The T Allele of TCF7L2 Rs7903146 Predicts Increased Blood Glucose After Seven Days of Bed Rest in Nondiabetic Older Adults in a Secondary Analysis of a Randomized Controlled Trial

Jean L. Fry (jfr282@uky.edu)
University of Kentucky
Katherine L. Thompson
University of Kentucky
Christopher S. Fry
University of Kentucky
Douglas Paddon-Jones
The University of Texas Medical Branch at Galveston
Emily J. Arentson-Lantz
The University of Texas Medical Branch at Galveston

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Abstract

Inpatient populations are at increased risk of hyperglycemia due to factors such as medications, physical inactivity and underlying illness, which increases morbidity and mortality. Unfortunately, clinicians have limited tools available to prospectively identify those at greatest risk. We evaluated the ability of 10 common genetic variants associated with development of type 2 diabetes to predict impaired glucose metabolism. Our research model is a simulated hospital stay (7 day bed rest protocol, standardized diet, and physical inactivity) and included a cohort of healthy older adults (n = 31, 65 ± 8 years) with baseline fasting blood glucose < 100 mg/dL. Participants completed a standard 75 g oral glucose tolerance test (OGTT) at baseline and post-bed rest. In multiple regression modeling, the transcription factor 7-like 2 (*TCF7L2) rs7903146* T allele predicted elevated 2-hour OGTT blood glucose (p = 0.03925). We show that the *TCF7L2 rs7903146* T allele confers risk for elevated 2-hour OGTT blood glucose in nondiabetic older adults following 7 days of bed rest.

Introduction

Nondiabetic patients who develop hyperglycemia during hospitalization have increased lengths of stay and mortality risk [1–6]. In critically ill patients, mortality increases incrementally with rising blood glucose, and patients reaching values above 300mg/dL have high mortality rates independent of diabetes diagnosis [3]. Currently, clinicians are unable to identify nondiabetic inpatients at risk for developing hyperglycemia, limiting their ability to initiate preventive therapy.

Dozens of common genetic variants are associated with increased risk for type 2 diabetes. For example, the odds of developing type 2 diabetes is 1.5 when having the the transcription factor 7-like 2 (*TCF7L2*) *rs7903146* T allele (*rs7903146*^{T}), which is established across many ethnic groups [7, 8]. The *TCF7L2 rs7903146*^{T} variant is also associated with impaired pancreatic function and elevated glycated hemoglobin in nondiabetic individuals [9, 10]. Though some genetic variants, including *TCF7L2 rs7903146*^{T}, are associated with elevated glycemic indicators in nondiabetic individuals, more evidence is needed to determine how genetic testing of these risk variants may support clinical decision making in the inpatient setting.

Inpatient hyperglycemia is multifactorial and mediated by factors like physical inactivity, medications, medical nutrition therapies, and underlying acute illnesses/chronic disease [2, 4, 5, 11]. Bed rest in healthy research subjects models the physical inactivity aspect of a hospital stay while avoiding the confounding influence of variable nutrition therapies and disease-related comorbidities.

We sought to determine if genetic testing for ten common type 2 diabetes risk variants could predict hyperglycemia during an oral glucose tolerance test (OGTT) challenge in healthy older adults following a 7 day bed rest protocol. Here we report on the ability *of MTNR1B (rs10830963), NOTCH2 (rs10923931), RASGRP1 (rs7403531), PROX1 (rs2075423), HHEX (rs1111875), IGF2BP2 (rs4402960), CDKAL1 (rs7754840), SLC30A8 (rs13266634), ZFAND6 (rs11634397), and TCF7L2 (rs7903146)* to predict changes

in fasting blood glucose, 2-hour OGTT blood glucose, and Matsuda Insulin Sensitivity Index (Matsuda-ISI) in 31 healthy older adults following a 7 day bed rest protocol.

