Estrogen plus progestin reduced the incidence of diabetes in postmenopausal women with coronary heart disease

Kanaya AM, Herrington D, Vittinghoff E, et al. **Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial.** Ann Intern Med. 2003;138:1-9.

QUESTION

In postmenopausal women with coronary heart disease (CHD), does hormone replacement therapy (HRT) prevent an increase in fasting glucose level and reduce the incidence of diabetes in those at risk?

DESIGN

Randomized (allocation concealed*), blinded (participants, investigators, and outcome assessors),* placebo-controlled trial with a mean follow-up of 4.1 years.

SETTING

20 clinical centers in the United States.

PARTICIPANTS

2763 postmenopausal women < 80 years of age (mean age 67 y, 89% white) who had objectively documented CHD. Exclusion criteria included CHD event ≤ 6 months or sex hormone use ≤ 3 months before entry, serum triglyceride levels ≥ 3.39 mmol/L, fasting glucose levels ≥ 16.5 mmol/L, and uncontrolled hypertension. 2029 women (mean age 67 y, 91% white) without diabetes were followed for incident diabetes with a follow-up of 98%.

INTERVENTION

Women were allocated to HRT consisting of conjugated estrogen, 0.625 mg plus medroxyprogesterone acetate 2.5 mg once daily (n = 1380, including 999 without diabetes), or placebo (n = 1383, including 1030 without diabetes).

MAIN OUTCOME MEASURES

Fasting glucose levels and incidence of diabetes (self-report of diabetes or fasting serum glucose level ≥ 6.9 mmol/L).

MAIN RESULTS

Analysis was by intention to treat. Increase in fasting glucose levels from baseline was lower in the HRT group than in the placebo group (P = 0.001) (Table). Cumulative incidence of diabetes was lower in the HRT group than in the placebo group (Table).

CONCLUSION

In postmenopausal women with coronary heart disease, hormone replacement therapy slowed increase in fasting glucose level and reduced the incidence of diabetes in those at risk.

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For correspondence: Dr. A.M. Kanaya, University of California at San Francisco, San Francisco, CA, USA. E-mail alkak@itsa.ucsf.edu. ■

*See Glossary.

Hormone replacement therapy (HRT) vs placebo in postmenopausal women with coronary heart disease at 4.1 years†

Outcomes	HRT	Placebo	Difference between groups (95% CI)	
Mean change (increase) from baseline in FSGL (mmol/L)	0.028	0.266	–0.233 (–0.372 to –0.100)§	
			RRR (CI)	NNT (CI)
Incidence of diabetes	6%	10%	35% (12 to 52)	31 (18 to 103)

†FSGL = fasting serum glucose level based on 2763 participants; incidence of diabetes is based on 2029 participants at risk. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.
§Information provided by author.

COMMENTARY

The study by Kanaya and colleagues showed that HRT reduced the risk for onset of diabetes by 35% in women with both normal and impaired fasting glucose at baseline. Other interventions that reduce the incidence of type 2 diabetes in patients with insulin resistance (without risking the small but measurable increase in cardiovascular events associated with HRT) do exist.

In the trial by the Diabetes Prevention Program Research Group (1), a 7% reduction in body weight in obese persons plus walking (30 min, 5 d per wk) reduced the risk for onset of diabetes by 58%. Trials using such weight loss drugs as sibutramine and orlistat have shown similar reductions in the onset of diabetes (2).

Drugs that directly reduce insulin resistance can also prevent the onset of type 2 diabetes. Such drugs include metformin, which reduced the incidence of diabetes by 31% in the trial by the Diabetes Prevention Program Research Group (1); troglitazone, a thiazolidinedione, which decreased the incidence of type 2 diabetes by 50% in high-risk Hispanic women (3); and acarbose, which reduced the risk for diabetes in participants with impaired glucose tolerance by 25% (4). Other drugs, including pravastatin (5), ramipril (6), and losartan (7), have been found to decrease the risk for type 2 diabetes.

Clearly HRT is not the method of choice to reduce the onset of type 2 diabetes. If pharmaceuticals are chosen rather than the more powerful lifestyle changes, one should choose drugs proven to decrease cardiovascular risk as well as type 2 diabetes. Such drugs include metformin, ramipril, losartan, and pravastatin.

Donald A. Smith, MD, MPH
Mount Sinai Medical Center
New York, New York, USA

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