Phosphodiesterase 5 Inhibition Improves β-Cell Function in Metabolic Syndrome

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OBJECTIVE — This study tested the hypothesis that phosphodiesterase 5 inhibition alone or in combination with ACE inhibition improves glucose homeostasis and fibrinolysis in individuals with metabolic syndrome.

RESEARCH DESIGN AND METHODS — Insulin sensitivity, β-cell function, and fibrinolytic parameters were measured in 18 adults with metabolic syndrome on 4 separate days after a randomized, crossover, double-blind, 3-week treatment with placebo, ramipril (10 mg/day), tadalafil (10 mg o.d.), and ramipril plus tadalafil.

RESULTS — Ramipril decreased systolic and diastolic blood pressure, ACE activity, and angiotensin II and increased plasma renin activity. Ramipril did not affect insulin sensitivity or β-cell function. In contrast, tadalafil improved β-cell function ($P = 0.01$). This effect was observed in women (331.9 ± 209.3 vs. 154.4 ± 48.0 32 $\mu \cdot \text{mmol}^{-1} \cdot \text{l}^{-1}$, respectively, for tadalafil treatment vs. placebo; $P = 0.01$) but not in men. There was no effect of any treatment on fibrinolysis.

CONCLUSIONS — Phosphodiesterase 5 inhibition may represent a novel strategy for improving β-cell function in metabolic syndrome.

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Metabolic syndrome affects over 20% of U.S. adults, predicts diabetes, and will soon overtake smoking as the premier cardiovascular risk factor (1). Progression to type 2 diabetes results from impaired insulin sensitivity and pancreatic β-cell dysfunction (2,3). ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may decrease diabetes in high-risk individuals (4). These agents can improve insulin sensitivity by preventing inhibitory effects of angiotensin II on GLUT4 translocation (5) or improve insulin secretion by preventing angiotensin II type 1 receptor–dependent inhibition of insulin release (6).

Nitric oxide (NO) may also contribute to salutary effects of ACEIs and ARBs on glucose homeostasis (7). NO stimulates muscle glucose uptake through cyclic guanosine monophosphate (cGMP) (7). In mice, inhibiting cGMP degradation by phosphodiesterase 5 increases insulin sensitivity and muscle glucose uptake (8). cGMP decreases apoptosis and increases intracellular calcium in pancreatic β-cells, suggesting an insulinotropic effect (9,10). We tested the hypothesis that decreasing degradation of cGMP would enhance any effect of ACE inhibition on insulin sensitivity or β-cell function in humans.

RESEARCH DESIGN AND METHODS

— Subjects with metabolic syndrome (National Cholesterol Education Program criteria) participated in a double-blind, randomized, and placebo-controlled crossover study.

Each subject was studied four times (see supplementary Fig. A1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc08-1862/DC1). Antihypertensive medications were withdrawn 3 weeks before the study. Participants were then randomized to one of four 3-week treatments (placebo plus placebo, ramipril [10 mg/day] plus placebo, tadalafil [10 mg o.d.] plus placebo, and ramipril plus tadalafil) separated by a 1-week washout period.

During the last week of treatment, subjects ate a nitrate-, sodium-, and calorie-controlled diet. On the last day, they collected a 24-h urine sample and fasted overnight. At 0730 h, supine blood pressure and heart rate were measured thrice, 2 min apart. Blood was drawn via venous catheter for plasma renin activity (PRA), ACE activity, angiotensin II, aldosterone, fibrinolytic parameters, NO metabolites, L-citrulline, L-arginine, and cGMP.

At 0800 h, subjects underwent a frequently sampled intravenous glucose tolerance test (additional information available in the online appendix). Insulin sensitivity index, glucose effectiveness index, homeostasis model assessment of insulin resistance, and β-cell function were calculated using a modified version of minimal model (MINMOD) formulas. Acute insulin response to glucose (AIR_g) was assessed from the area under the insulin curve for the first 10 min following dextrose infusion. Because AIR_g disregards changes in insulin sensitivity, we used disposition index, calculated from insulin sensitivity and AIR_g, as a more reliable indicator of β-cell function (2).

RESULTS

— Eighteen subjects completed the study. Characteristics can be found in supplementary Tables A1 and A2.

