Meta-analysis: Metformin Treatment in Persons at Risk for Diabetes Mellitus

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ABSTRACT

PURPOSE: We performed a meta-analysis of randomized controlled trials to assess the effect of metformin on metabolic parameters and the incidence of new-onset diabetes in persons at risk for diabetes.

METHODS: We performed comprehensive English- and non-English-language searches of EMBASE, MEDLINE, and CINAHL databases from 1966 to November of 2006 and scanned selected references. We included randomized trials of at least 8 weeks duration that compared metformin with placebo or no treatment in persons without diabetes and evaluated body mass index, fasting glucose, fasting insulin, calculated insulin resistance, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and the incidence of new-onset diabetes.

RESULTS: Pooled results of 31 trials with 4570 participants followed for 8267 patient-years showed that metformin reduced body mass index (−5.3%, 95% confidence interval [CI], −6.7–−4.0), fasting glucose (−4.5%, CI, −6.0–−3.0), fasting insulin (−14.4%, CI, −19.9–−8.9), calculated insulin resistance (−22.6%, CI, −27.3–−18.3), triglycerides (−5.3%, CI, −10.5–−0.03), and low-density lipoprotein cholesterol (−5.6%, CI, −8.3–−3.0%), and increased high-density lipoprotein cholesterol (5.0%, CI, 1.6–8.3) compared with placebo or no treatment. The incidence of new-onset diabetes was reduced by 40% (odds ratio 0.6; CI, 0.5–0.8), with an absolute risk reduction of 6% (CI, 4–8) during a mean trial duration of 1.8 years.

CONCLUSION: Metformin treatment in persons at risk for diabetes improves weight, lipid profiles, and insulin resistance, and reduces new-onset diabetes by 40%. The long-term effect on morbidity and mortality should be assessed in future trials.

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KEYWORDS: Diabetes mellitus; Insulin resistance; Meta-analysis; Metformin; Obesity; Risk factors

The prevalence of diabetes mellitus has been rapidly increasing, fueled by an epidemic increase in obesity and other metabolic risk factors.1-3 It is estimated that persons born in the year 2000 in the United States will have a 1 in 3 lifetime chance of developing diabetes.5 Diabetes is associated with a significant loss in life expectancy and is considered to be a risk equivalent of established coronary artery disease.6,5 For those who develop diabetes, cardiovascular morbidity and mortality are increased by 2- to 6-fold.6-8

Risk factors for the development of diabetes include obesity, a family history of diabetes, physical inactivity, insulin resistance, hypertension, dyslipidemia, vascular disease, and polycystic ovary syndrome.9 Body mass index (BMI), expressed as weight (kilograms) divided by height (meters) squared, is often used to classify overweight (BMI >25) and obesity (BMI >30).2 The metabolic syndrome consists of insulin resistance, obesity, dyslipidemia, and elevated blood pressure.10 Polycystic ovary syndrome is a common condition affecting approximately 5% of reproductive age women and is associated with infertility, obesity, insulin resistance, dyslipidemia, and hypertension.11

Strategies to prevent the development of diabetes are of great public health importance. Diet and exercise can improve insulin resistance and decrease the incidence of diabetes and future cardiovascular events, although long-term weight loss has proved difficult to maintain.12-17 In addition
to lifestyle measures, medications could be used to further decrease risk. Metformin, a biguanide agent that reduces weight and insulin resistance in persons with diabetes, has been shown to reduce the incidence of new-onset diabetes in persons at risk. The purpose of this meta-analysis is to pool data from randomized trials of metformin treatment in persons at risk for diabetes to quantify the effects on metabolic parameters and new-onset diabetes.

**MATERIALS AND METHODS**

**Study Selection**

We performed comprehensive English- and non-English-language searches of EMBASE, MEDLINE, and CINAHL databases from 1966 to November 2006 using the terms metformin, biguanide, or Glucophage, and scanned selected journals and references of identified articles. Studies were included if they were randomized controlled trials in persons without diabetes that compared metformin with placebo or no treatment, were of at least 8 weeks duration, and provided extractable data on metabolic parameters or the development of new-onset diabetes. We excluded trials evaluating lipodystrophy associated with human immunodeficiency virus infection, because the metabolic derangements may be different from other forms of metabolic syndrome.

