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Metformin in diabetes management: expanding benefits. Review

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A new diagnosis of type 2 diabetes mellitus (T2DM) is life-transforming, requiring a life-long burden of healthcare, the need to understand and accept the associated risks of adverse long-term outcomes, and financial and other consequences [1, 2]. The management of people at risk of developing T2DM, therefore, needs to be conducted with care, to avoid labeling them with the same kind of issues. Evidence has built in recent years that so-called «prediabetes» is associated with an increased long-term risk of death or cardiovascular disease, compared with people with normal glucose regulation, especially in people who already have atherosclerotic cardiovascular disease (Figure) [3]. This has led to an increasing interest in earlier intervention in the time course of dysglycemia, focusing on the period before T2DM.

Figure. Risks of adverse clinical outcomes associated with non-diabetic hyperglycaemia according to the presence or absence of atherosclerotic cardiovascular disease (ASCVD) from a meta-analysis of 129 studies involving a total of more than 10 million participants. Composites of acardiovascular disease (CVD) and bcoronary heart disease (CHD) were as reported in individual studies within this meta-analysis. All forms and definitions of non-diabetic hyperglycaemia were included, also as reported in individual studies. Drawn from data presented in reference [3].

Metformin has a therapeutic indication for the prevention or delay of a new diagnosis of T2DM in at-risk subjects in more than 60 countries [4]. Influential guidelines for the management of dysglycemia or cardiovascular risk now acknowledge a role for metformin for diabetes prevention in defined subgroups of people at risk of developing diabetes due to the presence of prediabetes/non-diabetic hyperglycemia [5].

We have conducted a narrative review based on a structured search strategy, focusing on the effects of metformin on the progression of non-diabetic hyperglycemia to clinical T2DM. The principal trials that demonstrated a significantly lower incidence of diabetes in at-risk populations randomized to metformin (mostly

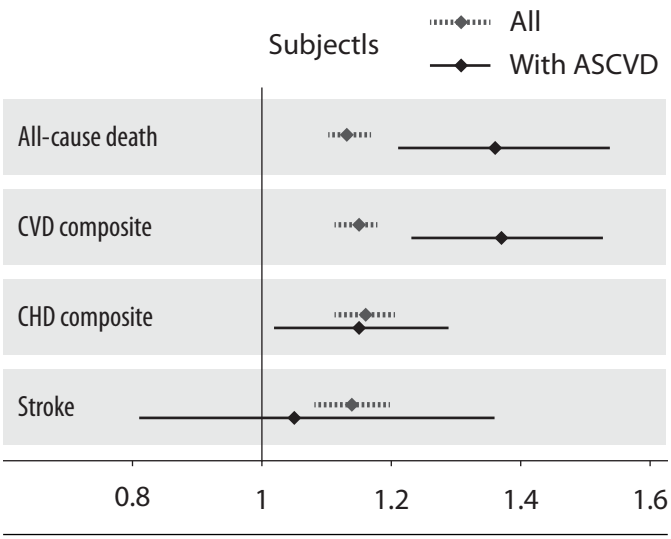

Figure. *Relative risk (95 % CI) for presence vs. absence of non-diabetic hyperglycaemia*

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with impaired glucose tolerance [IGT]) were published mainly from 1999 to 2012. Metformin reduced the 3-year risk of diabetes by -31 % in the randomized phase of the Diabetes Prevention Program (DPP), vs.-58 % for intensive lifestyle intervention (ILI). Metformin was most effective in younger, heavier subjects. Diminishing but still significant reductions in diabetes risk for subjects originally randomized to these groups were present in the trial's epidemiological follow-up, the DPP Outcomes Study (DPPOS) at 10 years (-18 and -34 %, respectively), 15 years (-18 and -27 %), and 22 years (-18 and -25 %). Long-term weight loss was also seen in both groups, with better maintenance under metformin. Subgroup analyses from the DPP/DPPOS have shed important light on the actions of metformin, including a greater effect in women with prior gestational diabetes, and a reduction in coronary artery calcium in men that might suggest a cardioprotective effect. Improvements in long-term clinical outcomes with metformin in people with non-diabetic hyperglycemia («prediabetes») have yet to be demonstrated, but cardiovascular and microvascular benefits were seen for those in the DPPOS who did not vs. did develop diabetes. Multiple health economic analyses suggest that either metformin or ILI is cost-effective in a community setting. Long-term diabetes prevention with metformin is feasible and is supported in influential guidelines for selected groups of subjects.