Results

Overall Effect of Bed Rest

Seven days of bed rest was associated with 2-hour OGTT blood glucose and serum insulin and reduced the Matsuda-ISI (Table 1). Also significantly increased following bed rest were 90-minute OGTT blood glucose (130.6 ± 27.1 vs. 145.8 ± 28.3 mg/dL; p = 0.006) and 60-minute and 120-minute OGTT serum insulin (45.4 ± 32.3 vs. 62.4 ± 72.7 μU/mL; p = 0.048 and 41.6 ± 36.9 vs. 63.8 ± 60.0 μU/mL; p = 0.001, respectively). All other glucose values and all insulin values from the OGTT were unchanged following bed rest (*data not shown*).

Table 1
Overall effect of seven days of bed rest on participant glycemic indicators

Outcome[1]	PreBR	PostBR	p-value[2]
Fasting Blood Glucose (mg/dL)	82.5 ± 6.4	80.9 ± 6.5	0.159
2-hour OGTT[3] Blood Glucose (mg/dL)	111 ± 25.4	134.1 ± 32.2	0.000*
2-hour Insulin (μU/mL)	41.6 ± 36.9	63.8 ± 60	0.001*
Matsuda-ISI	9.1 ± 4.1	7.5 ± 3.4	0.001*
[1] Data are presented as Mean ± SD.			
[2] Paired t-test p-value of pre-bed rest (PreBR) and post-bed rest (PostBR) values.			
[3] Oral Glucose Tolerance Test			

Models Predicting Increases in Blood Glucose

During model selection, the Feasible Solutions Algorithm identified the *TCF7L2 rs7903146*^{T} allele and its statistical interaction effect with baseline 2-hour OGTT blood glucose as a significant predictor of increased 2-hour OGTT blood glucose following bed rest when including baseline 2-hour OGTT blood glucose, age, and BMI as main effects in the model (p = 0.03925). The baseline 2-hour OGTT blood glucose and the *TCF7L2 rs7903146*^{T} allele together explained 23.65% of the variability in post-bed rest 2-hour OGTT blood glucose values, after controlling for age and BMI. (Figs. 1 and 2). No other genotype predicted glycemic outcomes or Matsuda-ISI following seven days of bed rest.

Discussion

Older adults with *TCF7L2 rs7903146^{T}* risk variants are more likely to have increased 2-hour OGTT blood glucose following seven days of bed rest. TCF7L2 is a transcription factor belonging to the Wnt signaling pathway present in pancreas, liver, and other tissues [12, 13]. Whole-genome chromatinimmunoprecipitation (ChIP) combined with massively parallel DNA sequencing (ChIP-Seq) analyses show that TCF7L2 binds directly to several genes involved in glucose metabolism, including *PCK1, FBP1, IRS1, IRS2, AKT2, ADIPOR1, PDK4 AND CPT1A* [14]. Carriers of the *rs7903146^{T}* allele exhibit impaired proinsulin conversion, higher proinsulin:insulin ratios, and greater likelihood of developing insulin-dependent type 2 diabetes [15–18], but not hepatic or extrahepatic insulin resistance [19, 20]. Paradoxically, some evidence indicates that liver and other tissues appear to be involved in *TCF7L2 rs7903146^{T}*-associated glucose intolerance and insulin secretion [21].

TCF7L2 risk alleles are associated with elevated post-OGTT and nocturnal blood glucose in nondiabetic adults [17, 18, 22, 23]. The *rs7903146^{T}* allele also associates with impaired glucose tolerance in adults with metabolic syndrome [22] and obese adolescents [17]. Healthy, middle-aged and older nondiabetic participants with *rs7903146^{T}* also exhibit higher nocturnal glucose [23]. However, similar to our findings, prior studies indicate that *rs7903146^{T}* does not affect *fasting* blood glucose in healthy middle-aged adults [24]. This suggests that fasting blood glucose may not be an optimal biomarker to screen individuals with *rs7903146^{T}* for risk of developing prediabetes and type 2 diabetes.