We chose 8 weeks as the minimum trial duration to allow for changes to occur in the metabolic parameters. For crossover trials with treatment durations of less than 12 weeks, a 4-week washout period was required for inclusion. For trials with multiple publications, the article with the most information was chosen as the reference. Interventions included metformin alone or in combination with lifestyle measures such as diet and exercise. The control groups received placebo or no drug treatment alone or in combination with lifestyle measures.

**Assessment of Validity**

The methodologic quality of each trial was assessed for the following quality domains: randomization and allocation concealment, blinding of patients and people administering the treatment, and reporting of dropouts and use of intention-to-treat analysis. Trials were characterized for each domain separately using a 3-point scale, and quality assessment was used for a sensitivity analysis.

**Data Extraction and Synthesis**

Two investigators extracted data from the trials, reconciling differences by consensus. In addition, we attempted to contact selected investigators for additional information. One investigator responded with additional information, but the trial was excluded because of insufficient data. For each variable, the net treatment effects were pooled to obtain a weighted mean difference using the fixed-effects model for continuous outcomes, with the confidence interval (CI) set at 95% significance. The analyses were performed using Review Manager 4.2 (Cochrane Library Software, Oxford, United Kingdom).

For trials that provided data on both fasting glucose and insulin, an index of insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR) using the formula: insulin (milliunits/liter) × glucose (millimolar) ÷ 22.5. We chose this method because it could be calculated easily and has been shown to closely correlate with the standard insulin sensitivity index.

Subgroup analyses, chosen a priori, were performed to evaluate the difference in results for trials of participants with and without known polycystic ovary syndrome and with and without obesity (defined as a mean trial BMI > or < 30, respectively). A post-hoc subgroup analysis evaluated trials with a daily dose of metformin greater than and less than the mean (1.6 g/day). The results of the subgroups were compared with each other by using the test of interaction.

The proportion of patients with new-onset diabetes to patients without diabetes reported from each trial was pooled to obtain a summary odds ratio using the fixed-effects model for dichotomous outcomes. Trials with and without new cases of diabetes were pooled to obtain the

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**CLINICAL SIGNIFICANCE**

- Metformin treatment in persons at risk for diabetes improves weight, lipid profiles, and insulin resistance, and reduces new-onset diabetes by 40%.
- The absolute risk reduction in new-onset diabetes is 6% in 1.8 years.
- Metformin treatment could be added to lifestyle changes such as diet and exercise.
- The effect of metformin on cardiovascular morbidity and mortality in persons without diabetes should be assessed in future trials.

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![Figure 1: Flow chart of trials search.](image-url)
Table 2  Mean Trial Characteristics

<table>
<thead>
<tr>
<th>Trials</th>
<th>No. of trials</th>
<th>Study participants</th>
<th>Duration (y)</th>
<th>Age (± SD) Treatment Control</th>
<th>BMI (± SD) Treatment Control</th>
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<td>All trials</td>
<td>31</td>
<td>4570</td>
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<td>620</td>
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<td></td>
<td>27.8 (3.2)</td>
<td>36.1 (4.0)</td>
</tr>
<tr>
<td>Without known PCOS</td>
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<td>3950</td>
<td>2.0</td>
<td>48.3 (6.9)</td>
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<td>47.7 (6.7)</td>
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<td>With obesity</td>
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<td>1.8</td>
<td>46.2 (10.1)</td>
<td>36.3 (1.6)</td>
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<td></td>
<td>45.7 (9.9)</td>
<td>34.4 (1.7)</td>
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<tr>
<td>Without obesity</td>
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<td>966</td>
<td>1.9</td>
<td>44.4 (7.2)</td>
<td>25.5 (1.2)</td>
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<td>44.2 (7.4)</td>
<td>26.8 (1.7)</td>
</tr>
</tbody>
</table>

PCOS = polycystic ovary syndrome; BMI = body mass index; SD = standard deviation.

absolute risk difference and exact 95\% CIs (StatXact 7, Cytel Software, Cambridge, Mass). The results were pooled using the fixed-effects method.

