg twice daily (n=26), liraglutide, 1·2 mg daily (n=49), exenatide extended release, 2 mg weekly (n=3), or dulaglutide, 1·5 mg weekly (n=3). Doses of GLP-1 receptor agonist were not modified during the study.

Glycaemic response was defined as normal if the participant had normal glucose tolerance according to the American Diabetes Association criteria and a 1-h plasma glucose concentration less than 8·6 mmol/L. Participants were considered to have moderate impairment in glucose tolerance if they had normal glucose tolerance and 1-h plasma glucose concentration more than 8·6 mmol/L, or impaired fasting glucose or impaired glucose tolerance, or both, and 1-h plasma glucose concentration less than 8·6 mmol/L. Participants were considered to have a severe abnormality in glucose tolerance if they had impaired fasting glucose or impaired glucose tolerance, or both, and 1-h plasma glucose concentration more than 8·6 mmol/L.

Matsuda index of insulin sensitivity[18] was calculated from oral glucose tolerance tests and compared with a reference group of 724 people with normal glucose tolerance (according to the American Diabetes Association criteria; appendix). If Matsuda index was less than the lowest 5% of the range of insulin sensitivity in the reference group, the participant had severe insulin resistance; participants whose Matsuda index was in the 6–25th percentile had moderate insulin resistance; and participants whose Matsuda index was more than the 25th percentile were insulin sensitive.

Insulin secretion was calculated as the ratio between the incremental area under the plasma C-peptide (C-pep) curve to the incremental area under the plasma glucose concentration (G) curve during oral glucose tolerance testing $(\Delta C\text{-pep}/\Delta G)_{0-120}$. The median value for $(\Delta C\text{-pep}/\Delta G)_{0-120}$ in 724 participants with normal glucose tolerance (appendix) reflected the normal value for insulin secretion. The ratio between the measured $(\Delta C\text{-pep}/\Delta G)_{0-120}$ to the normal level of insulin secretion was computed. We refer to this value as the insulin secretion index. Severe impairment of insulin secretion was defined as less than 50% of the insulin secretion index, moderate impairment was 50–70%, and normal secretion was more than 70%.

After a 10-h overnight fast, participants had a 2-h 75 g oral glucose tolerance test and plasma glucose, insulin, and C-peptide concentrations were measured at 0 min, 30 min, 60 min and 120 min. No medication was taken the morning of the test. All laboratory analyses were done at Providence Little Company of Mary Medical Center, Torrance, CA, USA. A baseline sample was obtained for plasma lipid, high-sensitivity C-reactive protein (latex-particle enhanced immunoturbidimetric assay; Beckman CX-9, Brea, CA, USA), and HbA_{1c} (high-performance liquid chromatography; BioRad-Variant Turbo II, Benicia, CA, USA) concentrations. During a routine office visit, blood pressure, height, and weight were measured, BMI was calculated, and medical history and a physical examination were done.

Follow-up visits and outcome

After therapy was initiated, participants were followed up every 6 months. Oral glucose tolerance tests were repeated at 6 months and subsequently every 2 years or sooner in participants in whom HbA_{1c} concentrations increased to more than 6·0% (48 mmol/mol) or fasting plasma glucose concentrations were more than 6·11 mmol/L. Participants who did not return for the initial 6-month follow-up were contacted by phone, mail, and email, and twice by a second mailed correspondence. The primary outcome was incidence of type 2 diabetes according to the American Diabetes Association criteria (fasting plasma glucose concentration at least

