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Effect of Phosphodiesterase Inhibition on Insulin Resistance in Obese Individuals

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Background—Obesity is associated with cardiometabolic disease, including insulin resistance (IR) and diabetes. Cyclic guanosine monophosphate (cGMP) signaling affects energy balance, IR, and glucose metabolism in experimental models. We sought to examine effects of phosphodiesterase-5 inhibition with tadalafil on IR in a pilot study of obese nondiabetic individuals.

Methods and Results—We conducted a randomized, double-blinded, placebo-controlled trial of adults age 18 to 50 years with obesity and elevated fasting insulin levels (≥10 μU/mL). Participants were randomized to tadalafil 20 mg daily or placebo for 3 months. Oral glucose tolerance tests were performed, and the effect of tadalafil on IR was examined. A total of 53 participants (mean age, 33 years; body mass index [BMI], 38 kg/m²) were analyzed, 25 randomized to tadalafil and 28 to placebo. In the overall sample, measures of IR did not differ between tadalafil and placebo groups at 3 months. However, in individuals with severe obesity (BMI ≥36.2 kg/m²), tadalafil use was associated with improved IR (homeostatic model assessment for IR), compared to placebo (P=0.02, respectively). Furthermore, one measure of β-cell compensation for IR (oral disposition index) improved with tadalafil in the overall sample (P=0.009) and in the subgroup with severe obesity (P=0.01).

Conclusion—Results of this pilot study did not show improvements in IR with tadalafil, compared to placebo. However, tadalafil may have favorable effects on β-cell compensation, particularly in individuals with severe obesity. Future studies evaluating the potential metabolic benefits of cGMP modulation in obesity are warranted.

Clinical Trial Registration—URL: ClinicalTrials.gov. Unique Identifier: NCT01444651. (J Am Heart Assoc. 2014;3:e001001 doi: 10.1161/JAHA.114.001001)

Key Words: cGMP • insulin resistance • obesity • phosphodiesterase type 5 inhibition

One in 4 U.S. adults is obese, and predictions suggest that, by 2030, more than half of the population will be obese.1 With the obesity epidemic there has been a concomitant doubling in the incidence of diabetes mellitus (DM) over the last 30 years, a trend most pronounced in those with body mass index (BMI) ≥30 kg/m²,2 underscoring the close link between obesity and metabolic disease.

Interestingly, obese individuals have lower natriuretic peptide levels, which, in turn, appear to be associated with greater insulin resistance (IR), regardless of BMI.3 Natriuretic peptides drive lipolysis in human adipocytes,4 and higher circulating levels in humans are associated with favorable visceral adiposity.5 In experimental studies, B-type natriuretic peptide (BNP) transgenic (Tg) mice were protected against...
obesity and IR, effects that are mediated by the cyclic guanosine monophosphate (cGMP)-signaling cascade. Furthermore, modulation of nitric oxide (NO) upstream of cGMP also has been shown to affect insulin action. Taken together, these data suggest that cGMP signaling affects energy balance, IR, and glucose metabolism. The mechanisms underlying metabolic effects of cGMP remain uncertain, but may be related to both vasodilation, resulting in increased perfusion and substrate delivery to metabolically active skeletal muscle as well as direct effects on peripheral glucose handling.

Sildenafil and tadalafil are phosphodiesterase type 5 (PDE5) inhibitors that prevent cGMP degradation and may represent a novel therapeutic approach in metabolic disease. In mice fed a high-fat diet (HFD), sildenafil administration increased energy expenditure and reduced IR. In a study of 18 individuals with metabolic syndrome (MetS), tadalafil administration (10 mg every other day for 3 weeks) was associated with improved pancreatic β-cell function, as assessed by oral glucose tolerance testing, when compared to placebo, and there were also modest trends toward reduced IR. However, changes in IR and other metabolic characteristics may take longer than 3 weeks to become evident. Furthermore, it has been shown that higher doses of tadalafil lead to greater plasma concentrations of tadalafil and thus may have greater therapeutic effects. Accordingly, we performed a randomized, double-blinded, controlled trial to examine the effects of 3 months of high-dose tadalafil treatment on IR and secretion in obese individuals.