To test for interstudy heterogeneity, the chi-square value was calculated for the assumption of homogeneity; statistical significance was indicated by \( P < .1 \). The fixed-effects method was chosen to report the results because minimal heterogeneity was seen in most of the analyses. When heterogeneity was noted, the results from both the fixed-effects method and random-effects method were reported.\(^{25}\)

Role of the Funding Source
The funding for this analysis came from salary support for Dr. Salpeter from Santa Clara Valley Medical Center and from a Podell Emeriti Award from Cornell University. The institutions had no role in the design, conduct, or reporting of the study. No sponsorship from the institutions or the pharmaceutical industry was provided to conduct this analysis.

RESULTS

Search Results
The search identified approximately 2000 articles, of which 92 were potentially relevant (Figure 1). Of these, 31 met inclusion criteria.\(^{14,15,26-54}\) Trials were excluded for the following reasons: 1 trial was not randomized, 37 trials did not provide a control group with placebo or no treatment, 11 trials were of less than 8 weeks duration, 7 trials did not provide extractable data, 3 trials evaluated human immuno-deficiency virus-infected patients, and 2 trials provided data on participants included in another trial. Additional infor-

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Figure 2  Effect of metformin on BMI in nondiabetic persons, percentage change. CI = confidence interval.
Table 1: Effect of metformin on HDL cholesterol, LDL cholesterol, and triglycerides in nondiabetic persons, percentage change. HDL = high-density lipoprotein; LDL = low-density lipoprotein; CI = confidence interval.  

Figure 3: Effect of metformin on HDL cholesterol, LDL cholesterol, and triglycerides in nondiabetic persons, percentage change. HDL = high-density lipoprotein; LDL = low-density lipoprotein; CI = confidence interval.

Study Year of Event Reference Weight % Weighted Mean Difference (test effect) 95% CI
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HDL cholesterol
Hediger 2000 (51) 1.4 20.8 [7.7 to 30.2] 0.014
Charles 1998 (29) 26.6 8.0 [1.8 to 3.7] 0.014
Charles 1998 (29) 109.5 3.6 [0.0 to 3.3] 0.001
Hew 2000 (52) 4.0 -4.9 [-6.8 to -2.2] 0.001
Tarrish 2001 (55) 1.9 -5.8 [-1.6 to -2.8] 0.001
Gambineri 2004 (43) 3.0 1.0 [0.1 to 0.0] 0.001
James 2005 (47) 1.5 1.5 [0.0 to 2.6] 0.001
Lewith 2004 (55) 6.1 7.2 [2.8 to 5.1] 0.001
Mogelton 2004 (53) 7.7 7.7 [0.1 to 0.0] 0.001
Ng 2000 (58) 0.6 4.5 [-0.2 to 3.1] 0.001
Richard 2005 (44) 3.8 1.1 [-0.2 to 1.0] 0.001
Rodriguez 2004 (46) 7.8 6.8 [0.6 to 1.5] 0.001
Sitteri 2004 (56) 0.5 1.3 [-0.8 to 1.0] 0.001
Stark 2005 (49) 6.0 0.5 [-0.0 to 0.0] 0.001
Vitale 2005 (50) 2.6 2.6 [1.7 to 3.3] 0.001
Total 100.0 5.0 [1.6 to 8.3] 0.001