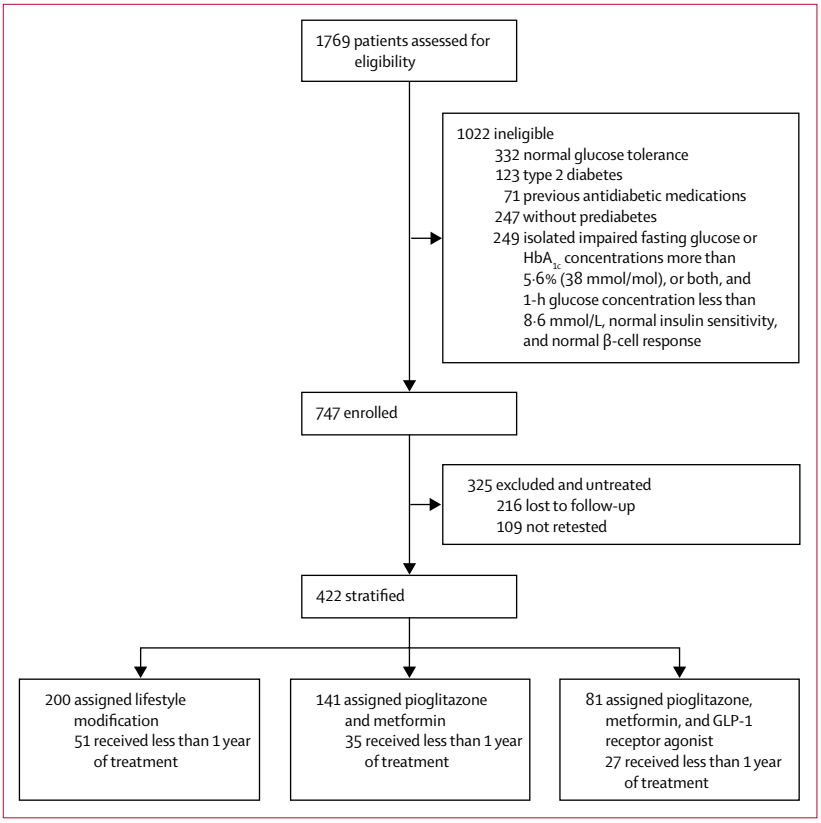

Figure 1: **Study profile**
GLP-1= glucagon-like peptide 1.

6·99 mmol/L, 2-h plasma glucose concentration at least 11·10 mmol/L, or HbA_{1c} concentration at least 6·5% [48 mmol/mol]). Safety was assessed during follow-up visits and recorded in the reviewed medical record.

Statistical analysis

Whole body insulin sensitivity was assessed with Matsuda index by use of plasma glucose and insulin concentrations during oral glucose tolerance testing.[18] Homeostasis model assessment-insulin resistance (HOMA-IR), which primarily reflects hepatic insulin resistance, was calculated as (fasting plasma glucose × fasting plasma insulin)/22·5.

Insulin secretion was calculated as $(\Delta C\text{-pep}/\Delta G)_{0-120}$. Area under the curve for plasma glucose, insulin, and C-peptide concentrations was calculated with the trapezoidal method. β-cell function was measured with the insulin secretion or resistance (disposition) index as the product of $(\Delta C\text{-pep}/\Delta G)_{0-120}$ and Matsuda index. Risk of progression to type 2 diabetes was compared in the three treatment groups with Cox proportional hazard model of time to event with adjustment for anthropometric or clinical parameters (age, sex, BMI, and ethnicity), baseline insulin sensitivity (Matsuda index), and baseline insulin secretion ($\Delta C\text{-pep}/\Delta G_{0-120}$). Because no participants converted to type 2 diabetes in the group receiving pioglitazone, metformin, GLP-1 receptor agonist, and lifestyle advice, we set the number of participants who converted to type 2 diabetes in this group to 1 to construct the Cox proportional hazard model. To identify predictors of progression to type 2 diabetes, a multivariate logistic regression model was created with progression to type 2 diabetes as the dependent variable and anthropometric or clinical parameters, baseline insulin sensitivity, baseline insulin secretion, and the change in β-cell function from baseline to follow-up as independent variables.

Values are expressed as mean (SEM). Differences between means were compared with two-way ANOVA, with time and treatment as factors. Categorical variables were compared with χ^2.

Results

1769 people at increased risk of diabetes were screened with 75-g oral glucose tolerance tests (figure 1). People were excluded if they: had normal glucose tolerance, 1-h glucose concentration less than 8·6 mmol/L, normal insulin sensitivity, and normal β-cell response (n=332); were identified with type 2 diabetes (n=123); had received previous antidiabetic medications (n=71); did not have prediabetes (n=247); had isolated impaired fasting glucose or HbA_{1c} concentrations more than 5·6% (38 mmol/mol), or both, but had 1-h glucose concentration less than 8·6 mmol/L, normal insulin sensitivity, and normal β-cell response (n=249).

