Should metformin be prescribed for pre-diabetes?

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Between 2003 and 2011, the prevalence of pre-diabetes in England increased from 11.6% to 35.3% of the adult population. Additionally, in 2011, 50.6% of the population who were overweight (BMI >25 kg/m^2) and over the age of 40 years had pre-diabetes (Mainous et al, 2014). Approximately 5–10% of people with pre-diabetes will go on to develop diabetes every year, although this annual conversion rate is variable depending on the population studied and the definition of pre-diabetes (Tabák et al, 2012).

With the increasing prevalence of pre-diabetes and type 2 diabetes, there are some reports of the benefits of metformin use in pre-diabetes to reduce the risk of developing diabetes (e.g. Hostalek et al, 2015). When considering the use of a medication for any new indication, we generally consider a few things: Is it safe? Does it make intuitive sense? And is there evidence that patients will benefit from it? I think, intuitively, commencing a medication for a risk factor so that we do not have to commence the same medication once diabetes is established does not make sense. There certainly is no conclusive evidence in support of widespread use of metformin in pre-diabetes.

What does the literature say?

Based on evidence from the Diabetes Prevention Program (DPP), the American Diabetes Association (ADA) recommends that metformin may be advisable in a very select group of people with pre-diabetes, especially if they have a BMI >35 kg/m^2, are less than 60 years of age or are a woman who has previously had gestational diabetes (ADA, 2014). Even though these recommendations are in place, only 3.7% of eligible individuals in a large US sample were prescribed metformin in a retrospective cohort analysis over a 3-year period (Moin et al, 2015).

The DPP is possibly the biggest and most discussed intervention trial comparing lifestyle intervention, metformin (850 mg twice daily) and placebo for the prevention of type 2 diabetes onset in over 3000 participants with pre-diabetes. The DPP showed that diabetes incidence was reduced by 58% with intensive lifestyle intervention and by 31% with metformin, compared with placebo (DPP Research Group, 2002). The DPP included 3234 participants with pre-diabetes; out of these, data from 3081 participants were used to perform a risk-stratified analysis to identify participants with much higher or much lower benefit from the interventions under investigation. Sussman et al (2015) found that only those in the highest-risk quartile for diabetes development benefited from metformin therapy (3-year absolute risk reduction, 21%; number needed to treat [NNT], 4.6). Participants in the lifestyle-modification groups, however, showed a 3-year absolute risk reduction of 28% for those in the highest-risk quartile (NNT, 3.5) and the absolute risk reduction was 5% for participants in the lowest quarter for predicted risk of type 2 diabetes (NNT, 20) (Sussman et al, 2015). Furthermore, in a 10-year follow-up study since the end of the DPP, diabetes incidence was reduced by 34% in the lifestyle group and 18% in the metformin group compared with placebo (Knowler et al, 2009).

A pooled analysis of 31 randomised controlled trials was conducted in 2008 to assess the effect of metformin on the incidence of new-onset diabetes. The authors showed that metformin reduced the absolute risk of diabetes in a high-risk population by 6% with a NNT of 17 in a mean time-period of 1.8 years (Salpeter et al, 2008). One thing to bear in mind with these results is that it is not clear whether oral glucose tolerance tests (OGTTs), which are used to diagnose the development of diabetes, were performed after a sufficient wash-out period following stopping metformin as it is possible that the pharmacologic action of metformin may have masked the diagnosis of some cases of diabetes in the trials (Salpeter et al, 2008).

The DPP Research Group did just that – conducted a wash-out study to determine whether the observed benefit of metformin in DPP was

"Before widespread use metformin for pre-diabetes can occur, a significantly higher level of evidence of the benefits is needed."

a transient pharmacological effect or a more sustained effect. They reported some interesting results. All participants assigned to medication who had not developed diabetes at the end of the DPP were asked to have a repeat OGTT after discontinuing the study medication for 1–2 weeks. Among the 1274 participants in the wash-out study, the odds of diabetes in the metformin group was lower than that in the placebo group (odds ratio [OR], 0.66; 95% confidence interval [CI], 0.54–0.82 [P<0.001]). After the wash-out, however, diabetes was more frequently diagnosed in the metformin participants (OR, 1.49; 95% CI, 0.93–2.38 [P=0.098]). Although the primary analysis of the DPP demonstrated that metformin decreased the risk of diabetes by 31%, the wash-out study showed that 26% of this effect can be accounted for by a pharmacological effect of metformin that did not persist when the drug was stopped (DPP Research Group, 2003).

Where next

When we consider the available evidence from studies like DPP, lifestyle intervention clearly trumps metformin in reducing the risk of progressing from pre-diabetes to diabetes. Prescribing metformin for people with pre-diabetes may also blur the distinction between the management of diabetes and pre-diabetes, and pose practical questions such as when to commence screening for diabetic complications once they are on metformin. The counter argument has always been that lifestyle interventions in clinical trials are difficult to reproduce in real life. This only pleads for more research and effort into developing effective lifestyle intervention strategies. The NHS Diabetes Prevention Programme is an ambitious nationwide lifestyle intervention programme for individuals at high risk of developing type 2 diabetes and is a big step in the right direction (see http://bit.ly/1HHDqzH). The prevalence of pre-diabetes is estimated to be 5.5 million in the UK and widespread use of a medication for such a condition will need a significantly higher level of evidence of benefit before this can be implemented.

Acknowledgement
Sunil Nair would like to acknowledge his colleague Dr David Ewins, Consultant Physician, Countess of Chester Hospital NHS Trust, for advice and editorial assistance with this comment.

Disclosures
Sunil Nair has no conflict of interest.

American Diabetes Association (2014) Standards of Medical Care in Diabetes—2014. *Diabetes Care* **37**: S14–80

DPP Research Group (2002) The Diabetes Prevention Program (DPP): Description of lifestyle intervention. *Diabetes Care* **25**: 2165–71

DPP Research Group (2003) Effects of withdrawal from metformin on the development of diabetes in the diabetes prevention program. *Diabetes Care* **26**: 977–80

Hostalek U, Gwilt M, Hildemann S (2015) Therapeutic use of metformin in prediabetes and diabetes prevention. *Drugs* **75**: 1071–94

Knowler WC, Fowler SE, Hamman RF et al (2009) 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* **374**: 1677–86

Mainous AG 3rd, Tanner RJ, Baker R et al (2014) Prevalence of prediabetes in England from 2003 to 2011: population-based, cross-sectional study. *BMJ Open* **4**: e005002

Moin T, Li J, Duru OK et al (2015) Metformin prescription for insured adults with prediabetes from 2010 to 2012: A retrospective cohort study. *Ann Intern Med* **162**: 542–8

Salpeter SR, Buckley NS, Kahn JA, Salpeter EE (2008) Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. *Am J Med* **121**: 149–57

Sussman JB, Kent DM, Nelson JP, Hayward RA (2015) Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program. *BMJ* **350**: h454

Tabák AG, Herder C, Rathmann W et al (2012) Prediabetes: a high-risk state for diabetes development. *Lancet* **379**: 2279–90

What do you think? **Should metformin be prescribed to people with pre-diabetes?**
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