LHD cholesterol
Hediger 2000 (51) 0.8 0.9 25.6 [0.4 to 25.5] 0.001
Charles 1998 (29) 36.2 3.5 0.6 to 3.7 0.001
Chow 2001 (42) 1.5 1.9 3.3 to 3.6 0.001
Freeman 2001 (55) 1.6 2.3 2.3 to 2.5 0.001
Gambineri 2004 (43) 0.6 4.1 2.9 to 5.0 0.001
James 2005 (47) 0.8 0.9 1.2 to 3.8 0.001
Klock 2002 (59) 0.2 0.0 0.0 to 0.0 0.001
Mogelton 2004 (53) 0.8 3.7 0.7 to 2.6 0.001
Ng 2000 (58) 0.5 0.0 0.0 to 0.0 0.001
Richard 2005 (44) 0.8 1.1 1.1 to 1.2 0.001
Rodriguez 2004 (46) 0.5 1.1 0.6 to 1.6 0.001
Sitteri 2004 (56) 0.2 1.9 1.1 to 1.9 0.001
Stark 2005 (49) 0.1 0.7 1.8 to 1.9 0.001
Vitale 2005 (50) 0.1 0.3 0.3 to 0.3 0.001
Total 100.0 5.6 [-3.3 to 10.5] 0.001

Triglycerides
Hediger 2000 (51) 2.1 1.4 [0.8 to 2.2] 0.001
Charles 1998 (29) 2.7 1.7 [1.1 to 1.7] 0.001
Charles 1998 (29) 2.7 1.4 [0.9 to 1.9] 0.001
Chow 2001 (42) 4.1 4.1 [0.7 to 2.7] 0.001
Freeman 2001 (55) 1.3 1.3 [0.0 to 2.6] 0.001
Gambineri 2004 (43) 1.8 1.8 [0.0 to 2.6] 0.001
Gianotti 1999 (53) 5.3 2.7 [0.8 to 3.1] 0.001
James 2005 (47) 1.8 1.8 [0.9 to 2.8] 0.001
Kawano 2001 (56) 1.8 1.8 [0.9 to 2.8] 0.001
Laboratory 2001 (17) 7.6 1.7 [0.1 to 2.5] 0.001
Mogelton 2004 (53) 3.8 2.7 [3.0 to 3.5] 0.001
Mogelton 2004 (53) 7.7 2.7 [0.6 to 10.0] 0.001
Mogelton 2004 (53) 3.6 0.0 [0.0 to 0.0] 0.001
Ng 2000 (58) 0.0 0.0 [0.0 to 0.0] 0.001
Richard 2005 (44) 0.0 0.0 [0.0 to 0.0] 0.001
Rodriguez 2004 (46) 0.0 0.0 [0.0 to 0.0] 0.001
Sitteri 2004 (56) 0.0 0.0 [0.0 to 0.0] 0.001
Stark 2005 (49) 2.3 2.3 [0.0 to 0.0] 0.001
Tarrish 2001 (55) 5.4 5.4 [0.0 to 0.0] 0.001
Vitale 2005 (50) 0.8 0.8 [0.0 to 0.0] 0.001
Total 100.0 5.3 [-3.8 to 10.5] 0.001

Data Synthesis

**Body Mass Index and Lipids.** Metformin treatment reduced BMI by 5.3% (95% CI 4.0-6.7) compared with placebo or no treatment (Figure 2). Metformin reduced BMI from baseline by 5.9%, with no change seen in the placebo group. Statistically significant reductions in BMI were seen in persons with polycystic ovary syndrome (−5.3%, CI, −7.2.−3.4) and without known polycystic ovary syndrome (−5.4%, CI, −7.2.−3.5), with obesity (−5.1%, CI, −5.5.−3.6) and without obesity (−6.3%, CI, −7.8.−4.9), and using a daily dose of metformin higher than average (−5.3%, CI, −6.8.−3.8) and lower than average (−5.5%, CI, −8.2.−2.8).

Metformin treatment increased high-density lipoprotein (HDL) cholesterol (5.0%, CI, 1.6-8.3) and reduced low-density lipoprotein (LDL) cholesterol (−5.6%, CI, −8.3.−3.0), LDL/HDL ratio (−8.5%, CI, −14.0.−2.6), and triglycerides (−5.3%, CI, −10.5.−0.03) compared with
placebo or no treatment (Fig. 3). No statistically significant differences were found between subgroups.

