

# Resveratrol improves glucose tolerance in older adults with IGT

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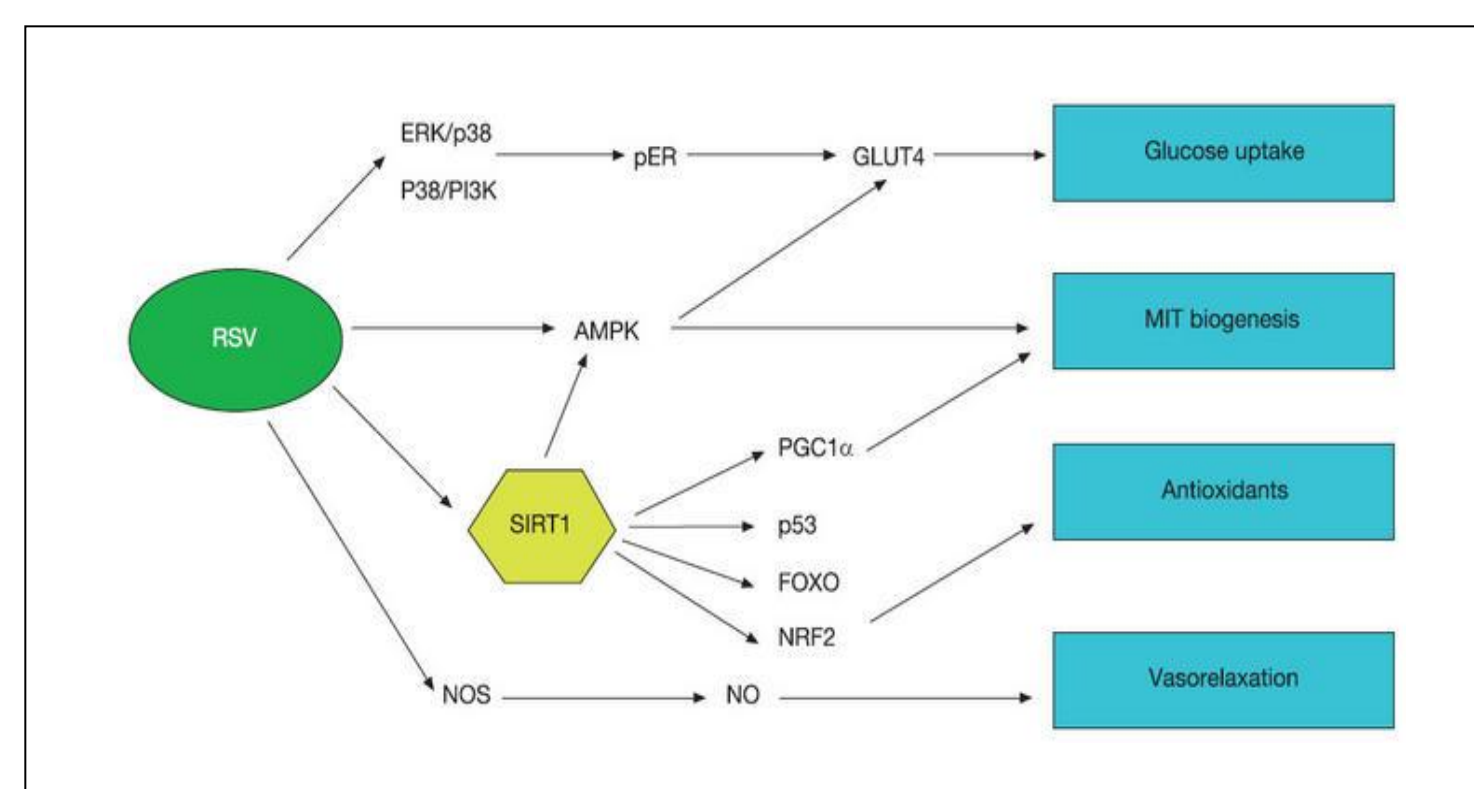
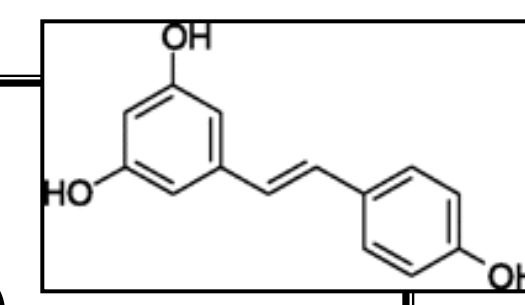
## Abstract