Young, healthy Caucasian men with *TCF7L2 rs7903146^{T}* risk alleles exhibit a lower first-phase insulin response (FPIR) to an intravenous glucose tolerance test (IGTT) compared with those with the homozygous C genotype both before and after 9 days of bed rest ($p = 0.01$ and $p = 0.0001$, respectively) [25]. Following bed rest, the participants with the *TCF7L2 rs7903146* risk variants also fail to show an incremental rise of FPIR in response to insulin resistance. Though FPIR is not a concept that is directly translatable outside of the context of an IGTT, the ability to rapidly secrete insulin in response to an OGTT in the early phase (up to 30 minutes after consumption of glucose) is a similar concept [26]. The liver responds to a robust early phase insulin response by reducing release of glucose, thereby limitng the overall blood glucose response to an OGTT or a meal, and this physiological trait that is lost in the development of type 2 diabetes [27]. Here we did not observe any relationship between *rs7903146^{T}* risk alleles and insulin measures or calculated insulin sensitivity at point after a 75 g glucose load, but we completed 2-hour OGTT, which are not directly comparable to the IGTT or the FPIR.

Periods of physical inactivity promote insulin resistance in healthy adults [28, 29]. If the reduced glucose tolerance we observed following a 7 day period of inactivity in healthy, nondiabetic adults persists, patients having *rs7903146^{T}* variants could be especially susceptible to long-term impairments in glucose metabolism following inpatient stays. Future research should evaluate how *rs7903146^{T}* affects blood glucose throughout hospital stay in both critically ill and non-critically ill hospital patients. Moreover, follow up studies should evaluate if *rs7903146^{T}* predicts long-term glucose intolerance following an extended period of disuse in clinical populations in patients after discharge. Finally, utilizing and OGTT, rather than fasting blood glucose, may be more appropriate for patients carrying the *rs7903146^{T} allele.*

Our analysis showed a clinically relevant association between the *TCF7L2 rs7903146^{T}* allele and risk of glucose intolerance after physical disuse; however, there were limitations. This study was not initially designed to test genotype-phenotype relationships. We recruited volunteers to test the effect of nutrition and physicial activity on a broad range of outcomes following bed rest. We feel confident that the genotype-phenotype relationship between *TCF7L2 rs7903146^{T}* and 2-hour OGTT blood glucose described here was not affected by the group assignment, however (Supplemental Table S4). This small study was conducted in generally healthy older adults and woud not be generalizable to other aged groups or those with acute or chronic illness.

Conclusion

We show for the first time that the TCF7L2 rs7903146 T allele associates with increased 2-hour OGTT blood glucose in nondiabetic, older adults following seven days of bed rest and physical disuse. If these findings can be replicated in a clinical setting, the *TCF7L2 rs7903146^{T}* allele may help clinicians identify nondiabetic inpatients at greater risk for hyperglycemia.

Methods

Participants

Thirty-one healthy older adults were recruited (65 ± 8 years), provided written informed consent, medically screened, and compensated for their time as part of a larger randomized-controlled trial. A fasting glucose > 100 mg/dl, recent corticosteroid use, or evidence of chronic disease (vascular disease, unmanaged elevated blood pressure, and kidney disease) were considered exclusionary criteria for the study. All enrolled participants were community-dwelling, able to complete activities of daily living, and considered to be generally healthy. The study protocol was conducted conducted within the inpatient unit of the Clinical and Translational Research Center at the University of Texas Medical Branch (UTMB) and in accordance with the Declaration of Helsinki and approved by the UTMB Institutional Review Board. All participants provided informed consent including consent for genetic analyses. Sample size was determined by subject enrollment in the parent study and available blood samples for genetic analyses (supplemental figure S1). Recruitment and collection of blood for this secondary analysis began after the initial enrollment period for the parent clinical trial. Participants included in the present analysis were enrolled between 03/26/2014 and 10/10/2017, the latter of which was the last enrollment for the parent grant. This study was registered though clinicaltrials.gov on 03/05/2013 (NCT01846130).