747 (42%) of 1796 people were identified as having intermediate or high risk of type 2 diabetes (figure 1) and were recommended pharmacological treatment. Of these people, 422 completed a mean follow-up of 32·09 months (SEM 1·24). 309 (73%), 223 (53%), 155 (37%), 104 (25%), 73 (17%), 53 (13%), and 20 (5%) of 422 participants completed 1, 2, 3, 4, 5, 6, and 7 years of follow-up, respectively. For patients treated for less than 1 year (figure 1), we used 6-month measurements in our analysis.

Of 422 participants with clinically significant physiological abnormalities, 81 (19%) at high risk of type 2 diabetes received pioglitazone, metformin, GLP-1 receptor agonist, and lifestyle advice, 141 (33%) with intermediate risk received pioglitazone, metformin, and lifestyle advice, and 200 (47%) who declined pharmacotherapy (76 high risk and 124 intermediate risk) had lifestyle intervention only.

Baseline clinical characteristics and laboratory data in the three groups are shown in the appendix. No significant differences were observed in fasting plasma glucose or HbA_{1c} concentrations at baseline between groups. Participants receiving GLP-1 receptor agonist, pioglitazone, and metformin had slightly higher BMI and 2-h plasma glucose concentrations than did participants receiving pioglitazone and metformin. Participants receiving GLP-1 receptor agonist, pioglitazone, and metformin had higher mean plasma glucose concentration during oral glucose

tolerance testing, were more insulin resistant (HOMA-IR and Matsuda index), and had poorer insulin secretion than did those receiving lifestyle therapy only. Participants receiving pioglitazone and metformin had measures of glucose tolerance, insulin sensitivity, insulin secretion, and β-cell function that were intermediate between the other two participant groups (appendix).

In participants receiving lifestyle intervention only, changes in mean bodyweight were not significant at follow-up (84·4 kg *vs* 84·7 kg, p=0·58; table). 84 (42%) of 200 participants in this group lost weight (4·8 kg, SEM 0·5), whereas 108 participants (54%) gained weight (3·6 kg, SEM 0·6) during the follow-up period. Weight was unchanged in the eight remaining participants. Changes in mean bodyweight were not significant (–0·6 kg, SEM 0·5; p=0·27) in participants receiving pioglitazone and metformin, whereas those receiving pioglitazone, metformin, and GLP-1 receptor agonist lost a mean of 1·8 kg (SEM 0·8 *vs* baseline, p=0·038, and *vs* lifestyle therapy group, p=0·041).

During follow-up, 28 participants converted to type 2 diabetes based on American Diabetes Association criteria. The annual incidence of type 2 diabetes was 4·1% (21 participants converted) in participants receiving lifestyle therapy only, 1·7% (seven participants converted) in participants receiving metformin and pioglitazone (p=0·0009 *vs* lifestyle), and 0% (no participants converted) in participants receiving metformin, pioglitazone, and GLP-1 receptor agonist (figure 2). The adjusted hazard ratio (HR) for progression to type 2 diabetes was 0·29 for participants receiving metformin and pioglitazone (95% CI 0·11–0·78; p=0·0009) and 0·12 (95% CI 0·02–0·94, p=0·04) for participants receiving metformin, pioglitazone, and GLP-1 receptor agonist compared with participants receiving lifestyle therapy only (figure 2). To calculate the HR in participants receiving metformin, pioglitazone, and GLP-1 receptor agonist, we assumed that one participant converted to type 2 diabetes. Low rates of conversion to type 2 diabetes (0·6 per year) occurred in people initially identified as prediabetic by impaired fasting glucose or HbA_{1c} criteria, but who were characterised as low risk (1-h plasma glucose concentration less than 8·6 mmol/L, normal Matsuda index, normal β-cell response) and who, therefore, were not offered any therapeutic intervention.