Resveratrol (RSV), a plant-derived polyphenol and Sirt1 activator, has shown promising effects on insulin secretion, insulin sensitivity and glucose tolerance in animal models. RSV is also reported to have anti-oxidant and cardio-protective properties, but none of these effects have been proven in humans. In a pilot study, we tested the hypothesis that RSV (via sirt1 activation or other mechanisms) would improve glucose metabolism and vascular function in older adults with impaired glucose tolerance (IGT). Ten subjects (age 72 ± 1 years, 3 men) with IGT were enrolled in a 4 week open-label study of RSV (daily dose 1, 1.5 or 2g). Outcomes were 3-hr glucose and insulin area under the curve (AUC) following a standard mixed meal (110g CHO, 20g protein, 20g fat) and calculated measures of insulin sensitivity (Matsuda index) and secretion (CIR<sub>30</sub>). RSV dose was given with the meal; glucose and insulin were measured 0, 30, 60, 120 and 180 minutes after the meal. Endothelial function was assessed by peripheral arterial tonometry (reactive hyperemia index, RHI) before and 90 minutes after the standard meal. Results did not differ by RSV dose, so data are combined in this analysis. At baseline, BMI was 29.1, waist circumference 87.5 cm, fasting plasma glucose (FPG) 110.5 mg/dl and 2-hr glucose 183.11 mg/dl. After 4 weeks of RSV, FPG was unchanged, but peak post-meal glucose (185.10 vs. 166.9 mg/dl, p=0.003) and 3-hr glucose AUC (469.23 vs. 428.19, p=0.001) declined. Matsuda index improved (3.1 ± 0.5 vs. 3.8 ± 0.5, p=0.03) and CIR<sub>30</sub> was unchanged (0.6 ± 0.1 vs. 0.5 ± 0.5, p>0.05), indicating the main effect was on insulin resistance. There was a trend towards improved post-meal RHI (pre-post meal delta -0.4 ± 0.2 vs. 0.2 ± 0.3, p=0.06). Weight, blood pressure and lipids were unchanged. Conclusions: At moderate doses, RSV lowers insulin resistance and thus post-meal plasma glucose in subjects with IGT. RSV shows promise for treatment of impaired glucose regulation, especially in an older population characterized by insulin resistance and postprandial hyperglycemia. These preliminary findings support the conduct of larger studies to further investigate the effects of resveratrol on metabolism and vascular function.

## BACKGROUND

### Resveratrol

- Polyphenolic phytoalexin found in red grapes, wine, nuts, berries and certain plants (Japanese knotweed)
- Reported to have anti-inflammatory, anti-oxidant and cardio-protective properties ("French paradox")
- Increases lifespan in yeast, worms, fruit flies, fish and rodents
- Improves glucose and insulin metabolism in rodent obesity models; stimulates insulin secretion in T2DM rodent model
- Thought to prevent age-related disorders (heart disease, diabetes, cancer, Alzheimer's dementia) by mimicking caloric restriction
- Proposed mechanisms include activation of sirtuin-1, a NADH-dependent histone deacetylase, and AMP kinase
- Studies in humans are limited and metabolic benefits remain unproven



Metabolic pathways affected by resveratrol include sirtuin-1 activation, which can affect glucose uptake, mitochondrial biogenesis and oxidation and nitric oxide production, which may induce vasorelaxation.

## HYPOTHESIS & AIMS

### Hypothesis

Treatment with resveratrol (via Sirt1 activation and/or other mechanisms) will result in improvements in insulin resistance, metabolic and vascular function in subjects with age-related glucose intolerance.