Prior gestational diabetes mellitus (GDM) and polycystic ovary syndrome (PCOS) are also important risk factors for developing clinical (permanent) T2DM. We have included a brief review of the literature that explored the potential of metformin to prevent diabetes onset in subjects with these conditions. These aspects are dealt with separately to the main subject of prevention or delay of T2DM.

The term, «prediabetes» remains widely used, including by the American Diabetes Association (ADA) in its Standards of Care for 2021 [6]. This term has attracted controversy, however, partly due to a perception that large numbers of people with «prediabetes» will never develop clinical diabetes, but are nevertheless associated with it, and thus become «medicalized» [7]. The World Health Organization has abandoned the term in favor of «*intermedia*te hyperglycemia».

Long-term epidemiologic follow-up of the population of the DPP has been conducted since the end of randomized treatment, in the 88 % of the DPP population who entered DPPOS [8]. All participants who were receiving metformin in the randomized phase who were eligible to continue receiving this treatment according to current guidelines, and who did not require changes to treatment according to their usual care physicians, were offered continued treatment with metformin 850 mg. All participants additionally received group-based lifestyle intervention, with subjects previously randomized to ILI receiving additional lifestyle support. The DPPOS Investigators did not provide recommendations on the use of metformin in the prior ILI group. Treatment with a placebo was discontinued.

A significant level of diabetes prevention was still evident in the metformin and lifestyle groups after 10 years of overall follow-up (3 years of randomized treatment + 7 years of epidemiological follow-up [9]. The overall incidence of T2DM/100 person-years during the full ten years of analysis was lowest in the prior ILI group (5.3 [4.8, 5.8]) than in the prior metformin group (6.4 [5.9, 7.1]) or the prior placebo group (7.8 [7.2, 8.6]). However, the incidence rate during the post-randomization (DPPOS) phase was higher for prior ILI (5.9 [5.1, 6.8]) than for prior metformin (4.9 [4.2, 5.7]). This anomalous finding was attributed to a depletion of genetically susceptible individuals in the prior metformin group (some of these had already developed diabetes before the DPPOS phase) and to a 1 kg average weight gain in the ILI group (weight loss was maintained in the prior metformin group) [10].

Diabetes prevention was still evident at average follow-up duration of 15 years and 22 years. Compared with the prior placebo group, reductions in diabetes incidence for prior metformin were -18 % at both time points, and for prior ILI were -27 and -25 %. Long-term diabetes prevention is therefore feasible with either intervention, and their efficacy appears to have converged to some extent over time.

There were no significant microvascular or macrovascular benefits at 22 years associated with either intervention (as seen elsewhere with ILI after 30 years of follow-up of the DaQing diabetes prevention trial [11]. However, prevention of diabetes per se was associated with a lower incidence of major adverse cardiovascular endpoints (-39 %), eye disease (-57 %), and kidney disease (-37 %). There was also a trend towards fewer strokes in the prior metformin group, and a trend for fewer cardiovascular events in those who started metformin before age 45 years, although there were too few events for a definitive analysis. The incidence of nephropathy (albumin: creatinine ratio i 30 mg/kg) was higher at 20 years follow-up in subjects aged i 60 years

in the prior metformin group (~0.3 %), compared with the other prior treatment groups (each ~0.2 %) [12].

Analysis at 15 years total follow-up showed that metformin was more effective in preventing diabetes in women with prior GDM and subjects with higher severity of non-diabetic hyperglycemia at baseline [13]. Metformin reduced the risk of diabetes by 17 % (based on measurement of fasting plasma glucose) or by -39 % (based on measurement of HbA1c) in this study [13].