Normal glucose tolerance (fasting plasma glucose concentration less than 5·55 mmol/L and 2-h glucose less than 7·77 mmol/L) was restored in 78 (39%) of

	Lifestyle			Metformin and pioglitazone			Metformin, pioglitazone, and GLP-1 receptor agonist		
	Pre-exposure (n=200)	Post-exposure (n=200)	p value	Pre-exposure (n=141)	Post-exposure (n=141)	p value	Pre-exposure (n=81)	Post-exposure (n=81)	p value
BMI (kg/m^2)	27·6 (0·4)	27·9 (0·4)	p=0·17	28·5 (0·4)	28·2 (0·5)	p=0·39	30·2 (0·7)	29·9 (0·8)	p=0·54
Weight (kg)	84·4 (1·5)	84·7 (1·5)	p=0·58	86·8 (1·7)	86·2 (1·5)	p=0·27	87·9 (2·2)	86·1 (2·3)	p=0·038
HbA_{1c} (%)	5·7 (0·03)	5·7 (0·03)	p=0·79	5·7 (0·03)	5·6 (0·03)	p=0·011	5·7 (0·04)	5·5 (0·05)	p<0·0001
Systolic blood pressure (mm Hg)	127 (1·3)	128 (1·6)	p=0·7	132 (1·6)	125 (1·4)	p=0·0024	125 (1·7)	123 (2·0)	p=0·15
Fasting plasma glucose (mmol/L)	5·66 (0·03)	5·49 (0·04)	p<0·0001	5·77 (0·44)	5·38 (0·06)	p<0·0001	5·77 (0·61)	5·05 (0·06)	p<0·0001
Fasting plasma insulin (nmol/L)	69·45 (4·2)	83·3 (4·2)	p=0·07	90·3 (5·6)	76·4 (3·5)	p=0·0062	111·1 (10·4)	76·4 (5·6)	p=0·0013
2-h plasma glucose (mmol/L)	6·66 (0·11)	7·05 (0·17)	p=0·023	6·94 (0·17)	6·33 (0·18)	p=0·0028	7·99 (0·22)	5·33 (0·17)	p<0·0001
Diastolic blood pressure (mm Hg)	75 (0·7)	75 (0·8)	p=0·81	79 (1·0)	76 (1·1)	p=0·035	76 (1·0)	77 (1·2)	p=0·47
LDL cholesterol (mmol/L)	2·49 (0·05)	2·22 (0·05)	p<0·0001	2·23 (0·05)	2·07 (0·05)	p=0·0047	2·38 (0·15)	2·12 (0·13)	p=0·0011
HDL cholesterol (mmol/L)	1·46 (0·03)	1·45 (0·04)	p=0·62	1·40 (0·03)	1·44 (0·04)	p=0·07	1·46 (0·04)	1·51 (0·05)	p=0·1
Triglycerides (mmol/L)	1·35 (0·07)	1·19 (0·05)	p=0·018	1·34 (0·07)	1·17 (0·01)	p=0·024	1·45 (0·08)	1·25 (0·07)	p=0·0028
Triglyceride to HDL ratio	1·05 (0·03)	0·94 (0·05)	p=0·1	1·07 (0·08)	0·93 (0·1)	p=0·045	1·10 (0·08)	0·91 (0·06)	p=0·0023
Non-HDL (mmol/L)	3·10 (0·08)	2·77 (0·52)	p<0·0001	2·87 (0·07)	2·64 (0·08)	p=0·0009	3·26 (0·16)	2·82 (0·13)	p<0·0001
High-sensitivity CRP (nmol/L)	21·9 (2·9)	20·95 (2·9)	p=0·67	20·0 (1·9)	22·9 (3·8)	p=0·47	38·1 (5·7)	19·05 (2·9)	p<0·0001
HOMA-IR	2·6 (0·1)	2·9 (0·1)	p=0·17	3·4 (0·2)	2·7 (0·1)	p=0·0021	4·0 (0·4)	2·6 (0·2)	p=0·00029
Matsuda index	4·2 (0·2)	3·7 (0·2)	p=0·0047	3·0 (0·2)	3·5 (0·2)	p=0·0011	3·0 (0·2)	4·4 (0·4)	p=0·00027
Mean plasma glucose during OGTT (mmol/L)	7·7 (0·78)	7·4 (0·78)	p=0·033	7·99 (0·11)	6·99 (0·111)	p<0·0001	8·38 (0·11)	6·44 (0·11)	p<0·0001
Insulin secretion*	0·14 (0·01)	0·15 (0·01)	p=0·73	0·13 (0·01)	0·18 (0·02)	p=0·014	0·10 (0·01)	0·18 (0·02)	p<0·0001
β-cell function†	0·56 (0·07)	0·57 (0·07)	p=0·75	0·35 (0·03)	0·62 (0·07)	p<0·0001	0·26 (0·02)	0·68 (0·08)	p<0·0001
β-cell response (%Δ)‡	63 (18)	60 (20)	p=0·1	57 (1)	64 (1)	p<0·0001	51 (1)	71 (2)	p<0·0001