### Aims

To assess the effects of resveratrol treatment (using doses up to 2 g/day) in older adults with impaired glucose tolerance on the following parameters:

- glucose and insulin levels during a standard mixed meal test
- insulin sensitivity
- inflammation and endothelial function
- safety and tolerability

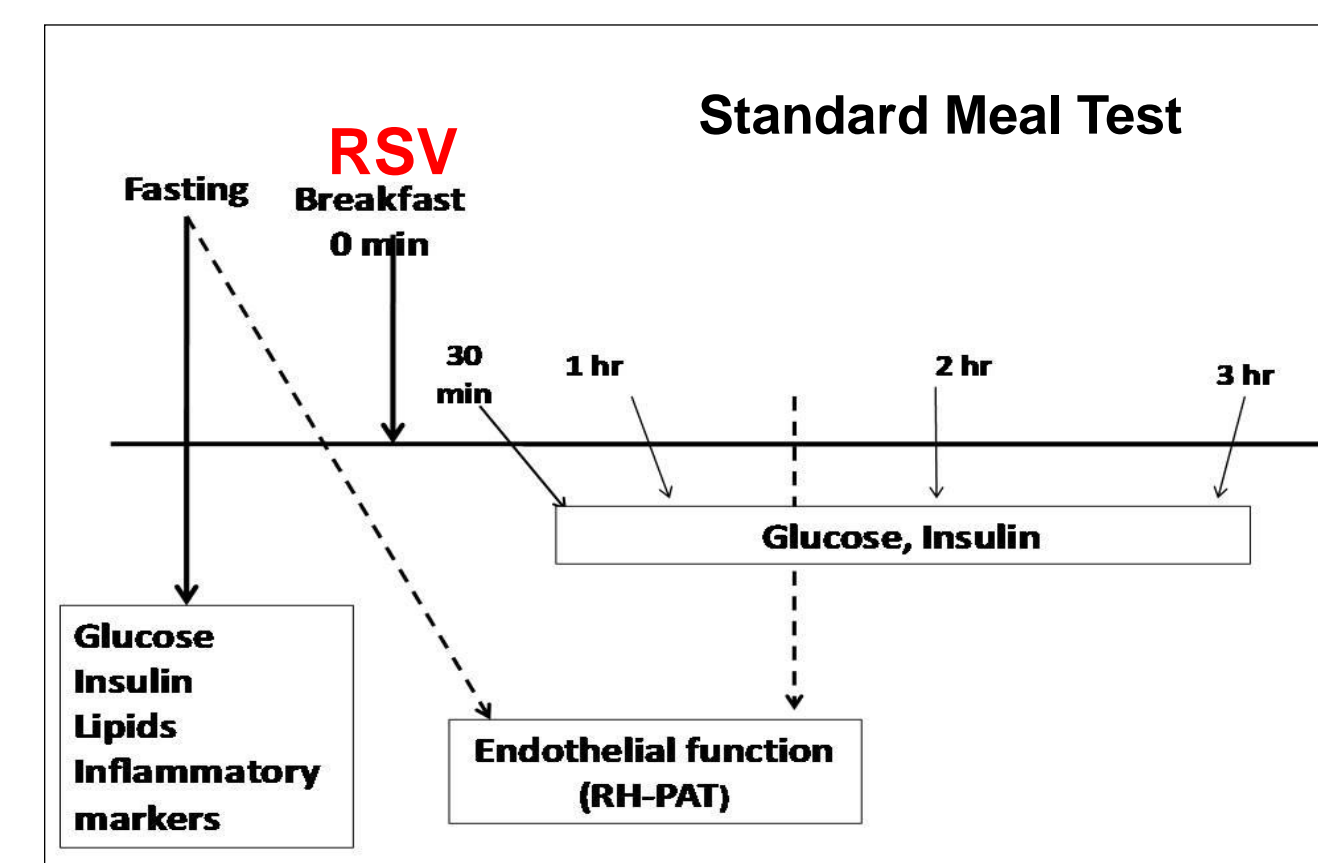
## MATERIALS AND METHODS

### Study Design

- Open-label study of resveratrol at 3 doses: 1, 1.5 and 2 g/day (given in divided doses)
- Standard meal test protocol at baseline and after 4 weeks of treatment
- Subjects age 60-80 with IGT on OGTT (2-hour glucose 140-199 mg/dl)