Methods

Study Design

We conducted a randomized, double-blinded, placebo-controlled trial at Massachusetts General Hospital (ClinicalTrials.gov Identifier NCT01444651; Boston, MA). Adults ages 18 to 50 years with obesity, defined as BMI ≥27 kg/m² and elevated fasting insulin levels ≥10 μU/mL, were included. Participants were excluded if they had a history of DM, hypertension, cardiac, renal, or liver disease, or any contraindications to receiving tadalafil, including screening systolic blood pressure <100 mm Hg, current therapy with nitrates or medications altering cytochrome P450 3A4 (CYP3A4), or history of nonarteritic ischemic optic neuropathy (please see Table 1 for full inclusion and exclusion criteria). Participants were randomized in a 1:1 fashion to receive either tadalafil 20 mg orally once a day or matching placebo for a total of 3 months, and randomization was stratified by sex. Medical history, anthropometrics, physical exam including seated blood pressure, and fasting blood draws were obtained at baseline, 6 weeks, and 3 months. All participants provided written informed consent, and the study was approved by the Partners Human Research Committee.

Laboratory Measurements

Participants underwent a standard 2-hour 75-g oral glucose tolerance test (OGTT) after a 12-hour overnight fast at the baseline and 3-month visits. Blood samples were obtained at 0-, 30-, 60-, 90-, and 120-minute time points. Plasma glucose measurements were obtained immediately using the hexokinase/glucose-6-phosphate dehydrogenase method (Roche Diagnostics GmbH, Mannheim, Germany) using a fully automated chemistry analyzer (Roche e501), with an interassay coefficient of variation of <2% at both low and high concentrations (60 and 338 mg/dL, respectively). The remainder of fasting EDTA plasma specimens were obtained

Table 1. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>Adults ages 18 to 50 years</td>
</tr>
<tr>
<td>Obesity (BMI ≥27 kg/m²)</td>
</tr>
<tr>
<td>Fasting insulin levels ≥10 μU/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>Systolic blood pressure &lt;100, &gt;150 mm Hg</td>
</tr>
<tr>
<td>Current antihypertensive medication use</td>
</tr>
<tr>
<td>Current use of organic nitrates</td>
</tr>
<tr>
<td>Current use of phosphodiesterase 5 inhibitors (sildenafil, tadalafil, vardenafil)</td>
</tr>
<tr>
<td>History of reaction to phosphodiesterase 5 inhibitors</td>
</tr>
<tr>
<td>Known HIV infection</td>
</tr>
<tr>
<td>Use of medications that strongly alter CYP3A4 activity</td>
</tr>
<tr>
<td>History of myocardial infarction, angina, uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, or seizure</td>
</tr>
<tr>
<td>Known nonarteritic ischemic optic neuropathy</td>
</tr>
<tr>
<td>History of hearing loss</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate &lt;60 mL/min per 1.73 m²</td>
</tr>
<tr>
<td>Hepatic transaminase (AST and ALT) levels greater than 3 times the upper limit of normal</td>
</tr>
<tr>
<td>Known pregnancy or those unwilling to avoid pregnancy during the course of the study</td>
</tr>
<tr>
<td>History of priapism</td>
</tr>
<tr>
<td>Use in excess of 4 alcoholic drinks daily</td>
</tr>
<tr>
<td>History of diabetes mellitus or use of anti diabetic medications</td>
</tr>
<tr>
<td>Known anemia (men, hematocrit &lt;36%; women, hematocrit &lt;38%)</td>
</tr>
<tr>
<td>Fasting insulin levels ≥100 μU/mL at time of oral glucose tolerance test</td>
</tr>
</tbody>
</table>

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CYP3A4, cytochrome P450 3A4; HIV, human immunodeficiency virus.
Assessments of IR and β-Cell Function

The primary outcome measure of the study was change in IR, as assessed by the homeostatic model assessment of insulin resistance (HOMA-IR) in the fasting state. We examined a second measure of IR, the Matsuda index, which utilizes measurements from the fasting state and 4 additional time points following an oral glucose load. Additional outcome measures in this pilot study included estimates of the insulinogenic index, which utilizes measurements from the fasting state and 30 minutes following the oral glucose load; the oral disposition index, which corrects the insulinogenic index by fasting insulin (thereby assessing the β-cell ability to compensate for IR), and the Matsuda disposition index, which corrects the insulinogenic index by the Matsuda sensitivity index. Details of calculations are summarized in Table 2.