Data are mean (SEM). Mean treatment duration was 31·0 months (SEM 1·8), 35·4 months (2·5), and 29·0 months (2·8) for treatment with lifestyle intervention, metformin and pioglitazone, and metformin, pioglitazone, and glucagon-like peptide 1 (GLP-1) receptor agonist, respectively. CRP=C-reactive protein. HOMA-IR=homeostasis model assessment-insulin resistance. OGTT=oral glucose tolerance test. *Insulin secretion calculated as the ratio between the incremental area under the plasma C-peptide (C-pep) curve and the incremental area under the plasma glucose concentration (G) curve during oral glucose tolerance testing—ie, $(\Delta C\text{-pep}/\Delta G)_{0\text{-}120}$. †β-cell function was calculated as $(\Delta C\text{-pep}/\Delta G)_{0\text{-}120}$ x Matsuda index. ‡β-cell response was calculated as log(adjusted C-pep/G)/200-log(adjusted Matsuda index) x 100. Data were adjusted to achieve non-negative values and equal contributions of C-peptide, glucose, and Matsuda index.

Table: **Effect of intervention on anthropometric, haemodynamic, lipid, and metabolic parameters**

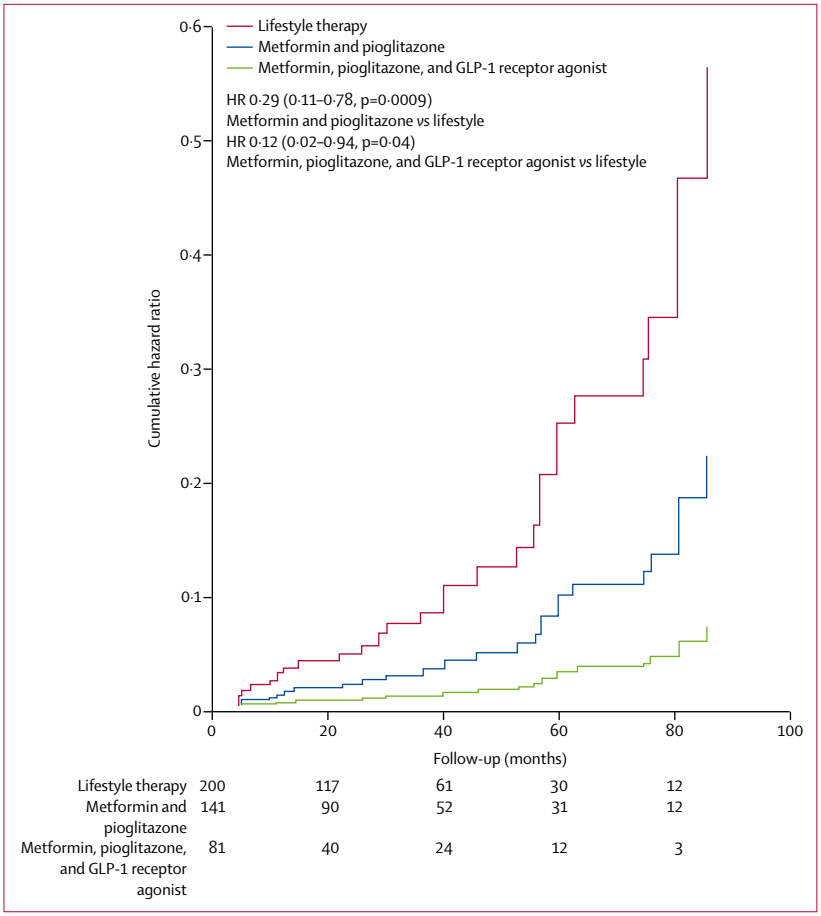

Figure 2: **Adjusted Cox hazard plot of type 2 diabetes risk in the three treatment groups**
Patients in the drug-treated groups also received lifestyle therapy. GLP1= glucagon-like peptide 1. HR=hazard ratio.