**Insulin Resistance and New-onset Diabetes.** Metformin treatment reduced fasting glucose (−4.5%, CI, −6.0−−3.0) and fasting insulin (−14.4%, CI, −19.9−−8.9) compared with placebo or no treatment. Calculated insulin resistance (HOMA-IR) was reduced by 23% (CI, 18.0-27.3) compared with the control group (Figure 4). No statistically significant differences were found between subgroups.

Metformin decreased new-onset diabetes by 40% (odds ratio 0.6; CI, 0.5-0.8) compared with placebo or no treatment (Figure 5). When all 31 trials with and without new cases of diabetes were pooled, metformin reduced the absolute risk of diabetes by 6% (CI, 4-8) during a mean trial duration of 1.8 years. Two of the trials provided 61% of the weight in the analysis.

**Interstudy Variability**

Evidence for interstudy heterogeneity was found in the analysis of fasting glucose (P = .04). Similar results were found when using the fixed-effects method (−4.5%, CI, −6.0−−3.0) or the random-effects methods (−4.5%, CI, −6.6−−2.4). No evidence heterogeneity was found in any other analysis (P > .2).

![Figure 4](image_url)  
**Figure 4** Effect of metformin on calculated insulin resistance in nondiabetic persons, percentage change. Homeostatic model assessment insulin resistance: fasting glucose (millimolar) × fasting insulin (millinol/liter) ÷ 22.5. CI = confidence interval.

![Figure 5](image_url)  
**Figure 5** Effect of metformin on the incidence of new-onset diabetes in nondiabetic persons, odds ratio. CI = confidence interval.
Sensitivity Analysis
A sensitivity analysis was used to evaluate the effect of including trials with the lowest quality scores. When the 2 open-label trials were excluded from the analysis,\textsuperscript{15,47} the results changed by less than 1 percentage point and remained statistically significant for all analyses.

DISCUSSION
Pooled results from 31 trials with 4570 participants followed for 8300 patient-years found that metformin treatment in persons at risk for diabetes reduced BMI and insulin resistance, improved lipid profiles, and decreased the incidence of new-onset diabetes by 40% compared with placebo or no treatment. The absolute risk reduction of diabetes was 6%, with a number needed to treat of 17 in 1.8 years. Diabetes risk factors studied in the trials included obesity, abdominal obesity, metabolic syndrome, polycystic ovary syndrome, impaired glucose tolerance or insulin resistance, family history of diabetes, hypertension, dyslipidemia, and peripheral vascular disease. Significant improvements were seen for those with and without known polycystic ovary syndrome and with or without obesity. Of note, 4 trials were in children and adolescents,\textsuperscript{35,36,51,55} with a similar mean reduction in BMI seen compared with adults.

This meta-analysis has several limitations. The study analyzed metabolic risk factors and not clinical outcomes such as cardiovascular morbidity or mortality. The minimum trial duration of 8 weeks may not be long enough to affect the incidence of diabetes, thus possibly underestimating the reduction seen in diabetes incidence. Measures of insulin resistance were calculated using the homeostatic model assessment and not more directly through euglycemic clamp techniques. However, these calculations can be easily made in large clinical trials and are closely correlated with the insulin sensitivity index measured by euglycemic clamp.\textsuperscript{23} The data for this meta-analysis came only from published trials so there is a potential for publication bias, although funnel plots of effect size versus standard error showed no evidence of bias. Subgroup analyses were performed according to characteristics of the trials and may have included overlap between conditions. For example, persons with polycystic ovary syndrome may have been included in trials evaluating metabolic syndrome, and persons with obesity may have been included in trials with a mean BMI less than 30. Other measures of obesity and insulin resistance, such as waist-to-hip ratio, glucose tolerance tests, and the insulin sensitivity index, were not studied in this analysis because there were not enough trials on these outcomes to analyze. Despite these limitations, this meta-analysis provides evidence that metformin has strong beneficial effects on metabolic parameters and diabetes risk.