Assessment of Vascular Function

Participants underwent noninvasive assessment of endothelial function at baseline and 3 months using reactive hyperemia peripheral arterial tonometry (EndoPAT device; Itamar Medical Ltd., Tokyo, Japan). This technique allows measurement of changes in digital pulse volume during reactive hyperemia and has been validated against invasive measures of endothelial function. In brief, participants were asked to refrain from smoking or caffeine consumption for ≥8 hours, and testing was conducted in the fasting state. Peripheral arterial tonometry probes were placed on both index fingers. After a 5-minute equilibration period, a blood pressure cuff was inflated to 200 mm Hg and kept inflated for 5 minutes. The cuff was then rapidly deflated in order to record the reactive hyperemic response, and reactive hyperemia index was calculated using the post-/preocclusion pulse volume ratio.

Applanation tonometry was used to determine arterial stiffness noninvasively (SphygmoCor device; AtCor Medical, Sydney, Australia). In brief, pulse wave analysis was performed on the right radial artery, and 10 sequential waveforms were acquired. Central aortic pressures and wave forms were obtained using a validated generalized transfer function. Ten waveforms were averaged to obtain augmentation pressure, the augmentation index (the ratio of augmentation pressure to pulse pressure), the augmentation index normalized to a heart rate of 75 bpm, and time to return of the reflected wave.

Statistical Analyses

Baseline characteristics in the tadala and placebo groups were summarized and compared using 2-sample t tests for normally distributed variables, Wilcoxon’s rank-sum tests for non-normally distributed variables, or the chi-square test statistic, as appropriate. We noted 3 extreme insulin outliers with insulin levels >6 standard deviations above the group mean (≥100 μU/mL). Because OGTT results cannot be interpreted in the nonfasting state, participants with a pre-OGTT insulin level ≥100 μU/mL were deemed nonfasting and excluded from the final analysis (n=3; Figure 1).

The primary outcome of this pilot study was the difference in IR, as measured by HOMA-IR, in the tadala versus placebo groups. Assuming a sample size of 75 randomized participants, we would have 80% power to detect a 0.7 standard deviation difference in the primary outcome between groups at P=0.05.

In order to evaluate the primary outcome of change in IR in the tadala compared to placebo groups, the change in HOMA-IR (“delta”) over the treatment course was calculated as the 3-month minus the baseline value. The effect of

<table>
<thead>
<tr>
<th>Biological Relevance</th>
<th>Glycemic Trait</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin resistance</td>
<td>HOMA-IR</td>
<td>(Fasting glucose × fasting insulin)/405</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Matsuda sensitivity index</td>
<td>10 000/SQRT (faster glucose × fasting insulin × (mean glucose from time 30, 60, 90, 120) × (mean insulin at time 30, 60, 90, 120))</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>Insulinogenic index</td>
<td>(Fasting insulin – insulin at time 30)/(fasting glucose – glucose at time 30)</td>
</tr>
<tr>
<td>Composite</td>
<td>Oral disposition index</td>
<td>Insulinogenic index/fasting insulin</td>
</tr>
<tr>
<td>Composite</td>
<td>Disposition index</td>
<td>Matsuda sensitivity index × insulinogenic index</td>
</tr>
</tbody>
</table>