Weight loss was an important determinant of diabetes prevention in the DPP/DPPOS. Average weight loss was greater for ILI than the other groups during the randomized phase of the DPP, but maintenance of long-term weight loss from years 6—15 was greatest for metformin [13]. Greater weight loss in year 1 (all groups), older age + continued metformin use (metformin group), and older age and no diabetes or family history of diabetes (ILI group) predicted long-term weight loss on active treatments. Subjects with higher physical activity before the DPP randomization had a greater risk of diabetes: this apparent paradox is explained by the observation that these subjects demonstrated less increase in activity and less weight loss than other subjects during the randomized phase of the trial. Weight loss in the DPP/DPPOS correlated with adherence to metformin [14].

Elevated coronary artery calcium (CAC) is a predictor of increased cardiovascular risk that is used widely in clinical cardiovascular risk assessment [15]. A study at 10 years of DPPOS follow-up (14 years on average in all) found a reduced level of CAC scoring (based on the severity of elevation, or on whether or not elevated CAC was present) in men in the prior metformin group, but not in other treatment groups, or women [16]. The effect in men was independent of other clinical variables or receipt of statin treatment and was hypothesized to represent a potential cardioprotective effect of metformin in men with non-diabetic hyperglycemia. Other evidence of a potential cardioprotective effect of metformin in people with non-diabetic hyperglycemia is available: for example, a prospective observational study reported improved coronary artery endothelial function in people with non-diabetic hyperglycemia (ADA criteria) who did vs. did not receive metformin as part of their usual care [17].

A pregnancy complicated by GDM increases the 10-year risk of future T2DM substantially [18]. For example, the risk of developing T2DM was 48 % higher over 10 years for women with vs. without prior GDM in the placebo group of the DPPOS [19]. Women with a history of GDM in the prior metformin and prior ILI groups in the DPPOS were at lower risk of subsequent development of T2D (relative risk reduction [RRR] -40 and -35 %, respectively, vs. women in the prior placebo group [19]. ILI was also effective in preventing diabetes in the subgroup without prior GDM (RRR –30 %), although metformin was not. These long-term effects were comparable to those seen in the earlier, randomized phase of the trial [20]. A feasibility trial is underway to support a future placebo-controlled trial that will evaluate the effects of metformin vs. placebo on health outcomes (including incident diabetes) in women with GDM [21].

PCOS is an insulin-resistant state that is the most common cause of anovulatory infertility [22]. Treatment with metformin has been shown to ameliorate the dysglycemia, overweight, and hyperandrogenism that characterizes PCOS, and guidelines recommend a second-line role for metformin in improving fertility in this population [23, 24]. Information is lacking on whether metformin can prevent the onset of T2DM in women with PCOS [25]. Several observational studies suggested a significant effect of metformin in reducing the risk of future GDM in women with PCOS; meta-analyses of randomized trials do not support such an effect, however [26, 27].

Internationally-influential guidance from Europe (jointly from the European Society of Cardiology [ESC] and the European Association of the Study of Diabetes [EASD]) [28], the ADA [6], and the UK National Institute for Health and Care Excellence (NICE) [29] stress lifestyle intervention as the initial intervention to reduce the excess risk of incident diabetes. This is consistent with the well-known association between increased risk of T2DM and overweight or obesity and physical inactivity. All people at risk of (or with) T2DM who can adopt an intensive lifestyle intervention should do so throughout life.

The ADA and NICE guidelines support the therapeutic use of metformin for diabetes prevention in defined circumstances, while the ESC/EASD guideline provides no recommendation on the pharmacologic management of non-diabetic hyperglycemia. Recommendations on the use of metformin generally reflect the findings of the DPP, favoring the use of metformin alongside lifestyle change for younger subjects with higher levels of BMI. Long-term safety monitoring is highlighted including the importance of periodic checks of vitamin B_{12} and renal function (to ensure that patients have not developed a renal contraindication to metformin). The NICE guidance notes additionally

that the evidence base for diabetes prevention has been gained with the immediate-release formulation, but that prolonged/extended-release formulation of metformin is now indicated for the prevention or delay of diabetes and may be useful for people who cannot tolerate immediate-release metformin.

