American Journal of
Preventive Medicine

REVIEW ARTICLE

Review of Metformin Use for Type 2 Diabetes Prevention

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Context: Prediabetes is prevalent and significantly increases lifetime risk of progression to type 2 diabetes. This review summarizes the evidence surrounding metformin use for type 2 diabetes prevention.

Evidence acquisition: Articles published between 1998 and 2017 examining metformin use for the primary indication of diabetes prevention available on MEDLINE.

Evidence synthesis: Forty articles met inclusion criteria and were summarized into four general categories: (1) RCTs of metformin use for diabetes prevention (n=7 and n=2 follow-up analyses); (2) observational analyses examining metformin use in heterogeneous subgroups of patients with prediabetes (n=9 from the Diabetes Prevention Program, n=1 from the biguanides and the prevention of the risk of obesity [BIGPRO] trial); (3) observational analyses examining cost effectiveness of metformin use for diabetes prevention (n=11 from the Diabetes Prevention Program, n=1 from the Indian Diabetes Prevention Program); and (4) real-world assessments of metformin eligibility or use for diabetes prevention (n=9). Metformin was associated with reduced relative risk of incident diabetes, with the strongest evidence for use in those at highest risk (i.e., aged <60 years, BMI ≥35, and women with histories of gestational diabetes). Metformin was also deemed cost effective in 11 economic analyses. Recent studies highlighted low rates of metformin use for diabetes prevention in real-world settings.

Conclusions: Two decades of evidence support metformin use for diabetes prevention among higher-risk patients. However, metformin is not widely used in real-world practice, and enhancing the translation of this evidence to real-world practice has important implications for patients, providers, and payers.

Am J Prev Med 2018;000(000):1–10. Published by Elsevier Inc. on behalf of American Journal of Preventive Medicine.

CONTEXT

More than 30 million U.S. adults have type 2 diabetes and diabetes-related healthcare costs account for 20% of healthcare spending.[1–3] Despite recent decreases in rates of diabetes-associated complications, the high prevalence of type 2 diabetes (referred to as diabetes throughout this manuscript) creates a significant societal burden.[2] Prediabetes is an intermediate metabolic state between normoglycemia and diabetes,[4] including either impaired glucose tolerance (IGT); impaired fasting glucose (IFG); or both conditions. The risk of progression to diabetes is greater for individuals with IGT and IFG close to the diagnostic boundary for diabetes. On average, about 15%–30% of

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0749-3797/$36.00
https://doi.org/10.1016/j.amepre.2018.04.038

adults with prediabetes are expected to progress to diabetes in 5 years.[5] From a population perspective, this risk is substantial given the high prevalence of prediabetes.

Accordingly, numerous studies have examined the efficacy of behavioral/lifestyle and pharmacologic interventions in preventing or delaying incident diabetes among individuals with prediabetes. Metformin is not approved by the Food and Drug Administration (FDA) for use in prediabetes, but several studies have examined its use for diabetes prevention over the past two decades. The objective of this study is to review the literature to better understand the current state of evidence surrounding metformin use for diabetes prevention.

EVIDENCE ACQUISITION

Data Sources and Searches

Standard strategies for literature reviews were used to identify studies, determine eligibility, and summarize findings as described below. A MEDLINE search was conducted using the following Medical Subject Heading terms and text words (*prediabetes* AND *metformin*). Searches were limited to literature published in English.

Study Selection

To be eligible, studies had to address metformin use for diabetes prevention or diabetes risk reduction as the primary outcome. Studies had to be published between January 1, 1998, and December 31, 2017. Randomized clinical trials and associated analyses (i.e., reports of longitudinal follow-up and subgroup analyses) were included. Trial protocols, reviews, commentaries/opinion pieces, and animal studies (i.e., non-human subjects) were excluded. Studies that examined metformin use in combination with other antihyperglycemic agents were also excluded.

Data Extraction and Quality Assessment

Studies were reviewed by one or more independent co-authors to assess initial eligibility. Data were extracted using a standardized template with no masking to author lists or journals. A multidisciplinary team with diverse expertise in both clinical and research disciplines including internal medicine, endocrinology, health services, epidemiology, and health economics contributed to this review. Two independent team members reviewed all eligible studies to confirm eligibility and accuracy of data extraction. Reference lists were also reviewed in detail, cited reference searches for included manuscripts were conducted, and discussions with topic experts also yielded additional studies for review. The Cochrane Risk of Bias Tool was used for quality assessment of RCTs.[6,7]

Data Synthesis and Analysis

Forty articles met inclusion criteria (a Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] flow diagram[8] is presented in Figure 1). After detailed review, manuscripts were further divided into four broad categories, as summarized in more detail below: (1) RCTs of metformin use for diabetes prevention (n=7 RCTs and n=2 follow-up analyses); (2) analyses examining metformin use in heterogenous subgroups of patients with prediabetes (n=9 subgroup analyses from the Diabetes Prevention Program [DPP], n=1 from the Biguanides and the Prevention of the Risk of Obesity [BIGPRO] trial); (3) analyses examining cost effectiveness of metformin use for diabetes prevention (n=11 analyses from the DPP, n=1 analysis from the Indian DPP); and (4) real-world assessments of metformin eligibility or use for diabetes prevention (n=9).

EVIDENCE SYNTHESIS

RCTs of Metformin Use for Diabetes Prevention

The DPP is the largest RCT examining metformin use for diabetes prevention.[9] Eligible participants from 27 U.S. medical centers were randomized to metformin (850 mg twice per day [bid], n=1,073); or an intensive lifestyle intervention (16 weekly, one-on-one lifestyle intervention sessions with a health coach and monthly follow-up thereafter, n=1,079); or placebo (n=1,082). Over 2.8 years of follow-up, diabetes incidence was significantly reduced by 31% (95% CI=17%, 43%) in the metformin arm and by 58% (95% CI=48%, 66%) in the intensive lifestyle intervention arm as compared with placebo. The intensive lifestyle intervention arm provided 39% (95% CI=24%, 51%) relative risk reduction of incident diabetes compared with metformin across the pooled sample and was also effective for individuals aged >60 years (where metformin was not significantly better than placebo). However, relative risk reduction for incident diabetes was comparable between the metformin and lifestyle intervention arms for participants with a BMI ≥35 and women with histories of gestational diabetes.

About 88% (n=2,776) of the DPP cohort enrolled in a long-term follow-up study known as the DPP Outcomes Study (DPPOS).[10,11] Over a total of 10 years of combined follow-up, diabetes incidence was reduced by 18% (95% CI=7%, 28%) in the metformin arm and by 34% (95% CI=24%, 42%) in the intensive lifestyle intervention arm, compared with placebo.[10] In the 15-year follow-up report, participant data were analyzed by intervention arm using an intent-to-treat analytic approach, and diabetes incidence was reduced by 18% in the metformin arm (hazard ratio [HR]=0.82, 95% CI=0.72, 0.93) and by 27% in the intensive lifestyle intervention arm (HR=0.73, 95% CI=0.65, 0.83), compared with placebo.[11]

Six additional randomized trials have examined metformin for diabetes prevention. As compared to the DPP, these were much smaller studies, with a total of 2,513 participants, from China,[12] India,[13,14] Pakistan,[15] Greece,[16] and the United Kingdom.[17] Eligibility criteria varied (i.e., IGT, or IFG, or BMI), as did metformin