Participants were assigned to one of five experimental conditions (protein consumption patterns, small bout of walking, or amino acid supplementation) [30–32] that were outside of the scope of this study. Collection and storage of blood for genotyping was initiated in the middle of the parent grant, so not all study participant could be included in the anlaysis. The study statistician confirmed that there were no significant relationships between the study interventions and primary study outcomes (2-hour OGTT

glucose and Matsuda-ISI) presented here ($p > 0.05$). A brief description of each study intervention is available in Supplemental Table S4.

The general experimental design is depicted in Fig. 3. Participant baseline characteristics are reported in Table 2. There were no significant differences in age, BMI, systolic blood pressure, diastolic blood pressure, fasting blood glucose or baseline 2-hour OGTT blood glucose between *TCF7L2 rs7903146* genotype groups (Supplemental Table S1).

Table 2
Participant demographics and baseline characteristics

Characteristic	Value[1]
Sex (Males/Females; [%])	18/13 (58% / 42%)
Age (years)	65 ± 8
BMI[2] (kg/m^2)	26.9 ± 2.9
Systolic blood pressure (mmHg)	129 ± 15
Diastolic blood pressure (mmHg)	75 ± 8
Ethnicity (number: [%])	Caucasian: n = 21 (68%) Hispanic: n = 4 (13%) Black: n = 4 (13%) Asian : n = 2 (6%)
[1] Values are presented as Mean ± Standard Deviation	
[2] BMI: body mass index	

Bed Rest

As previously reported [30–32] participants completed three days of diet-stabilization/testing followed by seven days of horizontal bed rest in the UTMB Institute for Translational Sciences–Clinical Research Center (ITS-CRC). Consistent with our previous horizontal bed rest studies, subjects were continuously monitored for safety [33]. All bathing and toiletry activities were performed without bearing weight.

Diet

Participants were provided isoenergetic diets (55% carbohydrate, 29% fat, and 16% protein). Individualized daily energy requirements were estimated using the Harris–Benedict equation with activity factors of 1.6 and 1.3 used for the ambulatory and bed rest period, respectively [30, 31, 33]. Water was provided ad libitum. The breakfast meal presented after each OGTT was adjusted to compensate for the 75 g glucose load. Energy and macronutrient intake, taking plate waste into account, were analyzed by

using Nutrition Data System for Research software (version 2011, Nutrition Coordinating Center, Minneapolis, MN).

Oral Glucose Tolerance Test and Serum Insulin

Standard 75 g glucose load (Glucola, Azer Scientific, Morgantown, PA) oral glucose tolerance tests were administered before and after the 7-day bed rest protocol. Whole-blood samples (0, 30, 60, 90, and 120 minutes) were analyzed on an YSI Bioanalyzer (YSI, Yellow Springs, OH). Serum insulin was measured using a commercially available enzyme-linked immunosorbent assay (MilliporeSigma, Burlington, MA). Matsuda Insulin Sensitivity Index (Matsuda-ISI) was determined using the Matsuda formulas [34].

Genotyping

Genomic DNA was extracted from whole blood samples using the DNeasy Blood Kit (QIAGEN, Germantown, MD) according to the manufacturer's instructions. TaqMan® Genotyping Assays (Thermo Fisher/Applied Biosystems, Foster City, CA) were used to genotype for *MTNR1B (rs10830963), NOTCH2 (rs10923931), RASGRP1 (rs7403531), PROX1 (rs2075423), HHEX (rs1111875), IGF2BP2 (rs4402960), CDKAL1 (rs7754840), SLC30A8 (rs13266634), ZFAND6 (rs11634397), and TCF7L2 (rs7903146)*. The work was performed by the Genomics Core at the University of Texas Medical Branch according to the manufacturer's instructions. Briefly, 5 ng of purified DNA was added to each well and dried down. Primers and all reagents were combined, and PCR was completed using an Applied Biosystems 7500 Fast Real-Time PCR System (Thermo Fisher/Applied Biosystems, Foster City, CA). Thereafter, Sequence Detection System (SDS) Software was used to perform a post-PCR plate read and analysis to call genotypes. Samples were run in triplicate and the core was able to make genotype calls for all participants and single nucleotide polymorphisms (SNP).