The diagnosis of diabetes mellitus is often made using oral glucose tolerance tests or fasting glucose levels, so it is possible that the pharmacologic action of metformin may have masked the diagnosis of some cases of diabetes in the trials. To test this hypothesis, 1 trial evaluated oral glucose tolerance tests 1 to 2 weeks after the stop of their trial and found that metformin still significantly reduced the risk of diabetes compared with placebo.\textsuperscript{50}

The mechanism of action of metformin is not fully understood, so it is not clear whether it exerts effects on insulin resistance that are independent of its effect on weight. Of note, metformin was at least as effective in weight loss for nonobese patients as for those with obesity. Diabetes is usually preceded by the development of obesity\textsuperscript{59,60} and insulin resistance.\textsuperscript{61,62} During weight loss associated with lifestyle modification, a 1% reduction in weight is associated with a reduction in insulin resistance of 3% to 7% and a decrement in new-onset diabetes of 5% to 15%.\textsuperscript{12,14,56,63-67} In this analysis, for each 1% reduction in BMI compared with placebo, metformin reduced insulin resistance by 5% and new-onset diabetes by 8%.

Most trials in the meta-analysis provided recommendations for exercise and diet in both the treatment and control groups, so the effect seen was a result of treatment in addition to lifestyle modification. However, it is not clear in most trials whether the modifications were actually implemented or met. Two trials evaluated the effect of intensive lifestyle modification alone compared with metformin on diabetes incidence.\textsuperscript{14,15} and pooled data show that lifestyle modification was significantly more effective than metformin. One trial\textsuperscript{45} evaluated the combination of intensive lifestyle measures and metformin on weight, and found that the combination produced the most significant reductions compared with either treatment alone.

Obesity, dyslipidemia, insulin resistance, hyperglycemia, and diabetes mellitus are all strong independent risk factors for cardiac events and death.\textsuperscript{7,8,68-72} For patients with dyslipidemia, a 5% reduction in LDL cholesterol has been shown to decrease cardiovascular mortality by 5%,\textsuperscript{73-78} and a 5% increase in HDL cholesterol, often associated with a reduction in triglycerides, reduces coronary events by 20%.\textsuperscript{76} It is possible that the metabolic changes seen with metformin treatment in persons without diabetes will result in a reduction in cardiovascular risk over time.\textsuperscript{79-79} A cost-effectiveness analysis using data from the Diabetes Prevention Program estimated that generic metformin treatment for adults with impaired glucose tolerance could increase life expectancy at a cost of $1800 per quality-adjusted life year gained.\textsuperscript{80}

In addition to the metabolic parameters studied in this meta-analysis, the trials evaluated other beneficial effects of metformin treatment that could reduce cardiovascular risk. Metformin was shown to reduce visceral fat mass, waist circumference, waist-to-hip ratio, systolic and diastolic blood pressure, left ventricular mass, urinary albumin excretion, tissue-type plasminogen activator antigen, and the incidence of metabolic syndrome, compared with placebo.\textsuperscript{14,27,29-32,34,36,43,44,46,48,49,53,54}

Metformin treatment has been well studied in women with known polycystic ovary syndrome. This common condition is characterized by chronic anovulation, infertility, and hyperandrogenism, and is often associated with dyslip-
idemia, obesity, and insulin resistance. Metformin treatment in polycystic ovary syndrome is highly effective in achieving ovulation and increasing pregnancy rates and has been shown to significantly reduce systolic and diastolic blood pressure. Metformin has been extensively studied for more than 50 years and has been shown to be safe even with long-term use. Observational studies and randomized trials indicate that metformin is the most effective drug for reducing cardiovascular morbidity and mortality in patients with diabetes and is considered first-line treatment. In this analysis, dropout rates were similar in the metformin and control groups. Gastrointestinal symptoms, such as nausea, abdominal discomfort, and diarrhea, were the only adverse events reported more frequently in the metformin group, and these symptoms rarely required discontinuation of treatment. Lactic acidosis is a rare metabolic condition that has been reported with metformin treatment, as well as with sulfonylureas and insulin, and is usually associated with serious concomitant conditions such as acute renal failure or shock. A meta-analysis of metformin treatment in diabetes found no cases of lactic acidosis in 48,000 patient-years of metformin treatment or in 38,000 patient-years in the non-metformin groups, despite the fact that 96% of the trials had allowed for the inclusion of at least one of the standard contraindications listed for metformin. Another class of antidiabetic agents, thiazolidinediones (rosiglitazone and pioglitazone), also work to reduce insulin resistance and could be used to prevent the development of diabetes. One trial compared rosiglitazone with placebo in persons with impaired glucose tolerance and found a 60% reduction in progression to diabetes during 3 years. However, there was a 3% increase in weight and a 7-fold increase in confirmed congestive heart failure compared with placebo. A recent meta-analysis found that rosiglitazone treatment in patients with diabetes increases myocardial infarction by 45%, with a trend toward increased death from all cardiovascular causes.

