Review Article ISSN 2639-9326

Diabetes & its Complications

Optimising the Use of Metformin for Diabetes Prevention

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Received: 05 May 2018; Accepted: 04 June 2018

Citation: Hostalek U, Gwilt M, Campbell I. Optimising the Use of Metformin for Diabetes Prevention. Diabetes Complications. 2018; 2(2): 1-6.

ABSTRACT

Lifestyle interventions will remain central to the management and prevention of non-communicable diseases, including type 2 diabetes. Successful deployment of lifestyle interventions requires considerable support, as most patients at risk of diabetes due to the prediabetic states of impaired glucose tolerance, impaired fasting glucose or gestational diabetes find it difficult to adhere to them sufficiently. Pharmacologic options will therefore be appropriate for many patients, alongside efforts to improve their lifestyles. Metformin remains the principal option for pharmacologic diabetes prevention, due to its proven efficacy in randomised diabetes prevention trials, its well understood tolerability and safety profiles, potential for cardiovascular protection for those who do go on to develop type 2 diabetes, and its low cost. Other treatments that have been shown to provide clinically significant protection from diabetes, such as thiazolidinediones, acarbose and basal insulin, have tolerability profiles that are challenging for populations with early dysglycemia. Management guidelines for diabetes prevention have acknowledged a role for metformin, particularly for heavier, younger subjects for whom lifestyle intervention has been insufficiently successful, but metformin has not yet been indicated for this purpose in most countries. This is changing now, as indicated for example by a new indication for metformin for diabetes prevention in the UK, for the convenient, once-daily, better tolerated extended release version. Metformin has been under use for diabetes prevention, and the availability of indications for diabetes prevention in more countries will facilitate its use in pragmatic regimes to protect people from type 2 diabetes.

Keywords

Metformin, Diabetes prevention, Lifestyle intervention.

Preventing type 2 diabetes is still an urgent health priority

Scale of the problem

We have heard much in recent years about the global type 2 diabetes pandemic: latest estimates from the International Diabetes Federation (IDF) tell us that 425 million people - one person in every eleven - has type 2 diabetes today, ten million more than just two years ago, and set to increase by another 200 million or so by 2045 [1]. We should remember that the diagnosis of type 2 diabetes is categorical, triggered by an increase in a measure of glycaemia (fasting, post-load or random plasma/blood glucose or HbA1c) to above predetermined cut-off points [2]. Levels of glycaemia present as a continuum of values and large number of individuals have non-diabetic hyperglycaemia (often referred to as "prediabetes"), where elevation of measures of glycaemia above the normal value are insufficient to support a diagnosis of type 2 diabetes, but confer a markedly increased risk of developing clinical type 2 diabetes in the near future [2].

The problem of non-diabetic hyperglycaemia (see Box 12- for an overview of principal diagnostic criteria) is substantial. The IDF have identified 352 million people worldwide as having impaired glucose tolerance (IGT). The prevalence of impaired fasting glucose (IFG) is more difficult to estimate precisely as it can vary considerably with the method of diagnosis [3] and different blood glucose cut-offs have been proposed. Nevertheless, for example, high prevalence rates for non-diabetic hyperglycaemia (American Diabetes Association [ADA] criteria unless stated) have been reported recently in large populations from North America of 16% (USA, based on FPG) [4], 36% (USA, based on HbA1c or FPG), [5] or 38% (Canada, based on HbA1c or FPG) [6], Mexico (44%,

based on HbA1c) [7], Russia (19%, based on HbA1c) [8], the Middle East (e.g. 15% in [IFG]) [9], South Africa (3% IFG, 18% IGT), [10] south Asia (10% in India [11], 22% in Bangladesh [12], both World Health Organization criteria), and East Asia (e.g. 36% in China, based on 2010 ADA criteria) [13].

Impaired glucose tolerance	Post-load glucose 7.8–11.1 mmol/L (140–200 mg/dL) 2 hours after a 75 g oral glucose tolerance test
Impaired fasting glucose	ADA: 5.6–6.9 mmol/L (100–125 mg/dL)a WHO: 6.1–6.9 mmol/L (110–125 mg/dL)
Elevated (non-diabetic) HbA1c	ADA: 5.7–6.4% (39–47 mmol/mol) NICE: 6.0–6.4% (42–47 mmol/mol)

Box 1: Principal criteria for diagnosis of different forms of non-diabetic hyperglycaemia.

Gestational diabetes mellitus (GDM) also increases the risk of subsequent development of type 2 diabetes [14,15]. The IDF estimate that one in six pregnancies worldwide is affected by hyperglycaemia, which if uncontrolled increases the risk of a range of adverse maternal and foetal outcomes [14].