Statistical Analyses

Prior to analysis, descriptive statistics were calculated for all available observations from each outcome, baseline characteristics, and genotype frequencies were calculated for each SNP (Supplemental Table S5). Pre-post bed rest comparisons of quantitative variables were made using paired t-tests. For each primary outcome (fasting glucose, 2-hour OGTT glucose and Matsuda-ISI), a one-way ANOVA was run to screen for any significant baseline differences with each parent study intervention and genotype groups (Supplemental Tables S2 and S4 show data for 2-hour OGTT glucose for TCF7L2 rs7903146 genotype and parent study internventions). Hardy Weinberg Equilibrium exact tests were also performed using the R package, HardyWeinberg [35]. Next, candidate multivariate regression models for each outcome were identified using the Feasible Solutions Algorithm [36, 37]. Each model included adjustments for age and BMI [24] (along with baseline value of the outcome, if appropriate). Potential explanatory variables included the 10 SNPs, age, BMI, and parent study intervention. Based on the candidate models from the Feasible Solutions Algorithm, a model was selected for each outcome variable. All analyses were performed in R version 3.6.1.

Declarations

Acknowledgements

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Author contributions

DPJ and EAL designed and executed the parent study. DPJ, EAL, JLF, and CSF participated in data collection and sample analysis. KLT and JLF performed data analysis. JLF and EAL prepared the manuscript. All authors read and approved the final manuscript.

Additional Information (including a Competing Interests Statement)

DPJ has participated on scientific advisory panels, provided educational seminars, and received travel reimbursements and honoraria from the American Egg Board, Leprino Foods, National Cattlemens Beef Association, National Dairy Council, Nestle Nutrition, Sabra Wellness and Nutrition, and the U.S. Dairy Export Council. JLF, EAL, CSF, and KT report no conflicts of interest.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