Hemodynamic and renin-angiotensin effects

Sodium excretion was similar during all treatments (supplementary Table A3). Ramipril significantly increased PRA and decreased ACE activity and angiotensin II (supplementary Table A3). Tadalafil did not affect the renin-angiotensin-aldosterone system or alter effects of ramipril.

Ramipril reduced systolic ($P = 0.01$) (Fig. 1) and diastolic blood pressure ($P < 0.001$). Tadalafil did not affect blood pressure but tended to enhance the

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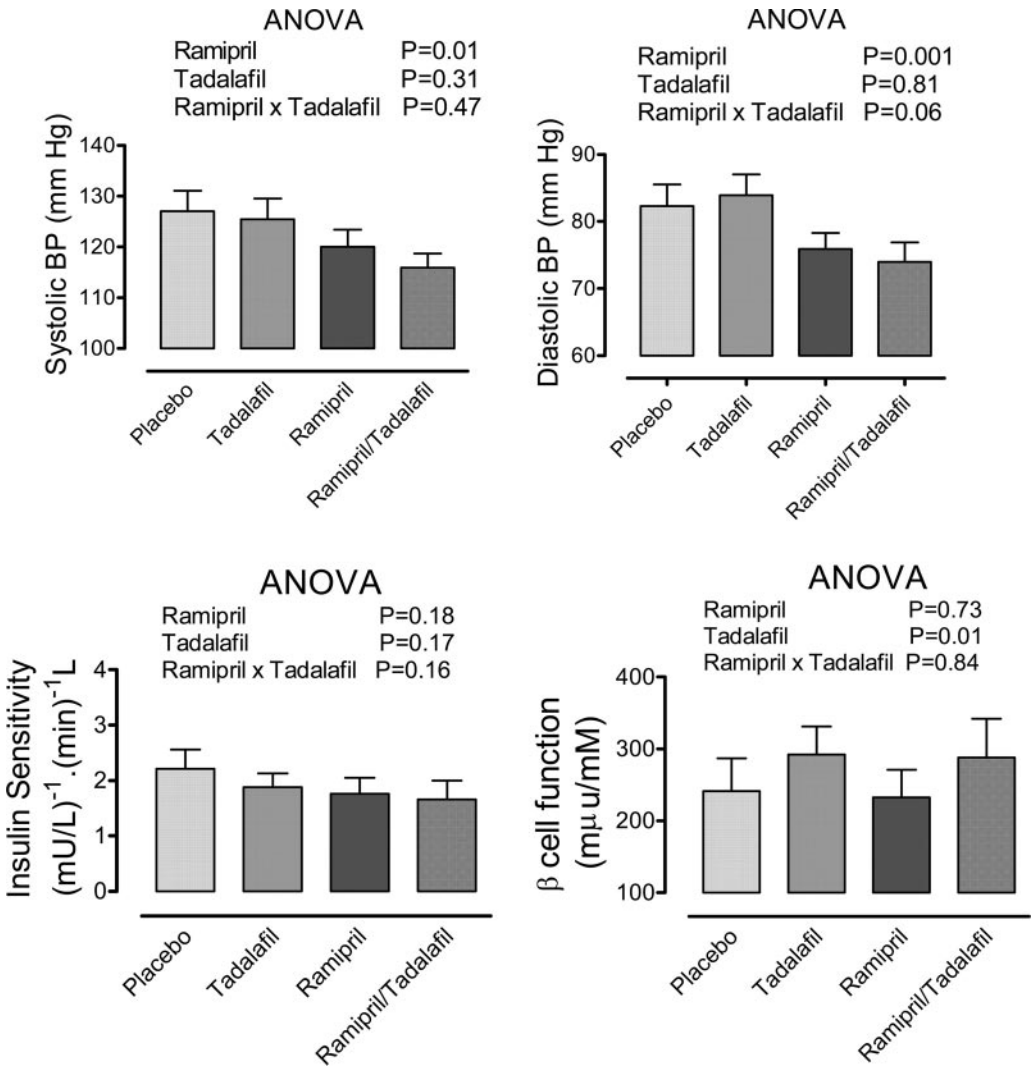

Figure 1—*Effect of treatment on systolic blood pressure (BP), diastolic blood pressure, insulin sensitivity, and β-cell function. Sex and race were included as covariates in the ANOVA. For β-cell function, data are presented as estimated marginal means after controlling for sex.*

ramipril effect on diastolic blood pressure ($P = 0.06$ for interaction, controlling for sex and race). No treatments impacted heart rate.

