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**Metformin for Prevention of Type 2 Diabetes**

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Metformin for prevention of type 2 diabetes

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What is metformin’s potential for the prevention of type 2 diabetes?

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DRUG INFORMATION ROUNDS

OBJECTIVE: To evaluate evidence from the medical literature that metformin is effective in preventing type 2 diabetes.

DATA SOURCES: Primary literature retrieval was accessed through MEDLINE (1966-December 2003) using the terms metformin, type 2 diabetes, and prevention.

DATA SYNTHESIS: Two studies evaluated metformin’s potential to prevent type 2 diabetes, finding that metformin maintained or reduced fasting blood glucose in non-diabetics. Recently, a large study showed that metformin may reduce the occurrence of diabetes by 31%.

CONCLUSIONS: These studies provided evidence that metformin may reduce the occurrence of type 2 diabetes. Since long-term efficacy has not been determined, further studies are needed.

KEY WORDS: metformin, type 2 diabetes, prevention
Ninety to ninety-five percent of all diabetics have type 2 diabetes. Type 2 diabetes is usually diagnosed in patients who are over the age of forty and overweight. There are three key pathophysiological defects that constitute this disease: insulin resistance, increased hepatic glucose production, and insulin deficiency. Diet and exercise may be the only treatment required in some patients, but in many cases, drug therapy may be needed to regulate blood glucose. Metformin targets insulin resistance by boosting the sensitivity of insulin receptors in the muscle tissue. It also decreases hepatic glucose production.\(^1\)

Over the last years, researchers have hypothesized that metformin may be beneficial in preventing type 2 diabetes. An early study by Fontbonne, et al., discussed the efficacy of metformin in preventing insulin resistance syndrome (IRS), which signals the future onset of this disease. The researchers conducted a randomized, double-blinded, multi-center clinical trial of 457 adults over one year. There were 324 patients who completed the study. The inclusion criteria were: upper body obesity, defined as a waist hip ratio of \(\geq 0.95\) in men and \(\geq 0.80\) in women, and an age range of 35-60 years in men and 40-65 years in women. Study participants were given either 850 milligrams of metformin or placebo taken twice daily. They were also given lifestyle and exercise advice. Researchers evaluated many parameters, including fasting blood glucose and weight loss. The metformin group had a fasting blood glucose increase of 0.2 mmol/L. The placebo group had an increase of 0.4 mmol/L. The difference between groups was statistically significant (p-value<0.05). Weight loss was seen in both groups, with two kilograms in metformin subjects and 0.8 kilograms in placebo subjects. The difference between groups was not statistically significant (p-value<0.06). Since this p-value approaches a level of significance, this raises a question about the possibility of a type II error (a false negative) being made in the weight loss analysis. This study, however, did show that metformin maintains fasting blood glucose levels. These results are limited, yet showed the need for a larger clinical study to prove metformin’s preventative effects.\(^2\)

A study by Freemark and Bursey (2001) considered the effects of metformin in preventing type 2 diabetes in adolescents who had pre-existing factors of this disease. The researchers conducted a randomized, double-blinded study of 32 adolescents. The inclusion criteria were: fasting hyperinsulinemia, severe obesity defined as a Body Mass Index (BMI) of 30kg/m\(^2\), and a family history of diabetes. They were given either metformin 500 milligrams or placebo twice daily. Blood glucose levels and BMI were tested monthly for six months. There were 29 subjects who completed the study. At completion, the metformin group had a statistically significant decline in fasting blood glucose levels from 84.9±2.2 mg/dL to 75.1±1.6 mg/dL, \((p<0.02)\). Placebo patients did not show
statistically significant changes, increasing from $77.2\pm2.2$ mg/dL to $82.3\pm2.7$ mg/dL. Metformin decreased BMI by 0.5 kg/m², while placebo BMI increased 0.9 kg/m². The difference in BMI between the groups was statistically significant ($p<0.02$). Therefore, metformin did significantly decrease BMI and blood glucose levels in pre-diabetic adolescents. The limitations of the study were: a small study size and a short period of time. Therefore, the study may not be applicable to the general population. The results should be confirmed in a larger study.

The Diabetes Prevention Program Research Group conducted a 2.8 year, randomized, double-blind, multi-center study on the potential of metformin in preventing type 2 diabetes. The researchers tested to see if treatment with metformin and/or major lifestyle changes would delay or prevent the onset of the disease. The inclusion criteria for subjects were: 25 years of age or older, a BMI of 24 kg/m² or greater, a fasting plasma glucose concentration of 95-125 mg/dL, and a plasma glucose concentration of 140-199 mg/dL two hours after a 75-g oral glucose load. Subjects were placed in three categories of therapy for the study. The first group received 850 milligrams of metformin twice daily and diet and exercise recommendations. The second group received a placebo twice daily and also received lifestyle recommendations. The third group was not given any medication but was put in a program to encourage drastic lifestyle changes. These changes were to reduce the BMI by seven percent with a healthy diet and 150 minutes of exercise per week. There were 3234 participants at completion of the study. Both the metformin group and the group that made radical lifestyle changes experienced a lower occurrence of diabetes. Type 2 diabetes occurred 58% less often in the group with radical lifestyle changes than the placebo group (95% confidence interval, 48 to 66 percent). In the metformin group, the disease occurred 31% less frequently than the placebo group (95% confidence interval, 17 to 43 percent). These changes vs. placebo were statistically significant. Although metformin was less effective than radical lifestyle changes, it was effective in preventing this disease from occurring. The researchers estimated that radical lifestyle changes would prevent one person out of every 6.9 people from progressing to type 2 diabetes, while metformin would prevent one person out of every 13.9 people.

Summary

These three studies have shown some potential benefits of metformin in pre-diabetic patients. The early study by Fontbonne, et al., indicated the potential of metformin to maintain blood glucose levels and possibly delay type 2 diabetes onset. Limitations to this study were a short duration and more appropriate outcome variables should have been used. These limitations may suggest that despite the positive results, the data was not conclusive. The study by Freemark and Bursey showed a decrease in blood glucose levels and BMI in adolescents taking metformin.
However, small study size and limited duration of the study indicate the need for further study. The best and most in-depth study regarding metformin and prevention is the Diabetes Prevention Program study. It showed that both metformin and radical lifestyle changes can significantly reduce the incidence of this disease during the study length of nearly three years. However, radical lifestyle changes can be difficult to implement and maintain for patients. For those patients that are unwilling to commit to or maintain radical lifestyle changes, metformin may be another potential choice to help prevent type 2 diabetes and the devastating complications associated with the disease. If left untreated, this disease can lead to serious problems, such as: diabetic neuropathy, cardiovascular disease, ophthalmic disease, and stroke. Recent controversy has emerged regarding the Diabetes Prevention Program study and metformin’s true efficacy in preventing type 2 diabetes. One opinion is that this research may be flawed because it failed to look at whether or not metformin disguises the onset of the disease by merely lowering blood glucose rather than actually delaying or stopping the progression to the disease.\(^5\) With the lack of long-term data in a larger population of patients, it seems impractical to advocate the use of metformin to prevent type 2 diabetes. Further studies must look at the long-term safety and true efficacy of metformin, along with its cost-effectiveness, before metformin should be considered for the prevention of type 2 diabetes.
References:


