Treating metabolic syndrome

Lifestyle change or medication?

Anna Emili MD Hani Abushomar MSc Kalpana Nair MEd MSc

Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 2005;142(8):611-9.

Research questions

What is the baseline prevalence of metabolic syndrome in the Diabetes Prevention Program? What are the effects of metformin and intensive lifestyle intervention therapy on metabolic syndrome's incidence and resolution?

Type of article and design

The Diabetes Prevention Program (DPP) was a randomized controlled trial of 3234 patients with impaired glucose tolerance at 27 study centres in the United States. Participants were assigned to 1 of 3 arms: 1) intensive lifestyle intervention, 2) treatment with metformin, or 3) placebo. This study was a secondary analysis of participants in the main trial who had metabolic syndrome. Metabolic syndrome was based on the National Cholesterol Education Program's Adult Treatment Panel III.

Relevance to family physicians

Canadians are living fast-paced lifestyles with little time for healthy meals and exercise. In 2004, approximately 25% of adult Canadians were obese and another 36% were overweight.[1] These numbers have nearly doubled over the past 20 years.[1] The World Health Organization has recognized obesity as a public health issue of epidemic proportions.[2]

The National Cholesterol Education Program's Adult Treatment Panel III defined metabolic syndrome as 3 or more of the following conditions: waist circumference greater than 102 cm in men and greater than 88 cm in women; serum triglyceride level of at least 1.7 mmol/L; high-density lipoprotein (HDL) level less than 1.03 mmol/L in men and less than 1.3 mmol/L in women; blood pressure of 130/85 mm Hg or greater; and fasting plasma glucose level of 6.2 mmol/L or greater.[3] Estimates suggest that 25% of individuals living in developing countries meet the criteria for metabolic syndrome.[4]

For trials that utilized the National Cholesterol Education Program's criteria for metabolic syndrome, the random effects estimates of combined relative risk were 1.27 (95% confidence interval [CI] 0.9-1.78) for all-cause mortality, 1.65 (95% CI 1.38-1.99) for cardiovascular disease, and 2.99 (95% CI 1.96-4.57) for diabetes mellitus.[5] Metabolic syndrome needs to be actively addressed with patients given that cardiovascular disease is the second most common cause of death in Canada[6] and that approximately 2.3 million Canadians have diabetes.[7]

The American Diabetes Association and the European Association for the Study of Diabetes released a joint statement addressing metabolic syndrome.[8] This statement questions the utility of labeling someone with metabolic syndrome, as there is no evidence that it will provide any further information regarding risk stratification beyond the presence of individual cardiac risk factors. The authors reported the current evidence that certain components of metabolic syndrome confer greater cardiovascular risk than others and that the number of components present is directly related to the level of cardiovascular risk. The statement recommends addressing all risk factors through lifestyle interventions, including healthy diet and exercise, and pharmacologic treatments if indicated.

Overview of study and outcomes

Participants were enrolled in the study between June 1996 and May 1999 using various sources, including community screenings and household mailings. The DPP had proposed enrolment of at least 50% women, 20% older than 65 years, and half of participants from an ethnic minority group (African-American, Hispanic, American-Indian, Asian-American, or Pacific Islander).

Main inclusion criteria included age of at least 25 years, body mass index of at least 24 kg/m^2, fasting plasma glucose level between 5.3 and 7.0 mmol/L, and glucose level between 7.8 and 11.1 mmol/L after glucose load. Different criteria existed for some ethnic minority groups. Exclusion criteria were recent myocardial infarction, diagnosis of diabetes, taking medications known to impair glucose tolerance, triglyceride level of at least 6.8 mmol/L (≥600 mg/dL), major illness, or symptoms of coronary artery disease.

The goal for those in the intensive lifestyle therapy arm was achieving and maintaining a weight reduction of at least 7% through a low-fat, low-calorie diet and moderate-intensity physical activity for at least 150 minutes weekly. The metformin group received standard lifestyle recommendations and 850 mg of metformin twice daily. The placebo group only received standard lifestyle suggestions.

All participants had their blood tested quarterly each year, fasting glucose levels tested twice each year, and fasting lipid levels and waist circumference measured once each year. Participants were followed for an average of 3.2 years (range 0.04-5.0 years). Study design was based on the intention-to-treat principle.

The primary trial demonstrated that both lifestyle change and metformin significantly reduced incidence of type 2 diabetes; lifestyle intervention was more effective than metformin.[1]

Results

At baseline, 53% of participants fit the criteria for metabolic syndrome with no differences across age or sex. Low HDL ($P=.01$) and high triglyceride levels ($P=.06$) were statistically more common in the placebo group than in the lifestyle or metformin groups. A previous publication had noted that by the end of the study curriculum (24 weeks), 50% of participants in the lifestyle group had achieved the 7% weight loss, with 38% attaining this goal at their most recent visit.[9] For the physical activity component, 74% achieved the goal (150 min/week) at the end of the curriculum period and 58% at the last visit. The reductions in caloric intake were as follows:

- placebo mean 249, SD 27;
- metformin mean 296, SD 23; and
- lifestyle mean 450, SD 26.

The incidence of metabolic syndrome after the 3-year study period was 53%, 47%, and 38% in the placebo, metformin, and lifestyle groups respectively. Lifestyle intervention decreased the incidence of metabolic syndrome by 41% (95% CI 28%-52%) compared with placebo ($P<.001$) and 29% (95% CI 13%-42%) versus metformin ($P<.001$). Metformin produced a reduction of 17% (95% CI 0%-31%) over placebo ($P=.03$). Lifestyle intervention was more successful among men than women (64% versus 37%, $P=.02$ for heterogeneity) and least effective in younger participants (25 to 44 years old). Metformin was no better than placebo among women ($P>.2$).

The incidence of the individual components in those participants who did not meet the criteria for metabolic syndrome at baseline had a similar pattern to the incidence of the syndrome itself. Lifestyle intervention was superior to placebo in decreasing the incidence of all factors apart from HDL level ($P<.001$). Metformin was significantly better than placebo at decreasing the incidence of high waist circumference and high fasting glucose level ($P<.001$).

Only lifestyle intervention had a significant effect on the resolution of metabolic syndrome over placebo ($P=.002$). By study completion, 18%, 23%, and 38% of the placebo, metformin, and lifestyle groups respectively no longer fit the criteria. Metformin reduced the prevalence of low HDL, increased waist circumference, and high fasting glucose levels ($P<.05$), while lifestyle intervention improved all components ($P<.05$).

Overall prevalence of metabolic syndrome increased in the placebo group from 55% to 61% ($P=.003$), but was statistically unchanged in the metformin group. The lifestyle group alone had a statistically significant decrease in prevalence of metabolic syndrome from 51% to 43% ($P<.001$).

The interventions were well tolerated. Musculoskeletal complaints were reported more frequently in the lifestyle group and gastrointestinal symptoms were more common in the metformin group.

Analysis of methodology

The design of the study—a randomized clinical trial—provides a level of validity that is not achievable through other observational study designs. Randomization of participants was appropriate and concealed, as the assignment was unknown until randomization. Determining eligibility of patients did not depend on the arm of the study to which patients were assigned. The intention-to-treat principle, a procedure used to avoid differential non-adherence, was applied by analyzing all patients in their initial randomization group regardless of whether they received the assigned intervention or not.

As described in a previous study, the distribution of risk factors for diabetes was similar between randomization groups.[9] This similarity confirms the appropriateness of randomization, and one can thus rule out any confounding effect of those factors on the results.[10,11]

The study was double-blinded for the assignment to placebo and metformin as patients and assessors were unaware which treatment group patients were in. The notably higher rate of gastrointestinal side effects might have undermined the blinding to treatment. The higher side-effect rates among the metformin group could explain the lower adherence to metformin when compared with placebo.[10,11]

There was no information about the completeness of the follow-up.[9,10,12] The very small decline in the number of participants from the beginning of the study to the second-year visits could be attributed mainly to participants developing diabetes. During the third year, however, there was a substantial decline in the number of participants, which could not be attributed merely to the development of diabetes.[10]

While a 4-year period was enough time to accumulate a considerable number of cardiovascular end points, there was no reporting of the number of cardiovascular events experienced by patients in each of the study arms. Although there is clear evidence in the literature about the association between cardiovascular disease and each of the lifestyle risk factors analyzed in the study, a direct association between the lifestyle intervention and cardiovascular events in the DPP would have been more useful.[9,10,12]

Application to clinical practice

This was a well-designed trial with high internal validity. The study was able to show that lifestyle intervention could decrease the incidence and prevalence of metabolic syndrome and virtually all its components at least as well as or better than a medication. There are practically no risks to lifestyle intervention, and the benefits to cardiovascular health are substantial. The question, and more important the challenge, becomes whether or not patients will be able to make the necessary lifestyle changes. The required lifestyle intervention undertaken in the DPP was of moderate intensity and might not be achievable for many patients. Participants in this study were volunteers who might have been more motivated than average family practice patients. Patients willing and ready to make lifestyle changes, however, should be encouraged to do so.

BOTTOM LINE

- Only lifestyle intervention had a significant effect on the resolution of metabolic syndrome over placebo (P=.002). By study completion, 18%, 23%, and 38% of the placebo, metformin, and lifestyle groups respectively no longer fit the criteria for metabolic syndrome.
- For those patients who are not ready to make lifestyle changes, we can offer them the option of starting metformin with the caveat that it appeared more effective in men.
- The health consequences of obesity, diabetes, and cardiovascular disease will overwhelm and cripple our health care system unless the current trend is stopped. This trial offers hopeful evidence regarding the effects of changing lifestyle factors.

POINTS SAILLANTS

- Seule l'intervention liée au mode de vie a eu des effets considérables par rapport au placebo sur le règlement du syndrome métabolique (P=,002). Au terme de l'étude, 18%, 23% et 38% respectivement des groupes prenant un placebo ou le metmorfin, ou ayant modifié leur mode de vie ne répondaient plus aux critères du syndrome métabolique.
- Nous pouvons offrir aux patients qui ne sont pas prêts à changer leur mode de vie l'option de commencer le metmorfin en se rappelant qu'il semble plus efficace chez l'homme.
- Les conséquences pour la santé de l'obésité, du diabète et des maladies cardiovasculaires vont surcharger et affaiblir notre système de santé, à moins de mettre un terme à la tendance actuelle. Cette étude offre des données scientifiques prometteuses quant aux effets produits par les changements au mode de vie.

Dr Emili *is a family physician practising in Dundas, Ont.* **Mr Abushomar** *and* **Ms Nair** *are PhD students in the Health Research Methodology program at McMaster University in Hamilton, Ont.*

Competing interests

None declared

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