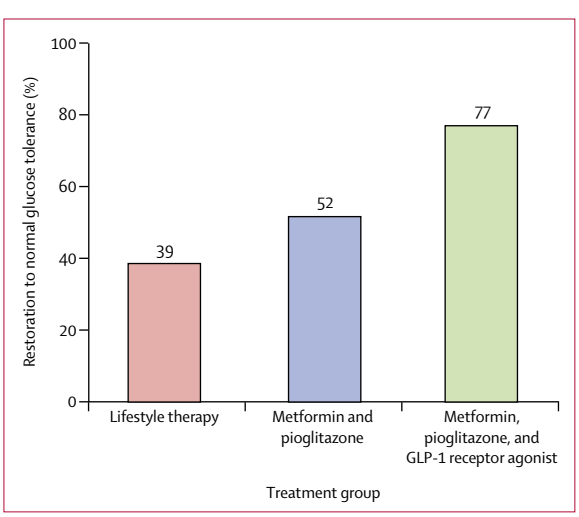

Figure 3: **Patients restored to normal glucose tolerance by treatment group**
GLP1= glucagon-like peptide 1.

200 participants receiving lifestyle therapy only, in 73 (52%) of 141 participants receiving metformin and pioglitazone, and in 62 (77%) of 81 participants receiving metformin, pioglitazone, and GLP-1 receptor agonist (figure 3). The number needed to treat to prevent progression to diabetes in participants receiving metformin and pioglitazone and those receiving metformin, pioglitazone, and GLP-1 receptor agonist was 41 and 24, respectively.

Participants receiving lifestyle intervention only had a small but significant decrease in fasting plasma glucose concentration. Fasting plasma glucose concentrations decreased significantly in participants receiving metformin and pioglitazone, whereas participants receiving metformin, pioglitazone, and GLP-1 receptor agonist had the greatest decrease in fasting plasma glucose concentrations (table). Metformin and pioglitazone and metformin, pioglitazone, and GLP-1 receptor agonist significantly reduced 2-h plasma glucose concentration, whereas 2-h plasma glucose concentration increased significantly in participants receiving lifestyle therapy only (table).

Matsuda index of insulin sensitivity decreased by 12% in participants receiving lifestyle therapy only (p=0·0047), whereas it improved significantly in participants receiving pioglitazone and metformin, and in those receiving metformin, pioglitazone, and GLP-1 receptor agonist by 17% (p=0·0001) and 47% (p=0·0001), respectively. β-cell function, measured with the disposition index, did not change (p=0·75) in participants receiving lifestyle therapy only, whereas it increased significantly in participants receiving metformin and pioglitazone (77%, p<0·0001) and those receiving metformin, pioglitazone, and GLP-1 receptor agonist (162%, p<0·0001; table).

At baseline, low insulin sensitivity, insulin secretion, and β-cell function were significant predictors of conversion to type 2 diabetes . High $(\Delta C\text{-pep}/\Delta G)_{0-120}$, disposition index, and Matsuda index at baseline were associated with low risk of progression to type 2 diabetes (data not shown). Following therapy (participants in all three treatment groups analysed collectively), the change in disposition index (β-cell function) was associated closely with risk of progression to type 2 diabetes (figure 4). The change in disposition index was the strongest predictor of progression to type 2 diabetes. Each one unit increment in disposition index during follow-up was associated with a 99% reduction in risk of conversion to type 2 diabetes.

No participant in any group reported symptoms of hypoglycaemia. Oedema was reported in two (1%) of 222 participants receiving pioglitazone and was mild in all cases. Nausea was reported in four (5%) of 81 participants treated with GLP-1 receptor agonist, was mild, resolved within 2–4 weeks, and did not result in discontinuation in any participants. Vomiting occurred in four (5%) of 81 participants treated with GLP-1 receptor agonist, was transient, and did not result in discontinuation of therapy. Bodyweight was either unchanged or decreased slightly in participants receiving metformin and pioglitazone.

Discussion

This retrospective observational study of real-world data is, to our knowledge, the first study to assess personalised interventions to reduce future diabetes risk. Future risk of type 2 diabetes was stratified on the basis of measurements of the pathophysiological defects characteristic of type 2 diabetes. Moreover, the intervention targeted these pathophysiological defects and was based on their severity. Participants with intermediate risk received therapy with pioglitazone and metformin, which target insulin resistance and preserve β-cell function. Because of the importance of β-cell dysfunction in progression from impaired glucose tolerance to type 2 diabetes, participants with severe defects (ie, high risk) received a GLP-1 receptor agonist in addition to metformin and pioglitazone. Thus, the risk category and intervention used for each participant was based on the severity of underlying pathophysiological defects.