Glucose expressed in mg/dL, insulin expressed in μU/mL. HOMA-IR indicates homeostatic model assessment of insulin resistance.
tadalafil versus placebo on the delta was examined using multivariable linear regression, adjusting for baseline values of a given trait. In secondary analyses, models were further adjusted for age and sex. Similar analyses were performed to assess the effect of tadalafil on β-cell function estimates, blood pressure, BMI, and vascular measures. In further exploratory analyses, we stratified our sample by median BMI and examined the effect of tadalafil on estimates of IR and β-cell function in participants with BMI ≥36.2 versus <36.2 kg/m². We tested for sex by treatment as well as weight category by treatment interactions. We examined the area under the curve (AUC) for glucose and insulin response curves following OGTT using the trapezoidal method. We calculated both the total AUC, as well as the incremental AUC, after accounting for baseline values. Treatment group-specific differences between 3-month and baseline AUC were examined using repeated-measures ANOVA. Because of outliers for the oral and Matsuda disposition indices, a sensitivity analysis was conducted after exclusion values outside of ±3 standard deviations around the mean.

We checked for a hyperbolic relationship between insulin sensitivity (as measured by Matsuda sensitivity index) and measures of β-cell function (fasting insulin and insulinogenic index), as previously reported. In brief, measures were natural log-transformed and linear regression used to determine the slope of the regression line. The association was deemed hyperbolic if the 95% confidence interval (CI) of slope of the regression line included −1. All analyses were conducted using SAS statistical software (version 9.1.3; SAS Institute Inc., Cary, NC).

Results

We screened 111 individuals, of whom 73 underwent randomization to receive tadalafil 20 mg daily versus matching placebo for the duration of 3 months (Figure 1). Of these, a total of 53 participants were included in the analysis, including 25 participants assigned to receive tadalafil and 28 to placebo. The 20 randomized participants excluded from the final analysis met the following criteria for early termination: 10 participants were lost to follow-up, 5 withdrew because of side effects (3 in the tadalafil group and 2 in the placebo group), 3 were excluded because of nonphysiological fasting insulin levels (defined as insulin ≥100 μU/mL, thought to be a result of the nonfasting state, rendering OGTT data uninterpretable), and 2 were excluded because of missing data.

Baseline characteristics were well balanced in both groups (Table 3), with a mean age of 33±9 years and 38% women. Participants were obese with a mean BMI of 37.7±6.8 kg/m², with 27% individuals classified as severely obese (BMI between 35 and 40 kg/m²) and 35% morbidly obese (BMI >40 kg/m²). BMI ranges were 27.7 to 53.5 kg/m² in the tadalafil group and 27.4 to 50.8 kg/m² in the placebo group.
Participants had elevated HOMA-IR (3.7±3.4 mg*μU/dL*mL) and normal fasting glucose concentrations (85±11 mg/dL).

Changes in IR and β-Cell Function With Tadalafil Treatment

There were no differences in the AUCs or corrected AUCs for insulin and glucose between the 3-month and baseline values for either the tadalafil or placebo groups (P>0.05 for all).

Baseline and 3-month values of IR and secretion traits are presented by treatment group in Table 4. Measures of IR were not statistically different between tadalafil and placebo groups (P>0.05 for all; Table 4), though trends appeared to favor tadalafil therapy. For example, HOMA-IR worsened in the placebo group, whereas there was relatively little change in the tadalafil group. Similarly, IR by the assessment of Matsuda index increased in the tadalafil group, whereas it decreased in the placebo group. Participants in the tadalafil group had improved overall β-cell function, as estimated by the oral disposition index, which assesses the ability of the β-cell to compensate for IR, improved in the tadalafil group compared to the placebo group (Figure 2; P=0.009). Similarly, the Matsuda disposition index supported a trend toward benefit in the tadalafil group (P=0.05; Table 4). The insulinogenic index, an estimate of β-cell function that did not assess insulin secretion in the context of IR, was not different in the treatment groups. Secondary analyses further adjusting for age and sex did not materially alter the results. There were no significant sex by treatment interactions (P>0.05 for all). A sensitivity analysis excluding outliers ±3 standard deviations outside the mean demonstrated improved oral disposition index and Matsuda disposition index in the tadalafil, compared to the placebo, group (P=0.003 for both).