Non-diabetic hyperglycaemia promotes adverse clinical outcomes

Rates of progression from non-diabetic hyperglycaemia to clinical type 2 diabetes are high. For example, about 15-16% of European subjects with non-diabetic hyperglycaemia progressed to type 2 diabetes annually [16,17], and 74% of individuals who had non-diabetic hyperglycaemia at age 45 in a large cohort in the Netherlands progressed to diabetes at some time in their lives [18]. A meta-analysis calculated incidence rates of type 2 diabetes of 36/1000 patient-years for non-diabetic hyperglycaemia based on HbA1c or IFG (ADA criteria), 47% for IGT (WHO criteria), and a much higher rate of 70% for concurrent IGT and IFG [19]. Longitudinal studies and meta-analyses have associated non-diabetic hyperglycaemia with an increased risk of adverse cardiovascular outcomes and mortality [20-24]. Figure 1 summarises the results of one recent (2016) meta-analysis incorporating data from a total of 1,611,339 subjects [24]. The risk of adverse cardiovascular outcomes appears to be higher when prediabetes is diagnosed by elevated Hb1Ac rather than fasing or post-load blood glucose, with a substantial proportion of the excess risk accounted for by cardiometabolic risk factor that cluster with hyperglycaemia [24a].

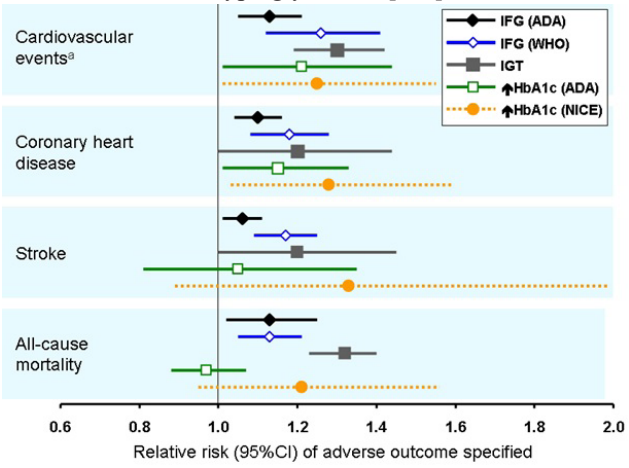

Figure 1: Association of different definitions of non-diabetic hyperglycaemia with adverse clinical outcomes from a large meta-analysis.

[a]Composite of cardiovascular events as defined in original source publications. Impaired fasting glucose (IFG) was diagnosed according to criteria proposed by the American Diabetes Association (ADA), World Health organization (WHO) or the national Institute from Health and Care Excellence (NICE); note that the criteria for impaired glucose tolerance (IGT) is common between these institutions. See Box 1 for explanation of the different diagnostic criteria. Drawn from data presented in ref 24.

What we know today about diabetes prevention

Lifestyle intervention

Intensive lifestyle interventions (at least 150 min of moderate exercise per week and improvements in diet relating to reduced animal products and more fibre) reduced the 2-3-year risk of type 2 diabetes by 58% (relative to a usual care arm) in subjects with IGT and additional risk factors for type 2 diabetes in both the Diabetes Prevention Program (DPP) in the USA [26] and the Diabetes Prevention Study (DPS) in Finland [27]. Additionally, improved diet or more physical activity were similarly effective in reducing the risk of diabetes in the DaQing study in China [28]. Other successful lifestyle-based diabetes prevention trials in subjects with IGT were conducted in South Asian populations [29,30]. Lifestyle intervention in a Japanese population with IFG at baseline demonstrated significant diabetes prevention only in subjects who also had IGT at baseline, however [31]. Finally, observational data from the USA (Cardiovascular Health Study) found a significant association between better lifestyle habits and reduced risk of diabetes [32].

Longer-term, observational post-trial follow-up suggests maintained benefit from randomisation to the lifestyle intervention in the DPP, DPS and DaQing studies, in terms of improved health behaviours and persistent protection from diabetes, compared with the respective control groups [33-35]. These reports included demonstration of increased risk of long-term complications of diabetes, especially among those who progressed to diabetes relative to those who did not. Importantly, 23-year follow-up from the DaQing population demonstrated maintained prevention or delay of type 2 diabetes together with a reduced long-term risk of cardiovascular or all-cause mortality [35].

