Phosphodiesterase 5 Inhibition Improves Beta Cell Function in the Metabolic Syndrome

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

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Objective: This study tested the hypothesis that phosphodiesterase 5 inhibition alone or in combination with angiotensin-converting enzyme inhibition improves glucose homeostasis and fibrinolysis in individuals with metabolic syndrome.

Research Design and Methods: Insulin sensitivity, beta cell function and fibrinolytic parameters were measured in eighteen adults with metabolic syndrome on four separate days after randomized, crossover, double-blind, 3-week treatment with placebo, ramipril (10mg/d), tadalafil (10mg/od), and ramipril+tadalafil.

Results: Ramipril decreased systolic and diastolic blood pressure, angiotensin-converting enzyme activity and angiotensin II and increased plasma renin activity. Ramipril did not affect insulin sensitivity or beta cell function. In contrast, tadalafil improved beta cell function (p=0.01). This effect was observed in women (331.9±209.3µM/mM during tadalafil versus 154.4±48.0µM/mM during 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 beta cell function in metabolic syndrome.
Metabolic syndrome affects over 20 percent of United States adults, predicts diabetes and will soon overtake smoking as the premier cardiovascular risk factor.\(1\)

Progression to type 2 diabetes mellitus (T2DM) results from impaired insulin sensitivity and pancreatic beta cell dysfunction.\(2; 3\) Angiotensin-converting enzyme 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 (Ang) II on glucose transporter 4 translocation\(5\) or improve insulin secretion by preventing \(\text{AT}_1\) 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 (PDE5) increases insulin sensitivity and muscle glucose uptake.\(8\) cGMP decreases apoptosis and increases intracellular calcium in pancreatic beta 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 beta cell function in humans.

METHODS

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

Each subject was studied 4 times (see Figure A1 in the online appendix at http://care.diabetesjournals.org).

Antihypertensive medications were withdrawn 3 weeks prior to study. Participants were then randomized to one of four 3-week treatments [placebo+placebo, ramipril(10mg/d)+placebo, tadalafil(10mg/od)+placebo, and ramipril+tadalafil] separated by one-week washout.

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

At 0800, subjects underwent frequently-sampled intravenous glucose tolerance test (additional information is available in the online appendix). Insulin sensitivity index \((S_I)\), glucose effectiveness \((S_g)\), HOMA insulin resistance and beta cell function were calculated using a modified version of MINMOD. Acute insulin response to glucose (AIRg) was assessed from the area-under-the-insulin-curve for the first 10 minutes following dextrose infusion. Because AIRg disregards changes in insulin sensitivity, we used disposition index (DI), calculated from insulin sensitivity and AIRg, as a more reliable indicator of beta cell function.\(2\)

RESULTS

Eighteen subjects completed the study. Characteristics appear in Tables A1 and A2 of the online appendix.

Hemodynamic and Renin-Angiotensin Effects—Sodium excretion was similar during all treatments (see Table A3, in the online appendix). Ramipril significantly increased PRA and decreased ACE activity and Ang II (Table A3 in the online appendix).
Tadalafil did not affect the renin-angiotensin-aldosterone system or alter effects of ramipril. Ramipril reduced systolic (p=0.01, Figure) and diastolic BP (p<0.001). Tadalafil did not affect BP, but tended to enhance the ramipril effect on diastolic BP (p=0.06 for interaction, controlling for gender and race). No treatment impacted heart rate.

Glucose Homeostasis—Neither ramipril nor tadalafil affected insulin sensitivity (Figure). No treatment altered glucose effectiveness, a measure of insulin-independent glucose disposal (0.017±0.006min⁻¹, 0.017±0.008min⁻¹, 0.017±0.009min⁻¹, 0.015±0.007min⁻¹ for placebo, tadalafil, ramipril and ramipril+tadalafil, respectively).

Ramipril did not affect beta cell function. In contrast, tadalafil significantly improved beta cell function after controlling for gender (p=0.01) (Figure) or baseline fasting glucose (p=0.05). In subgroup analysis, tadalafil improved beta cell function in females (154.4±48.0μu/mM, 331.9±209.3μu/mM, 229.1±202.1μu/mM, and 259.7±95.8μu/mM during placebo, tadalafil, ramipril, ramipril+tadalafil, respectively; p=0.01 for tadalafil effect), not in males. There was a trend toward improved beta cell function during tadalafil in individuals with baseline fasting hyperglycemia (195.3±103.1μu/mM, 278.7±114.0μu/mM, 157.2±52.6μu/mM, and 210.6±72.3μu/mM during placebo, tadalafil, ramipril, and ramipril+tadalafil, respectively; p=0.06 for tadalafil) but not in those with normal fasting glucose. There was no effect of race and no interactive effect of ramipril and tadalafil on beta cell function.

Ramipril (p=0.02) and tadalafil (p=0.02) improved the disposition index in females, but not males, after controlling for fasting glucose. This was attributable to synergistic effect of ramipril and tadalafil on the disposition index (1001.8±909.5u, 977.8±728.5u, 1308.8±976.2u, 1982.2±1982.2u during placebo, tadalafil, ramipril and ramipril+tadalafil, respectively; p=0.05 for ramipril x tadalafil).

DISCUSSION

The PDE5 inhibitor tadalafil, alone or in combination with ramipril, improved basal and glucose-stimulated beta 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 T2DM. Loss of beta cell function and impaired insulin sensitivity both contribute to the development of diabetes.(2) Beta cell dysfunction may play a greater role than previously appreciated, in that pancreatic beta 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 PDE5 inhibition on beta cell function. Pancreatic beta cells express endothelial NO synthase (eNOS). (12) Previous studies provide conflicting data, however, regarding the effect of NO on beta cell function, with some suggesting that NO suppresses insulin secretion(13; 14) and others indicating 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 the women with metabolic syndrome may have confounded this gender 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 mellitus in clinical trials.(4) Although ACEIs and ARBs improve glucose uptake and/or insulin secretion in

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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 beta 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 beta cell function in the 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 beta cell dysfunction in the pathogenesis of T2DM, these data suggest a novel therapeutic intervention in a high-risk population.

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REFERENCES
Figure Legend
Effect of treatment on systolic (SBP), diastolic blood pressure (DBP), insulin sensitivity and beta cell function. Gender and race were included as covariates in the ANOVA. For beta cell function data are presented as estimated marginal means after controlling for gender.