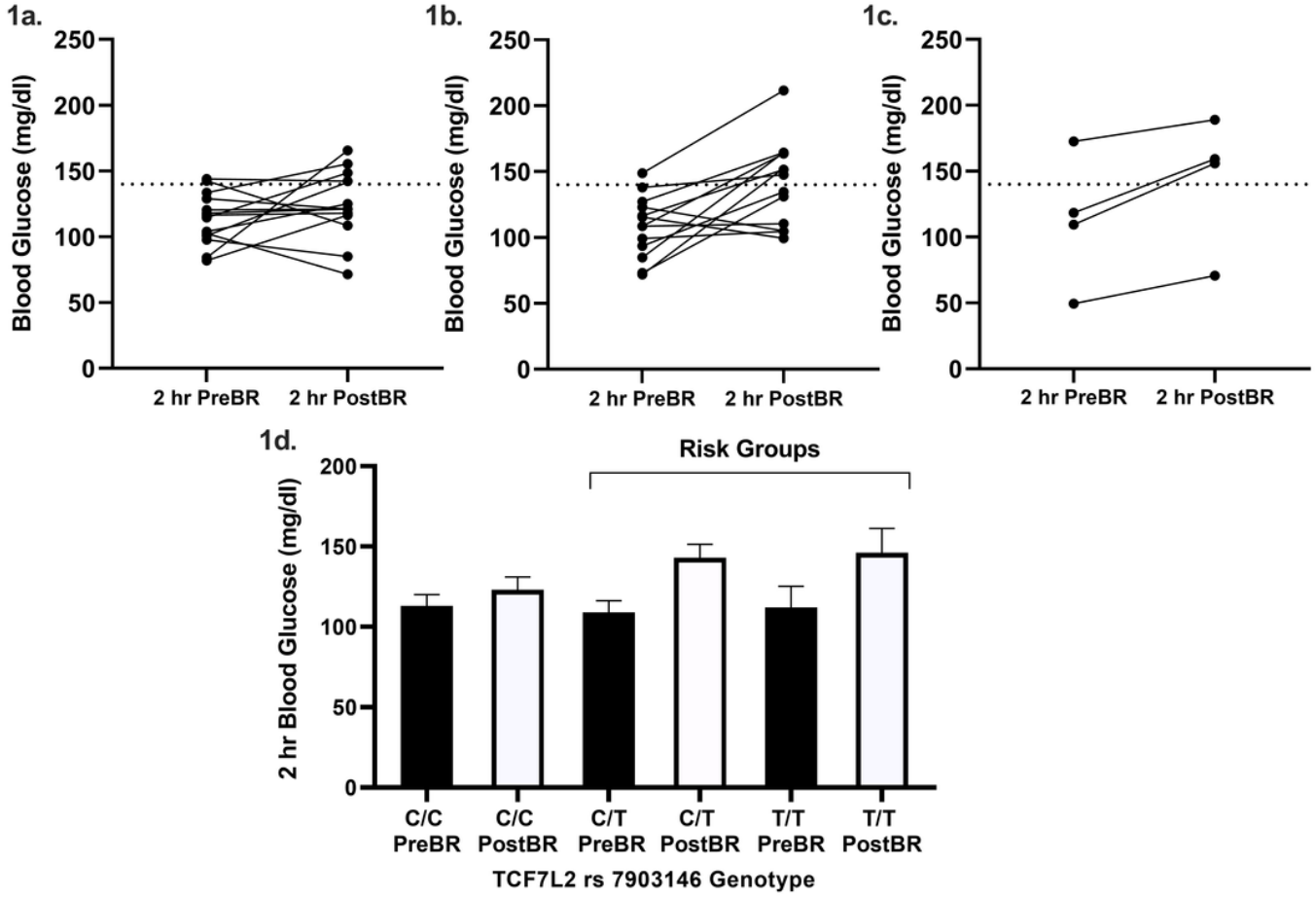

Figure 1

1a. Individual 2-hour OGTT blood glucose changes in C/C genotype group; 1b. Individual 2-hour OGTT blood glucose changes in C/T genotype group 1c. Individual 2-hour OGTT blood glucose changes in T/T genotype group; The dotted line on 1a, 1b and 1c is 140 mg/dl, which is the cutpoint for a normal 2-hour blood glucose value during an OGTT. 1d. Average 2-hour OGTT blood glucose by genotype variant group. Data are shown as mean ± SEM. (p=0.03925 for overall model)