Glucose homeostasis

Neither ramipril nor tadalafil affected insulin sensitivity (Fig. 1). No treatments altered glucose effectiveness, a measure of insulin-independent glucose disposal (0.017 ± 0.006, 0.017 ± 0.008, 0.017 ± 0.009, and 0.015 ± 0.007 min^{-1} for placebo, tadalafil, ramipril, and ramipril plus tadalafil, respectively).

Ramipril did not affect β-cell function. In contrast, tadalafil significantly improved β-cell function after controlling for sex ($P = 0.01$) (Fig. 1) or baseline fasting glucose ($P = 0.05$). In a subgroup analysis, tadalafil improved β-cell function in women (154.4 ± 48.0, 331.9 ± 209.3, 229.1 ± 202.1, and 259.7 ± 95.8 $\mu \cdot mmol^{-1} \cdot l^{-1}$ during placebo, tadalafil, ramipril, and ramipril plus tadalafil treatment, respectively; $P = 0.01$ for tadalafil effect) but not in men. There was a trend toward improved β-cell function during tadalafil treatment in individuals with baseline fasting hyperglycemia (195.3 ± 103.1, 278.7 ± 114.0, 157.2 ± 52.6, and 210.6 ± 72.3 $\mu \cdot mmol^{-1} \cdot l^{-1}$ during placebo, tadalafil, ramipril, and ramipril plus tadalafil treatment, respectively; $P = 0.06$ for tadalafil) but not in subjects with normal fasting glucose. There was no effect of race and no interactive effect of ramipril or tadalafil on β-cell function.

Ramipril ($P = 0.02$) and tadalafil ($P = 0.02$) improved the disposition index in women but not in men after controlling for fasting glucose. This was attributable to a synergistic effect of ramipril and tadalafil on the disposition index ($1{,}001.8 \pm 909.5$, 977.8 ± 728.5, $1{,}308.8 \pm 976.2$, and $1{,}982.2 \pm 1{,}982.2$ units during placebo, tadalafil, ramipril, and ramipril plus tadalafil, respectively; $P = 0.05$ for ramipril plus tadalafil).

CONCLUSIONS — The phosphodiesterase 5 inhibitor tadalafil, alone or in combination with ramipril, improved basal and glucose-stimulated β-cell function. The latter effect was independent of insulin sensitivity, as indicated by improvement in the disposition index (2).

Metabolic syndrome, an insulin-resistant state, frequently progresses to type 2 diabetes. Loss of β-cell function and impaired insulin sensitivity both contribute to the development of diabetes (2). β-Cell dysfunction may play a greater role

than previously appreciated in that pancreatic β-cell apoptosis precedes overt diabetes in high-risk individuals (10) and surgical reduction of pancreatic mass causes impaired glucose tolerance and diabetes (11).

To our knowledge, no prior human or animal studies have reported an effect of phosphodiesterase 5 inhibition on β-cell function. Pancreatic β-cells express endothelial NO synthase (12). Previous studies provide conflicting data, however, regarding the effect of NO on β-cell function, with some suggesting that NO suppresses insulin secretion (13,14) and others indicating that NO enhances insulin secretion (12,15).

Tadalafil improved islet cell function in women studied but not in men. A higher frequency of fasting hyperglycemia among women with metabolic syndrome may have confounded this sex difference. Alternatively, women may be more sensitive than men to decreased cGMP degradation. In support of this possibility, three of six women studied, but no men, reported muscle aches during tadalafil treatment.

ACEIs improve glucose homeostasis or decrease diabetes incidence in clinical trials (4). Although ACEIs and ARBs improve glucose uptake and/or insulin secretion in vitro and in rodents, studies in humans provide mixed data regarding their effects on insulin resistance (4). We did not detect an effect of ramipril on insulin sensitivity or β-cell function but did detect an effect of ramipril on disposition index in women. Tadalafil enhanced this effect, again suggesting cGMP-dependent improvement in insulin secretion.

Tadalafil improves β-cell function in metabolic syndrome. Studies are needed to determine whether the effect of tadalafil is limited to women or related to the magnitude of hyperglycemia. Given the increasing role attributed to β-cell dysfunction in the pathogenesis of type 2 diabetes, these data suggest a novel therapeutic intervention in a high-risk population.

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