Accordingly, the efficacy of intensive lifestyle interventions is proven beyond doubt, and should be recommended for all people at risk of (or indeed with) type 2 diabetes [36]. However, multiple barriers impede patients' adherence to lifestyle interventions, including significant cultural barriers in some countries, especially for women [37]. Half or more people with non-communicable diseases may not adhere to lifestyle recommendations recommended by their physician [38,39]. As preventing diabetes per se appears key to improving long-term outcomes in people with non-diabetic hyperglycaemia, as described above, pharmacological therapy may be appropriate for such subjects, in parallel with continued encouragement to undertake lifestyle improvements.

Diabetes prevention with metformin

Evidence base

Metformin was shown to reduce the conversion of IGT to type 2 diabetes in a number of randomised trials, relative to placebo or usual care/standard lifestyle advice control groups, as described briefly below The risk reduction for metformin 850 mg BID in the DPP was 31% vs. placebo plus standard lifestyle change [26]. The efficacy of metformin for diabetes prevention was greater in people with more severe hyperglycaemia at baseline (48% relative risk reduction [RRR] for people with FPG 6.1-6.9 mmol/L [110-125 mg/dL]), in younger subjects (RRR 48% for age 25-44 years), and in people with BMI ≥35 kg/m^2, where the RRR for type 2 diabetes (53%) was similar to that of lifestyle intervention (51%) [33]. Metformin and intensive lifestyle intervention reduced the risk of diabetes similarly in the DPP when HbA1c was used as a marker of increased diabetes risk [40].

The Indian Diabetes Prevention Program demonstrated similar RRRs vs. a usual care group for metformin 500 mg BID (26%) or for metformin + a lifestyle intervention modelled on the DPP (-28%) [30]. Other, smaller diabetes prevention trials with metformin included small randomised studies in Pakistan (RRR 77% for metformin) [29] and China [41], and a cluster-randomised trial in China (RRR 88% for metformin and 87% for acarbose) [42]. One study (CANOE) demonstrated a RRR for diabetes of 66% with a combination of metformin 500 and rosiglitazone 2 mg BID [43]. A further study, the Early Diabetes Intervention Trial, did not find a reduction in type 2 diabetes risk with metformin-based regimens [44].

Metformin also reduced the incidence of diabetes over 10 years of post-trial follow-up by 40% follow-up in women with prior GDM in the DPP Outcomes Study (DPPOS), compared with 35% for prior randomisation to intensive lifestyle intervention [14]. Overall, the evidence for a protective effect of metformin on new-onset type 2 diabetes in at-risk subjects is compelling.

The DPP Outcomes Study (DPPOS) continues to follow participants from the DPP for clinical outcomes, and will define the effects of metformin treatment on long-term cardiovascular outcomes in subjects with non-diabetic hyperglycaemia. One analysis from the DPPOS cohort has shown that prior randomisation to metformin in the DPP was associated with reduced coronary artery calcium score, a marker of the burden of atherosclerosis, in men (but not women) [45]. A proportion of metformin-treated subjects with IGT will go on to develop T2D, and the potential for metformin to improve long-term macrovascular outcomes in people with newly-diagnosed type 2 diabetes was demonstrated some twenty years ago in the randomised UK Prospective Diabetes study (UKPDS) [46], as well as in numerous observational studies (reviewed elsewhere [47,48].

Moreover, early intensive glycaemic control with metformin in the UKPDS was associated with long-term cardiovascular benefits ten years after the conclusion of the randomised phase of the trial. The ongoing randomised, controlled glucose lowering in non-diabetic hyperglycaemia trial is currently evaluating the effects of metformin XR on clinical cardiovascular outcomes in a population of people with IGT and elevated cardiovascular risk.

Optimising adherence with metformin

Sixty years of clinical experience with metformin have left us with detailed knowledge of its safety profile, which is appropriate for long-term administration to people at risk of diabetes [47,48]. The well-known gastrointestinal tolerability issues with metformin, and the need for multiple daily intakes of standard, immediate-release (IR) metformin tablets can be a barrier to successful treatment for some people, however. Prolonged-release (XR) formulations of metformin are available suitable for once-daily administration are available, which helps to reduce the treatment burden. Randomised, head-to-head trials have found that the antihyperglycaemic efficacy of BID IR metformin and QD XR metformin (at the same overall daily dosages) were essentially identical in populations of mainly Caucasian [49] or of Chinese [50] origin who were receiving their first antihyperglycaemic therapy for type 2 diabetes.

These studies found a similar incidence of gastrointestinal side-effects with IR and XR metformin. However, observational data have shown that a majority people with type 2 diabetes unable to tolerate IR metformin due to gastrointestinal side-effects were able to take this therapy following a switch to XR metformin [51]. Further retrospective analyses support improved gastrointestinal tolerability after switching from IR to XR metformin (half of these patients switched due to gastrointestinal side-effects on IR metformin) [52] and improved adherence with XR vs. IR metformin [53].