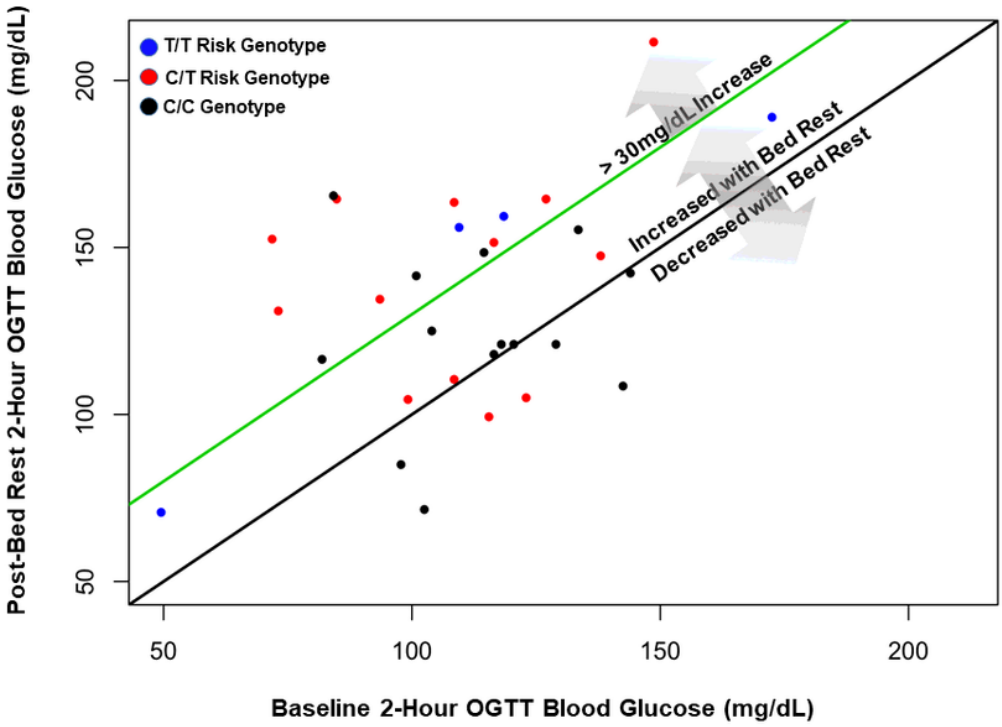

Figure 2

Association of PreBR 2-hour OGTT blood glucose with PostBR 2-hour OGTT blood glucose. The black line represents no change in 2-hour OGTT glucose following 7 days of bed rest. The green line represents a 30mg/dL increase in blood glucose after the 7 day bed rest protocol. Individuals with the C/C risk genotype are shown as black circles, C/T risk variants are red circles and T/T risk variants are blue circles. (p=0.03925 for overall model).

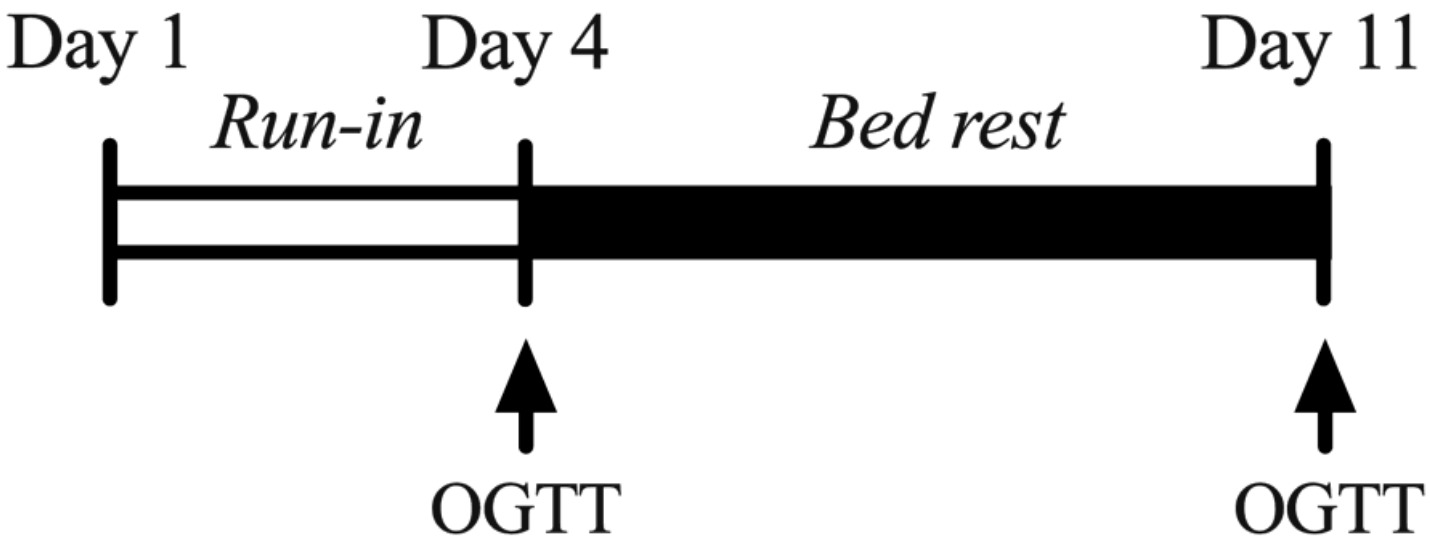

Figure 3

Overall study design: Nondiabetic participants spent 2 inpatient days completing a period of diet stabilization before undergoing a baseline oral glucose tolerance test (OGTT), followed by seven days of bed rest, and a post-bed rest OGTT.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigureS1ParentStudyCONSORTFlowDiagram.doc
- SupplementaryTables.docx