This study shows for the first time in a primary care setting that oral glucose tolerance testing can quantify insulin sensitivity and β-cell response in high-risk individuals and direct targeted pharmacological therapy.[3–6,11,19] The results of our analysis show that pharmacological treatment with antidiabetic agents that target insulin resistance (pioglitazone[11,20]) and β-cell dysfunction (pioglitazone[21,22] and GLP-1 receptor agonist[11,23,24]) markedly reduces development of type 2 diabetes in a real-world setting. Compared with those on lifestyle therapy alone, participants receiving metformin and pioglitazone had a 71% decrease in future type 2 diabetes risk, whereas those receiving metformin, pioglitazone, and GLP-1 receptor agonist had an 88% reduction in risk. Despite more severe impairment in glucose tolerance and pathophysiological abnormalities in participants receiving metformin, pioglitazone, and GLP-1 receptor agonist than the other two treatments (appendix), no participant converted to type 2 diabetes. The reduction in type 2 diabetes risk caused by a combination of low-dose pioglitazone (15 mg) and low-dose metformin (850 mg) was similar to that observed in the CANOE study[25] (2 mg rosiglitazone and 1000 mg metformin). These results show that the addition of low-dose thiazolidinedione to low dose-metformin has greater efficacy in reducing type 2 diabetes risk than does full-dose metformin therapy as shown in the Diabetes Prevention Programme.[14] Because treatment with low-dose metformin and pioglitazone has few side-effects and is affordable, it is an effective and low-cost intervention for participants at high risk of prediabetes. A larger study with longer duration is warranted to examine whether low-dose pioglitazone and metformin will reduce the risk of developing microvascular complications, which is required by the US Food and Drug Administration for approval of pharmacotherapy for diabetes prevention. Improved glycaemic control was observed with low doses of pioglitazone (15 mg/day) and metformin (850 mg/day), explaining the low incidence of side-effects and high compliance.

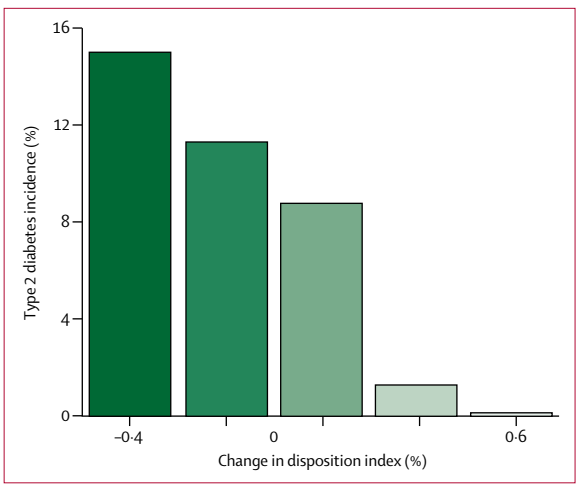

Figure 4: **Association between incidence of type 2 diabetes and change in disposition index, independent of therapy used**

Previous prospective epidemiological studies showed that about 40% of participants who convert to type 2 diabetes had normal glucose tolerance at baseline.[2] We previously showed that participants with a 1-h plasma glucose concentration of more than 8·6 mmol/L manifest similar high risk of developing type 2 diabetes to that in participants with impaired glucose tolerance.[5–7] About a quarter of participants in the study had normal glucose tolerance with 1-h plasma glucose concentration of more than 8·6 mmol/L. The annual incidence of type 2 diabetes in participants with normal glucose tolerance and 1-h plasma glucose concentration of more than 8·6 mmol/L was higher than in participants with impaired fasting glucose or impaired glucose tolerance, or both (4·8% *vs* 3·8%). The incidence of diabetes was equally reduced in these two groups by treatment with metformin and pioglitazone (to 1·7% and 1·9%, respectively) and metformin, pioglitazone, and GLP-1 receptor agonist (to 0% and 0·7%). Therefore, this study is the first to identify a subgroup of individuals with normal glucose tolerance (ie, 1-h plasma glucose concentration more than 8·6 mmol/L) who should be considered as having prediabetes and documents effective interventions that reduce their future risk of type 2 diabetes.