We evaluated the association between measures of insulin sensitivity and β-cell function. Specifically, in a linear regression model with log-transformed Matsuda sensitivity index as the independent variable, and log-transformed fasting insulin as the dependent variable, the slope of the regression line was −0.87 (95% CI, −1.03 to −0.71), suggesting a hyperbolic relationship.

Tadalafil Effects on IR and β-Cell Function Were Most Pronounced in the Severely Obese

In exploratory analyses, we stratified our sample by median BMI. Participants with BMI ≥36.2 kg/m² were more insulin resistant at baseline with a mean HOMA-IR of 4.6±3.2, compared with 2.9±3.4 mg*μU/dL*mL in participants with BMI <36.2 kg/m². In the severely obese, tadalafil treatment was associated with improved IR, as estimated by HOMA-IR (P=0.02) and the Matsuda sensitivity index (P=0.04; Table 5). Tadalafil also appeared to have a beneficial effect on β-cell function when corrected for level of IR, compared to placebo.
in the severely obese \((P=0.01\) for oral disposition index; \(P=0.007\) for Matsuda disposition index). In contrast, no significant differences were noted between the tadalafl and placebo groups among participants with BMI <36.2 kg/m\(^2\). There were no significant interactions of BMI subgroup and treatment assignment \((P>0.10\) for all).

**Tadalafl Effect on Clinical, Vascular, and Laboratory Measures**

Individuals assigned to tadalafl had a trend toward lower systolic and diastolic blood pressures, when compared to placebo \((P=0.08\) and \(P=0.09\), respectively). There were no significant differences in change in BMI or vascular measures between treatment groups (Table 4). There were no differences in plasma cGMP concentrations between individuals treated with tadalafl, compared to placebo, either at baseline or 3-month follow-up.

Tadalafl was tolerated well by most participants. Five participants in the tadalafl group (20%) and 1 participant in the placebo group complained of headaches during the course of the study, and 3 participants in the tadalafl group reported back or leg pain. A total of 3 participants withdrew from the tadalafl group (1 because of headache and 2 because of back/leg aches), and 2 participants withdrew from the placebo group (1 because of blurry vision and 1 because of arm pain).

**Discussion**

We conducted a randomized, placebo-controlled pilot study to examine the effect of PDE5 inhibition on glucose metabolism in obese individuals. Oral tadalafl at 20 mg daily was reasonably well tolerated for the 3-month study. Though we found no significant improvements in estimates of IR after 3 months of
tadalafil treatment, compared to placebo, estimates of β-cell function, when viewed in the context of IR, improved in the tadalafil group, when compared to placebo.

Notably, when stratified by BMI in subgroup analyses, we found that tadalafil treatment was associated with improved measures of IR, compared to placebo, among severely obese participants. Though the results of subgroup analyses in our modest sample have to be viewed as exploratory, this finding warrants further study in the future.

The oral disposition index estimates pancreatic β-cell function adjusted for a given background of insulin sensitivity. In prospective studies, abnormalities in the disposition index precede the development of clinical diabetes and reflect inadequate insulin release early in the disease process. Our study findings suggest that tadalafil may have favorable metabolic effects in obese insulin-resistant individuals even before the development of clinical diabetes, particularly in the severely obese.

The effect of tadalafil on β-cell function has previously been studied in a small human trial of 18 patients with MetS. In that study, tadalafil improved β-cell function in women, but not men, and no effects on IR were noted. In the current study, targeting participants with evidence of IR, we found trends both in improved IR and β-cell function. These differences may be the result of higher dose and longer duration of tadalafil treatment, compared to the previous study, reflecting short-versus long-term effects of phosphodiesterase inhibition.