Studies to date suggest that only a small proportion of people with non-diabetic hyperglycemia receive metformin for this condition. For example, a study from the USA reported that the prevalence of self-reported «prediabetes» increased from 5.1 % in 2005—2006 to 7.4 % in 2013—2014, with a corresponding increase in the use of metformin from 2.4 to 8.3 % over this period [30]. Also in the USA, only 0.7 % of adults with «prediabetes» were reported to receive metformin between 2005 and 2012 [31]. Only 1.9 % of people with prediabetes and BMI i 35 kg/m^2, a subgroup with strong support for metformin use in guidelines (see above) were reported to have received metformin in this study. Similarly, a third US study found that only 8.1 % of a population of younger people (age < 60 years) with non-diabetic hyperglycemia (HbA1c 5.7—6.4 %) at high risk of diabetes through prior GDM and BMI i 35 kg/m^2 received metformin [32].

The cluster-randomized Prediabetes Informed Decisions and Education (PRIDE) study explored the outcomes of shared decision-making on treatment options among a population of 515 subjects who were about to undertake a diabetes prevention intervention [33]. Pharmacists discussed the contents of evidence-based clinical decision aids for the principal approaches to diabetes prevention. Most subjects opted for ILI (55 %), compared with metformin (9 %), or both (15 %), while 26 % declined both. Women and older patients were more likely to choose ILI while increasing BMI predicted higher take-up of both ILI and metformin. Metformin appears to be underused among the population of subjects eligible for it.

The main side-effect of metformin seen in people with T2DM (gastrointestinal upsets, such as diarrhea, abdominal pain, and nausea/vomiting) were apparent in the DPP/DPPOS [14] and other randomized trials; these can be minimized by careful initial dose titration, a (usually temporary) dose reduction where necessary, or use of an extended-release formulation [34, 35]. No significant safety issues were observed in the randomized phase of the DPP, and during 7—8 years of follow-up thereafter in the DPPOS. Twenty-two cases of hypoglycemia were reported among the 531 participants in the IDDP [36], a side-effect not usually associated appreciably with metformin in populations with T2DM. Careful titration from a low starting dose may be useful in non-diabetic subjects, to limit the incidence of side-effects [37].

Lactic acidosis is an extremely rare complication of the treatment of T2DM with metformin, and the contraindications of this agent are designed to avoid its use during the settings of severe renal impairment and hypoperfusion/hypoxia that might predispose to metformin-associated lactic acidosis [38]. The prevalence of these conditions in subjects with non-diabetic hyperglycemia has not been investigated to our knowledge, but it is likely to be lower than in people with T2DM of long duration who may be receiving metformin and who may be at risk of developing potential contraindications to metformin, such as severe chronic kidney disease.

Reduced levels of vitamin B_{12} is a well-known side-effect of metformin treatment during treatment for T2DM [39, 40] and has been observed in the DPPOS [40]. The authors recommended period screening and B_{12} supplementation, where required, during treatment with metformin.

Metformin has been in continuous clinical use for more than six decades in the management of T2DM, and its tolerability and safety profiles are well-understood [41]. There is no evidence to suggest that the long-term safety of metformin differs according to the severity of dysglycemia. It is reasonable to assume that the well-established safety and tolerability profiles of metformin observed in people with diabetes will likely apply to people taking metformin to prevent or delay T2DM, at least until further evidence accumulates relating to the therapeutic profile of metformin specifically in people with non-diabetic hyperglycemia.

Numerous reports [42, 43] have concluded that metformin and ILI based on the DPP are effective and cost-effective approaches to reducing the risk of diabetes in people with non-diabetic hyperglycemia. A systematic review published in 2017 calculated that median incremental cost-effectiveness ratios [ICER] were GBP 7490/quality-adjusted life-year (QALY) for ILI and GBP 8428/QALY for metformin; however, variations between studies in their populations, definitions of non-diabetic hyperglycemia, the nature of the interventions and assumptions used in constructing health economic models contribute to considerable variations in the results of individual studies [44].