Reduced levels of vitamin B12 are another well-known side effects of metformin and this was observed in the prediabetic population of the DPPOS [53a]. Routine periodic test of B12 in patients receiving metformin may be advisable in line with existing guidelines.

Regulatory issues

Metformin has been recommended for selected types of patients in major guidelines for diabetes prevention for some years. For example, the ADA guideline includes consideration of metformin for people at risk of diabetes with BMI ≥35 kg/m^2, age <60 years, women with prior GDM and those with increasing HbA1c despite lifestyle intervention, largely in line with the findings of the DPP [36]. Similarly, the guideline from the Asociación Latinoamericana de Diabetes recommends metformin for people at risk of type 2 diabetes who respond inadequately to lifestyle intervention [54]. NICE advocate the use of clinical judgement in initiating metformin for people at risk of diabetes whose HbA1c or FPG has deteriorated despite lifestyle intervention, or for people unable to undertake lifestyle intervention, especially where BMI is >35 kg/m^2. Other country- or regional-specific recommendations on the use of metformin for diabetes prevention are summarised elsewhere [55].

The use of metformin for preventing diabetes has been hindered

by a lack of licensed indication in most countries, however. This is beginning to change, as shown for example by a recent update to the UK indication for prolonged release metformin (Glucophage® SR; see Box 2), which permits the use of metformin in circumstances similar to the guidelines summarised above [56]. This removes an important barrier to the use of this agent, including its once-daily formulation, for the prevention or delay of diabetes. It is recommended to start metformin XR (SR) therapy with a low dose (500mg or 750mg once daily) and to up-titrate according to the patient's need and tolerability. Maximum daily dose is 2000mg.

> Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with IGT* and/or IFG*, and/or increased HbA1C who are:
> – at high risk for developing overt type 2 diabetes mellitus (see section 5.1) and
> – still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle change for 3 to 6 months
>
> Treatment with Glucophage SR must be based on a risk score incorporating appropriate measures of glycaemic control and including evidence of high cardiovascular risk (see section 5.1).
>
> Lifestyle modifications should be continued when metformin is initiated, unless the patient is unable to do so because of medical reasons.
>
> Extract from the Summary of Product Characteristics for Glucophage® SR, a preparation of prolonged-release metformin available in the UK [64].

Box 2: Text recently added to the UK indication for prolonged-release metformin supporting its use of for diabetes prevention.

Other approaches to diabetes prevention

Thiazolidinediones (pioglitazone and rosiglitazone) have been shown to reduce the incidence of diabetes in people with IGT (see also the CANOE study, described above, which evaluated a combination of rosiglitazone and metformin) [57,58]. Safety concerns have restricted the use of these agents in recent years, however, and they are not generally considered suitable for use in patients with pre-diabetic dysglycaemia. Similarly, the finding of reduced incidence of type 2 diabetes in people with IGT randomised to basal insulin glargine or standard care is interesting, but unlikely to influence clinical practice in this area [59]. Acarbose reduced the risk of type 2 diabetes modestly in the randomised STOP-NIDDM [60] and ACE [61] trials, although a suggestion of improved cardiovascular outcomes associated with acarbose in the former trial was not confirmed by the latter.

It is well known that overweight/obesity is an important factor in the progression from non-diabetic hyperglycaemia to overt type 2 diabetes; accordingly, it is perhaps not surprising that surgical [62] or pharmacologic [63,64], interventions to achieve weight loss have resulted in clinically significant protection from future diabetes in trial populations or subpopulations with IGT. Finally, prandial insulin secretagogue, nateglinide [65], and the angiotensin II receptor blocker, valsartan [66] were without effect on diabetes risk in the large, randomised NAVIGATOR study in people with IGT and risk factors for cardiovascular disease.

Looking ahead

Messages have been mixed in recent years regarding a role for this agent in the prevention or delay of type 2 diabetes. On the one hand, influential guidelines have recommended its use in selected patients, but on the other, physicians must prescribe metformin off-label for these patients in most countries. This situation and the observation that only one person in eight with non-diabetic hyperglycaemia knows they have the condition [67], has likely limited the use of metformin in this setting. A retrospective analysis from 2015 in the USA showed that less than 4% of adults of working age with prediabetes were prescribed metformin [68]. Accordingly, the new label for metformin for diabetes prevention in the UK is a welcome development, especially as it includes the XR formulation that is helpful for people who find the IR formulation difficult to take due to gastrointestinal side-effects. Wider availability of licensed indications for metformin will in future broaden the prospects for pragmatic regimens for diabetes prevention for people whose metabolic control continues to deteriorate despite lifestyle intervention.

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