The cGMP pathway appears to regulate glucose metabolism, both through upstream activation of NO or the natriuretic peptide receptor. Previous animal studies have demonstrated that inhibition or deficiency of NO leads to IR, and that NO itself augments insulin release. Similarly, BNP Tg mice fed an HFD were protected against IR. Furthermore, administration of sildenafil improved energy expenditure and reduced IR in a mouse model. Taken together, these data suggest that PDE5 inhibitors may improve glucose metabolism by preventing cGMP degradation within metabolically active tissues. The mechanisms by which cGMP improve glucose metabolism are not completely understood, and mechanistic inferences cannot be drawn from our pilot study. Previous experimental studies have implicated vasodilatory effects that may improve substrate delivery to skeletal muscle or direct effects on cellular glucose transport in skeletal muscle and vascular IR.

Though we did not observe changes in plasma concentrations

Table 5. Effect of Tadalafil on Indices of Insulin Resistance and β-Cell Function According to Degree of Obesity

<table>
<thead>
<tr>
<th></th>
<th>BMI &lt;36.2 kg/m² (n=26)</th>
<th></th>
<th>BMI ≥36.2 kg/m² (n=27)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta Estimate (SE)*</td>
<td>P Value</td>
<td>Beta Estimate (SE)*</td>
<td>P Value</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.59 (2.41)</td>
<td>0.81</td>
<td>−2.99 (1.16)</td>
<td>0.02</td>
</tr>
<tr>
<td>Matsuda sensitivity index</td>
<td>−0.08 (1.02)</td>
<td>0.94</td>
<td>2.05 (0.92)</td>
<td>0.04</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>0.78 (1.08)</td>
<td>0.48</td>
<td>1.30 (0.71)</td>
<td>0.08</td>
</tr>
<tr>
<td>Oral disposition index</td>
<td>1.43 (1.50)</td>
<td>0.35</td>
<td>3.98 (1.50)</td>
<td>0.01</td>
</tr>
<tr>
<td>Matsuda disposition index</td>
<td>6.62 (6.16)</td>
<td>0.29</td>
<td>7.16 (2.43)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HOMA-IR, homeostatic model assessment of insulin resistance.
*Beta estimates represent difference in (3-month/baseline) trait between the tadalafil and placebo group, adjusted for baseline value.
of cGMP, this may not fully reflect changes within metabolically active tissues.

Several limitations deserve mention. This was a pilot study, and our sample size may have limited our power to detect more modest effects. We observed favorable trends in IR derived from fasting and post–oral glucose load blood samples, rather than measures from more-intensive physiologic assessment. The hyperinsulinemic euglycemic clamp may have provided a more-precise estimate of insulin sensitivity. Still, the estimates used in this study are correlated with clamp-derived measures of IR.\textsuperscript{13,14,28} Future studies should undertake more-precise measurements of IR. More than half of our study sample was severely obese, and exploratory subgroup analyses suggested that potential benefits of tadalafl on glucose handling were more pronounced in the severely obese. This may limit the generalizability of our findings to broader populations, although the mean BMI in our study was comparable to a previous human study examining metabolic effects of tadalafl.\textsuperscript{10} We did not detect differences in plasma cGMP concentrations, which may be because of our modest sample size. It also may be that plasma cGMP concentrations do not necessarily reflect cGMP activity at the tissue level, or that cGMP concentrations need to be understood within the context of other signaling molecules, such as natriuretic peptides. Last, dose-response effects of tadalafl on metabolic traits are not known because only one dose was tested, and long-term effects are not known given the 3-month duration of the study.

In conclusion, we did not find a significant improvement in IR with tadalafl in obese individuals in our study. However, exploratory findings suggest that PDE5 inhibition may have favorable metabolic effects with regard to \(\beta\)-cell function when accounting for IR in obese individuals, particularly those with severe obesity. Though weight loss remains the mainstay of treatment for severe obesity, in light of rising rates of obesity and concomitant cardiometabolic disease, additional, well-powered studies evaluating potential metabolic benefits of cGMP modulation in obese individuals are warranted.

Acknowledgment

The authors thank Jonathan S. Williams, MD, of Brigham and Women’s Hospital for serving as the data safety monitor of the study.

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Disclosures

Dr Wang has served as a consultant for Pfizer, Inc.

References


