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Dietary isoflavone intake is associated with evoked responses to inflammatory cardiometabolic stimuli and improved glucose homeostasis in healthy volunteers

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Abstract *Background and aims:* Consumption of foods that modulate inflammatory stress in genetically-prone individuals may influence development of cardiometabolic diseases. Isoflavones in soy-derived foods function as phytoestrogens, have antioxidant and anti-inflammatory activity, inhibit protein-tyrosine kinase activity, and may be atheroprotective. We examined the relationship between soy food consumption and inflammatory responses to endotoxemia, postprandial responses to oral lipid tolerance test (OLTT), and insulin sensitivity from frequently sampled intravenous tolerance tests (FSIGTT).
Methods and results: We administered low-dose endotoxin (LPS 1 ng/kg) to induce transient endotoxemia in young, healthy volunteers ($N = 215$) of African (AA), and European (EA) ancestry as part of the GENE Study. We further supported these findings in two independent samples: the MECHE Study and NHANES. Soy food consumption was a significant predictor of peak cytokine response following LPS. Individuals with moderate-high (>1.48 mg/day, $N = 65$) vs. low-no (<1.48 mg/day, $N = 150$) isoflavone consumption had significantly higher tumor necrosis factor alpha (TNFα) post-LPS (AUC, $P = 0.009$). Further, high-isoflavone consumers were protected against inflammation-induced decline in insulin sensitivity (S_I) in GENE. We observed significant differences by soy consumption in the interferon gamma (IFNγ) response to OLTT, and the insulin response to OGTT in MECHE, as well as significantly lower fasting insulin, and 2-hour glucose post-OGTT in EA NHANES subjects.
Conclusion: We demonstrate that soy consumption may influence inflammatory and metabolic responses. In research of nutritional exposures, measuring evoked phenotypes may be more informative than describing resting characteristics.
The GENE Study was registered under NCT00953667 and the MECHE Study under NCT01172951, both at clinicaltrials.gov.

Abbreviations: LPS, lipopolysaccharide; FSIGTT, frequently sampled intravenous glucose tolerance test; OGTT, oral glucose tolerance test; OLTT, oral lipid tolerance test; GENE, Genetics of Evoked responses to Niacin and Endotoxemia Study; MECHE, Metabolic Challenge Study; NHANES, National Health and Nutrition Examination Survey; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

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Introduction

Inflammation is a key component of several cardiometabolic diseases, including obesity, type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (CVD) [1]. While many factors, including genetic, environmental and microbial, influence the development of a pro-inflammatory state, habitual diet may be a key inflammatory regulator [2]. We utilize evoked endotoxemia (LPS) in healthy individuals as a model of physiological responses to inflammatory stimuli, inflammation-induced insulin resistance, and cardiometabolic risk [3–5], with relevance to postprandial metabolic endotoxemia [6]. Dietary components which modulate response to LPS may influence transient postprandial inflammatory stress, affect ability to appropriately resolve inflammatory stimuli, and influence chronic cardiometabolic disease and diet-induced obesity.

Bioactive food compounds may have important health-modulating effects. Dietary plant-derived phytochemicals have anti-inflammatory and antioxidant properties that may be protective against disease development [7]. Isoflavones, primarily genistein (~50–60%), daidzein (~30–40%), and glycitein (~5–10%), are found in high concentrations in soy-derived foods [8]. Isoflavones function as phytoestrogens [9], inhibit protein-tyrosine kinase activity [10], and may have an anti-proliferative effect on cancer cells [11]. Although human epidemiological and interventional data remain inconclusive, mounting evidence suggests that isoflavones may be atheroprotective [12,13].

As part of the Genetics of Evoked Responses to Niacin and Endotoxemia (GENE) Study [4], we administered a low dose of endotoxin (LPS 1 ng/kg) to induce a controlled inflammatory response. We found that dietary isoflavone intake was associated with the inflammatory response to endotoxemia, and with endotoxemia-induced changes in insulin sensitivity. The findings were supported by complementary analyses in two independent samples; the MECHE study (www.ucd.ie/jingo/) and NHANES (www.cdc.gov/nchs/nhanes.htm).

Methods

GENE study population

Details of the GENE Study have been published previously [4]. Briefly, healthy volunteers (N = 294), non-smokers, age 18–45, BMI 18–30 kg/m^2, African American (AA) or European (EA) ancestry were recruited to an inpatient endotoxin challenge (1 ng/kg LPS), and frequently sampled intravenous glucose tolerance tests (FSIGTT) pre- and post-LPS at the University of Pennsylvania (UPenn) Clinical and Translational Research Center (CTRC). Subjects who completed dietary records (N = 215) were analyzed here. An overview of the GENE-Diet Study is shown in Fig. 1. The GENE study was conducted in accordance with UPenn's IRB with regulatory oversight by the FDA (LPS: IND# 5984) and an NIH-appointed data-safety and monitoring board.

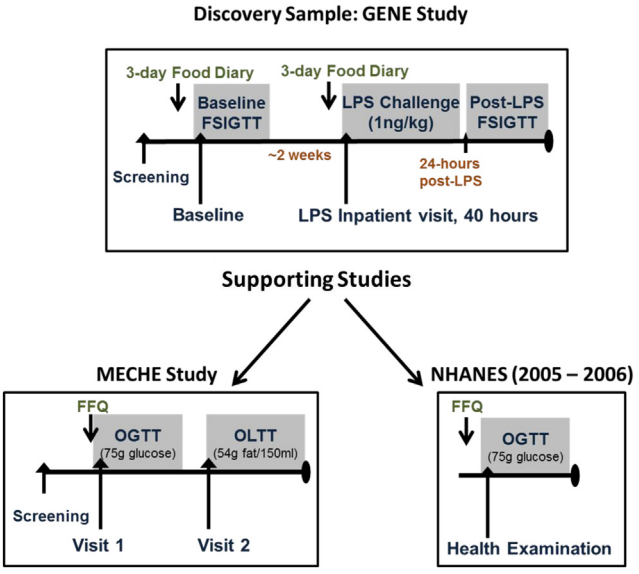

Figure 1 Overview of the discovery and validation/extension studies. The relationship between dietary isoflavone intake with inflammatory markers and insulin resistance was assessed in the GENE-LPS Diet Study sample (N = 215). Findings were supported by complementary analyses in the MECHE Study (N = 129) and the NHANES 2005–2006 sample (N = 884).

All subjects provided informed written consent. The GENE Study was registered under NCT00953667 at Clinicaltrials.gov.

GENE dietary analysis

Subjects received counseling from a CTRC dietician at study initiation to ensure adherence to AHA recommendations (55–60% carbohydrate; 10–15% protein; <30% fat; <7–10% SFA; <300 mg cholesterol/day), and were instructed in the use of food records. Subjects completed 3-day records on two separate occasions; before the LPS inpatient visit, and before a separate inpatient visit (±2–4 weeks). Results were averaged across the 6 days of records for each subject to obtain an estimate of habitual consumption, and these averages used in subsequent dietary analysis. Subjects did not receive any specific counseling related to soy food intake and there was no dietary intervention implemented. Subjects who completed all dietary records were included in the current analysis (N = 215 completed). Nutrient data were analyzed using Food Processor 8.1 (ESHA Research, Salem, OR).

GENE LPS inpatient visit

The inpatient LPS visit lasted ~40 h, as described [4]. Following overnight acclimatization, LPS (1 ng/kg) was administered intravenously by a licensed physician investigator. Anthropometric measurements were recorded and multiple clinical variables assessed regularly during the visit. Serial blood draws were taken, and serum and