Some studies adapted the DPP-based ILI for delivery within a community setting. The PREVENT-DM

study, described above, is an interesting example of this approach, in its use of community health workers («promotoras») to support people with the study interventions in its urban environment [45], as maintaining adherence to a lifestyle change is central to optimizing the benefits from it [46]. The use of «Diabetes Prevention Mentors» did not enhance the effectiveness of a community-based diabetes prevention initiative in the UK, however [47]. The nature of a lifestyle intervention is critical to its effectiveness and cost-effectiveness, however. A recent report from the UK found that low-impact lifestyle intervention was highly cost-effective compared with no intervention, at an incremental cost-effectiveness ratio [ICER] of GBP 44/quality-adjusted life-year (QALY), but would deliver only a 7 % reduction in diabetes incidence over 10 years [48]. Metformin was cost-effective at an ICER of GBP 372—5224/QALY, and ILI at an ICER of GBP 2775—7376/QALY, depending on whether diabetes was diagnosed using plasma glucose or HbA1c; metformin was cost-effective compared with either lifestyle intervention when HbA1c was used for diagnosing diabetes. The cost itself is a factor, irrespective of cost-effectiveness. For example, a recent report from Singapore concluded that ICERs of USD 36,663 for ILI (based on the DPP and adapted to local conditions) or metformin (USD 6367) was cost-effective from a societal perspective [49]. However, the authors concluded that the ILI would need to be delivered at a lower cost to be feasible for use as a strategy for diabetes prevention in Singapore.

SUMMARY

The potential of metformin to delay or prevent new-onset T2DM in people with IGT is proven beyond doubt by multiple randomized, controlled trials. Intensive lifestyle intervention was more effective than metformin in preventing diabetes in the DPP and elsewhere, although the efficacy of these interventions was similar in the lowest age category and highest BMI category in the main analysis of the randomized phase of the DPP. Accordingly, lifelong support for an improved lifestyle should be offered to all at risk of diabetes, but guidelines support a role for metformin in people for whom lifestyle intervention is ineffective or impractical, especially where obesity is severe. Physicians and people with non-diabetic hyperglycemia need to make individualized and shared decisions on whether treatment with metformin is appropriate for that individual.

Importantly, clinically and statistically significant levels of diabetes prevention were present two decades after the cessation of randomized treatment in the DPP/DPPOS, for people initially randomized to either ILI or metformin, relative to those initially randomized to placebo. The RRR for diabetes in the prior metformin group remained the same at 10, 15, and 22 years of follow-up at -18 %. These findings were especially notable as there was no effort to maintain DPP-randomized treatments during the DPPOS (although eligible patients in the metformin group were offered continued treatment). These data attest to the feasibility of long-term diabetes prevention with metformin.

We have yet to see improved clinical cardiovascular or microvascular outcomes in members of either the prior ILI or prior metformin groups from the DPPOS, or elsewhere. The observation from 22 years of follow-up that prevention/delay of diabetes per se in these groups combined was associated with significant outcomes benefits was encouraging. Further follow-up and more clinical events will be required to establish whether the cardiovascular benefits observed in people with T2DM randomized to metformin in the UK Prospective Diabetes study will be observed in the DPPOS population previously randomized to metformin.

Further data to support a precision medicine approach for targeting the most appropriate subjects to receive metformin will also be useful. We know that weight loss is a crucial part of any intervention for diabetes prevention, and this has been observed with metformin in the DPP. The observation in the DPP that women with GDM benefitted especially from treatment with metformin (and that women without prior GDM did not) requires further study. The potential for metformin to prevent/delay diabetes in other populations, such as those with PCOS, may be of interest in the future. Further study of populations with isolated IFG would be of interest, as metformin has not yet been clearly shown to reduce the incidence of diabetes in this population, but metformin was more effective in subjects with IGT with higher vs. lower fasting plasma glucose in the DPP. Finally, diabetes prevention studies have used varying dosing schedules for metformin, and the optimal dose of metformin for this purpose has yet to be defined.

Conflicts of interest: none.