The incidence of type 2 diabetes is strongly correlated with decline in β-cell function (figure 4), independent of the therapy used. This finding underscores the clinical use of a simplified β-cell score that identifies individuals at future risk of type 2 diabetes who have normal glucose tolerance, as well as prediabetic individuals (impaired fasting glucose or impaired glucose tolerance, or both), who can benefit from pharmacological intervention to prevent progression to type 2 diabetes.

This study has some limitations. First, this was a retrospective observational study of real-world data from clinical practice, not a randomised trial. Nonetheless,

there was a well matched time-control group comprised of high-risk and intermediate-risk participants who refused pharmacological therapy. In this group conversion rate to type 2 diabetes was 4·1% per year. Additionally, cardiovascular studies,[26,27] have shown that real-world studies can provide substantive data regarding randomised controlled trials done in the community setting. Second, our data were derived from a single clinical practice with a primarily Caucasian, insured population. A larger, multicentre study with a diverse, multiethnic population is needed to show applicability to other populations. Third, clinical decisions on patient management were made on the basis of future risk of type 2 diabetes and patient–physician collaboration. Acknowledging potential bias introduced by this method, the patient–physician interaction is an essential component of real-world practice. Fourth, debate remains about whether the results reflect the prevention or masking of diabetes through pharmacological treatment. This question cannot be answered by the present study since all participants will continue to be treated for the primary prevention of type 2 diabetes and cardiovascular events. Furthermore, as previously shown in ACT NOW[28] and the study by Bunck and colleagues,[24] discontinuation of therapy (pioglitazone and GLP-1 receptor agonists, respectively) resulted in return of glucose intolerance, just as discontinuation of statin and antihypertensive therapy has been shown to cause return of hypercholesterolaemia and hypertension. About 60% of participants receiving a GLP-1 receptor agonist were treated with liraglutide and the remaining participants received other GLP-1 receptor agonists. Although we believe that all GLP-1 receptor agonists have qualitatively similar biological effects, some modest differences exist between various agents (eg, short acting *vs* long acting). Nonetheless, it should be noted that none of the participants who received triple therapy developed type 2 diabetes. Fifth, because combination therapy was used in each treatment arm, determining the contribution of each agent alone to the reduction in diabetes incidence is not possible. Sixth, all insulin measurements were done in a single lab using the same assay because insulin assay lacks standardisation. Seventh, concerns regarding the complexity of this approach are understandable; however, the study was done in a community internal medicine and endocrinology practice, the oral glucose tolerance test can be done in most clinical laboratories, and formulae for measuring insulin sensitivity and β-cell function are published and validated. Nonetheless, a further simplified method of characterising risk and assisting practitioners would be advantageous. Eighth, regarding cost, combined metformin and pioglitazone treatment is effective and costs about US$10 per month in the USA, and, depending on insurance coverage, the cost of GLP-1 receptor agonists can be as much as US$500–600 per month or as little as no out-of-pocket cost to the patient. The cost of branded GLP-1 receptor agonists in Germany, Netherlands, and the UK is approximately US$140 per month.[29,30] As the time for generic GLP-1 receptor agonists approaches, the cost will decrease considerably. Last, the lifestyle intervention used in the study was not as intensive as in the Diabetes Prevention Program; nonetheless, the intervention is consistent with the standard of care used by primary care physicians in the community.

This retrospective observational study of real-world data obtained in a community setting shows that targeted therapy directed to correct underlying pathophysiological disturbances present in individuals at high risk of diabetes can markedly reduce the development of type 2 diabetes.

Contributors

JPA and RJR designed the study in consultation with RAD. MA-G, JPA, and RJR generated the data. RAD and MA-G generated graphical representations of the data. All authors wrote the manuscript and analysed the data.

Declaration of interests

JPA and RJR are cofounders of Robust For Life. RAD is on the advisory boards of AstraZeneca, Novo Nordisk, Janssen, Intarcia, and Boehringer Ingelheim, receives research support from AstraZeneca and Janssen, and is on the speaker's bureaus of Novo Nordisk and AstraZeneca. RJR is on the speaker's bureaus of Lilly and Janssen. MA-G declares no competing interests.

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