ELECTRONIC SUPPLEMENTARY MATERIAL (ESM)

ESM Text

Here, we report additional information on the eligibility criteria and study design that is required by the CONSORT checklist.

Inclusion Criteria:

- Body mass index (BMI) of 27-38 kg/m^2
- 18 - 40 years of age
- Ratio of waist-to-hip circumferences is either >0.84 ("apple"-type body shape) or <0.77 ("pear"-type body shape)
- Must be willing to drink deuterium-labeled water (^2H_2O) and undergo a drug intervention for 16 weeks
- If not using pharmaceutical (hormonal) contraception (i.e. birth control pills, vaginal ring, injections, implant, or skin patch), must agree to use a double barrier method as a form of birth control to prevent pregnancy
- If applicable, hormonal contraception must have been started at least 2 months before entering the study. If enrolled, subject must also agree not to alter hormonal birth control method, dose, or regimen throughout the duration of the study.

Exclusion Criteria:

- Significant changes in the diet or level of physical activity within the past month
- History of clinically diagnosed diabetes or a fasting blood glucose > 6.1 mmol/L
- Have heart, kidney, lung, thyroid, liver disease or abnormal liver enzymes that are, in the opinion of the medical investigator, clinically significant and represent a problem for study inclusion
- An average screening blood pressure >140/90 mmHg
- Self-reported positive test for human immunodeficiency virus, hepatitis B and hepatitis C
- Chronic use of systemic glucocorticoids, systemic adrenergic-stimulating agents, anti-psychotic/antidepressant medications, thiazoladinediones, and other medications that cause clinically significant weight gain, weight loss or are known to make changes in fat cell number/size. Contraceptive use acceptable.
- Smoking or use of tobacco products in the last 6 months
- Pregnancy or breastfeeding, or planned pregnancy for the upcoming 6 months
- Previous bariatric or other surgeries for obesity
- Use of over the counter or prescription weight loss products
- Diagnosed psychotic conditions.
- Been diagnosed with congestive heart failure or hemodynamically significant congenital heart defect
- Has been diagnosed with bladder cancer
- Has a history of swelling in arms, hands, feet, ankles or lower legs (if MI feels warranted).

Trial Dates: Participants were recruited and enrolled in the study from October 2011 to August 2016.

Important Changes to the Study Protocol After Trial Commencement: In order to enhance recruitment and enrollment, the WHR limits (>0.84 or <0.77) were removed to accept the full continuum of WHR.

Randomization: William Johnson, Ph.D., a statistician at Pennington Biomedical Research Center, used SAS v9.4 to generate the block (size 4) randomisation code sequence with a 1:1 allocation ratio. The randomisation sequence was stored in password-protected files. The study coordinator enrolled the participants, and the PBRC pharmacist assigned participants to interventions. The participants and all other study staff involved in assessing and analyzing outcomes were blinded throughout the intervention. All assessments were conducted blinded.

Adverse Events. There were no serious adverse events reported in the study. Forty-four adverse events were reported that were possibly related to the study intervention, with 19 occuring in the placebo group and 25 in the pioglitazone group. Both the placebo group and the pioglitazone group reported events related to study procedures including: dermatologic and pain from adipose tissue biopsies (6 vs. 7); dizziness and headaches from the $^{2}H_{2}O$-labeled water (8 vs. 16); and dermatologic and gastrointestinal from the study drug (4 vs. 2). Participants also reported instances of gastrointestinal (2 vs. 0), nausea (1 vs. 0), edema (1 vs. 0), chest pain (1 vs. 0), weight gain (1 vs. 0), and flatulence (1 vs. 0).

ESM Table 1: Baseline cardiovascular risk factors of participants in the placebo (PLB) and pioglitazone (PIO) groups

	PLB Week 0	**PIO Week 0**	**Δ PIO vs PLB**	***p*-value PIO vs PLB**
Mean BP (mmHg)	110.7 ± 1.8	108.7 ± 1.8	-2.0 ± 2.6	0.44
Total CHOL (mmol/L)	4.6 ± 0.2	5.1 ± 0.2	0.5 ± 0.3	0.16
LDL (mmol/L)	2.6 ± 0.2	3.0 ± 0.2	0.4 ± 0.3	0.13
HDL (mmol/L)	1.6 ± 0.08	1.5 ± 0.08	-0.03 ± 0.1	0.77
Total CHOL: HDL	3.03 ± 0.16	3.34 ± 0.15	0.31 ± 0.22	0.16
TRIG (mmol/L)	0.9 ± 0.1	1.1 ± 0.1	0.2 ± 0.2	0.24

Values presented as mean ± SD; **Δ = difference between PIO vs PLB**
Abbreviations: Placebo group, PLB; Pioglitazone group, PIO; Blood Pressure, BP; Cholesterol, CHOL; Low-Density Lipoprotein, LDL; High-Density Lipoprotein, HDL; Triglycerides, TRIG

ESM Figure 1. CONSORT Diagram.