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ABSTRACT

We have conducted a narrative review based on a structured search strategy, focusing on the effects of metformin on the progression of non-diabetic hyperglycemia to clinical type 2 diabetes mellitus. The principal trials that demonstrated a significantly lower incidence of diabetes in at-risk populations randomized to metformin (mostly with impaired glucose tolerance) were published mainly from 1999 to 2012. Metformin reduced the 3-year risk of diabetes by -31 % in the randomized phase of the Diabetes Prevention Program (DPP), vs.- 58 % for intensive lifestyle intervention. Metformin was most effective in younger, heavier subjects. Diminishing but still significant reductions in diabetes risk for subjects originally randomized to these groups were present in the trial's epidemiological follow-up, the DPP Outcomes Study (DPPOS) at 10 years (-18 and -34 %, respectively), 15 years (-18 and -27 %), and 22 years (-18 and -25 %). Long-term weight loss was also seen in both groups, with better maintenance under metformin. Subgroup analyses from the DPP/DPPOS have shed important light on the actions of metformin, including a greater effect in women with prior gestational diabetes, and a reduction in coronary artery calcium in men that might suggest a cardioprotective effect. Improvements in long-term clinical outcomes with metformin in people with non-diabetic hyperglycemia («prediabetes») have yet to be demonstrated, but cardiovascular and microvascular benefits were seen for those in the DPPOS who did not vs. did develop diabetes mellitus. Multiple health economic analyses suggest that either metformin or intensive lifestyle intervention is cost-effective in a community setting. Long-term diabetes prevention with metformin is feasible and is supported in influential guidelines for selected groups of subjects. Future research will demonstrate whether intervention with metformin in people with non-diabetic hyperglycemia will improve long-term clinical outcomes.

Keywords: type 2 diabetes mellitus, prediabetes, prevention, metformin.

РЕЗЮМЕ

Метформін у лікуванні діабету: розширення можливостей. Огляд

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В огляді на основі стратегії структурованого пошуку розглянуто вплив метформіну на прогресування недіабетичної гіперглікемії до клінічного цукрового діабету 2 типу. Основні дослідження, які продемонстрували значно нижчу захворюваність на діабет у групах ризику, рандомізованих на прийом метформіну (переважно з порушенням толерантності до глюкози), здебільшого опубліковані з 1999 до 2012 р. Метформін знижував 3-річний ризик виникнення цукрового діабету на –31 % у рандомізованій фазі Програми профілактики діабету (DPP), та на -58 % для інтенсивного втручання у спосіб життя (ILI). Метформін був найефективнішим у молодих осіб із більшою масою тіла. Статистично значуще зниження ризику виникнення цукрового діабету для осіб, рандомізованих у ці групи, виявлено в епідеміологічному спостереженні за результатами дослідження DPP Outcomes Study (DPPOS) через 10 років (–18 і –34 % відповідно), 15 років (-18 і -27 %), і 22 роки (–18 і –25 %). Довгострокову втрату маси

тіла також зафіксовано в обох групах з кращим результатом на тлі прийому метформіну. Аналіз підгруп DPP/DPPOS дав змогу виявити дію метформіну, зокрема його більший ефект у жінок із попереднім гестаційним діабетом в анамнезі та зниження рівня кальцію в коронарних артеріях у чоловіків, що може свідчити про кардіопротекторний ефект. Поліпшення віддалених клінічних результатів застосування метформіну в осіб із недіабетичною гіперглікемією («переддіабет») ще не продемонстровано, але серцево-судинні та мікросудинні переваги відзначено у тих осіб, в яких у дослідженні DPPOS не розвинувся діабет. Численні економічні аналізи в галузі охорони здоров'я показують, що метформін є економічно ефективним для профілактики цукрового діабету. Довгострокова профілактика цукрового діабету за допомогою метформіну можлива та підтримується міжнародними настановами для окремих груп пацієнтів. Подальші дослідження продемонструють, чи поліпшить віддалені клінічні результати втручання з метформіном в осіб із недіабетичною гіперглікемією.

Ключові слова: цукровий діабет 2 типу, переддіабет, профілактика, метформін.

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