CONCLUSIONS

Metformin treatment in persons at risk for diabetes results in modest improvements in weight, LDL cholesterol, HDL cholesterol, triglycerides, and fasting glucose, and substantial reductions in insulin resistance and the development of diabetes. For those at risk for diabetes, implementation of intensive lifestyle modifications is clearly the most successful approach to reducing weight and diabetes incidence. However, standards of care should include the use of metformin in addition to diet and exercise if these lifestyle modifications alone are not sufficient. Future long-term trials will be needed to show that the metabolic benefits of metformin treatment result in a reduction in cardiovascular morbidity and mortality.

References


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<tr>
<th>Study, Year (Reference) Duration</th>
<th>Participants</th>
<th>Study Group</th>
<th>No.</th>
<th>Mean Age (y)</th>
<th>Mean BMI</th>
<th>Dropout %</th>
<th>Intervention</th>
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<td>Nonobese women with PCOS</td>
<td>Metformin</td>
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<td>Insulin resistance and family history of diabetes</td>
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<td>Adolescents with morbid obesity</td>
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<td>Impaired glucose tolerance</td>
<td>Metformin</td>
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<td>Knowler et al156 Fujimoto et al27</td>
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<td>Participants</td>
<td>Study Group</td>
<td>No. n</td>
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<td>Mean BMI</td>
<td>Dropout %</td>
<td>Intervention</td>
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<td>Abdominal obesity with and without PCOS</td>
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<td>31.1</td>
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<td>10</td>
<td>850 mg</td>
<td>BID; Placebo</td>
<td>All with diet</td>
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<td>Ramachandran et al 2006&lt;sup&gt;15&lt;/sup&gt; 156 wk</td>
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<td>Control 20</td>
<td>34.7</td>
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<td>15</td>
<td>500 mg</td>
<td>BID; Placebo</td>
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<td>Obesity with insulin resistance</td>
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<td>Rodriguez-Moctezuma et al 2004&lt;sup&gt;40&lt;/sup&gt; 8 wk</td>
<td>Family history of diabetes</td>
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<td>Peripheral vascular disease</td>
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<td>0</td>
<td>850 mg</td>
<td>TID; Placebo</td>
<td>All patients with ideal body weight</td>
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<td>Srinivasan et al 2006&lt;sup&gt;53&lt;/sup&gt; 26 wk</td>
<td>Children and adolescents with obesity and insulin resistance</td>
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<td>14.3</td>
<td>1 g BID</td>
<td>Placebo</td>
<td>Crossover trial</td>
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<td>Stakos et al 2005&lt;sup&gt;49&lt;/sup&gt; 104 wk</td>
<td>African-Americans with insulin resistance and family history of diabetes</td>
<td>Control 97</td>
<td>41.0</td>
<td>NS</td>
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<td>Mean weight 90.1 kg</td>
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<td>Sturrock et al 2002&lt;sup&gt;41&lt;/sup&gt; 13 wk</td>
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<td>Metabolic syndrome</td>
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<td>31</td>
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<td>BID; Placebo</td>
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PCOS = polycystic ovary syndrome; BMI = body mass index; LSM = lifestyle modification; BID = 2 times per day; TID = 3 times per day; NS = not significant.