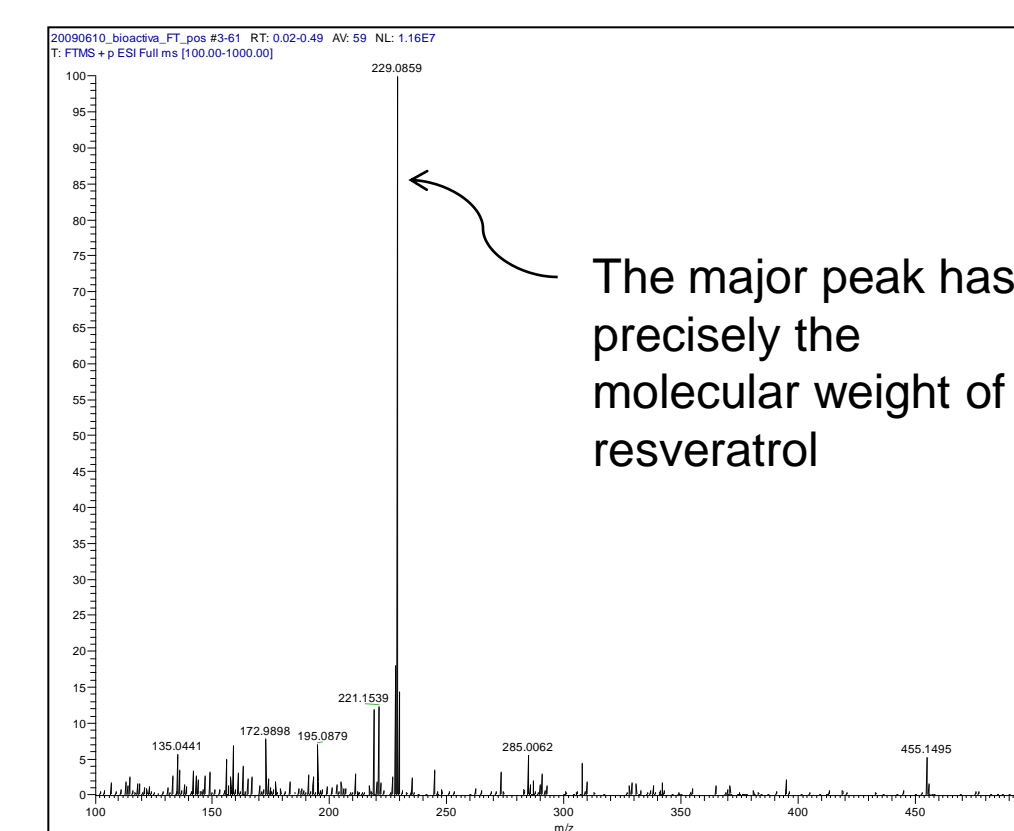
### Standard Meal Test

- Standard breakfast consists of 110g carbohydrate, 20g protein and 20g fat.
- Glucose and insulin measured at 0, 30, 60, 120, 180 min post-meal; fasting lipids and hsCRP.
- RH-PAT performed fasting and at 90 minutes post-meal
- Resveratrol dose given with meal



### Endothelial function

- Assessed by reactive hyperemia peripheral arterial tonometry (RH-PAT), which measures finger pulse wave amplitude at baseline and during post-occlusion hyperemia.
- Reactive hyperemia index (RHI) is the ratio of the average pulse amplitude in the post-hyperemic phase divided by the average baseline amplitude.
- RHI is correlated with coronary endothelial function and predicts CVD events
- RHI previously reported to decline postprandially in subjects with IGT (Crandall, et al. JCEM 2009)



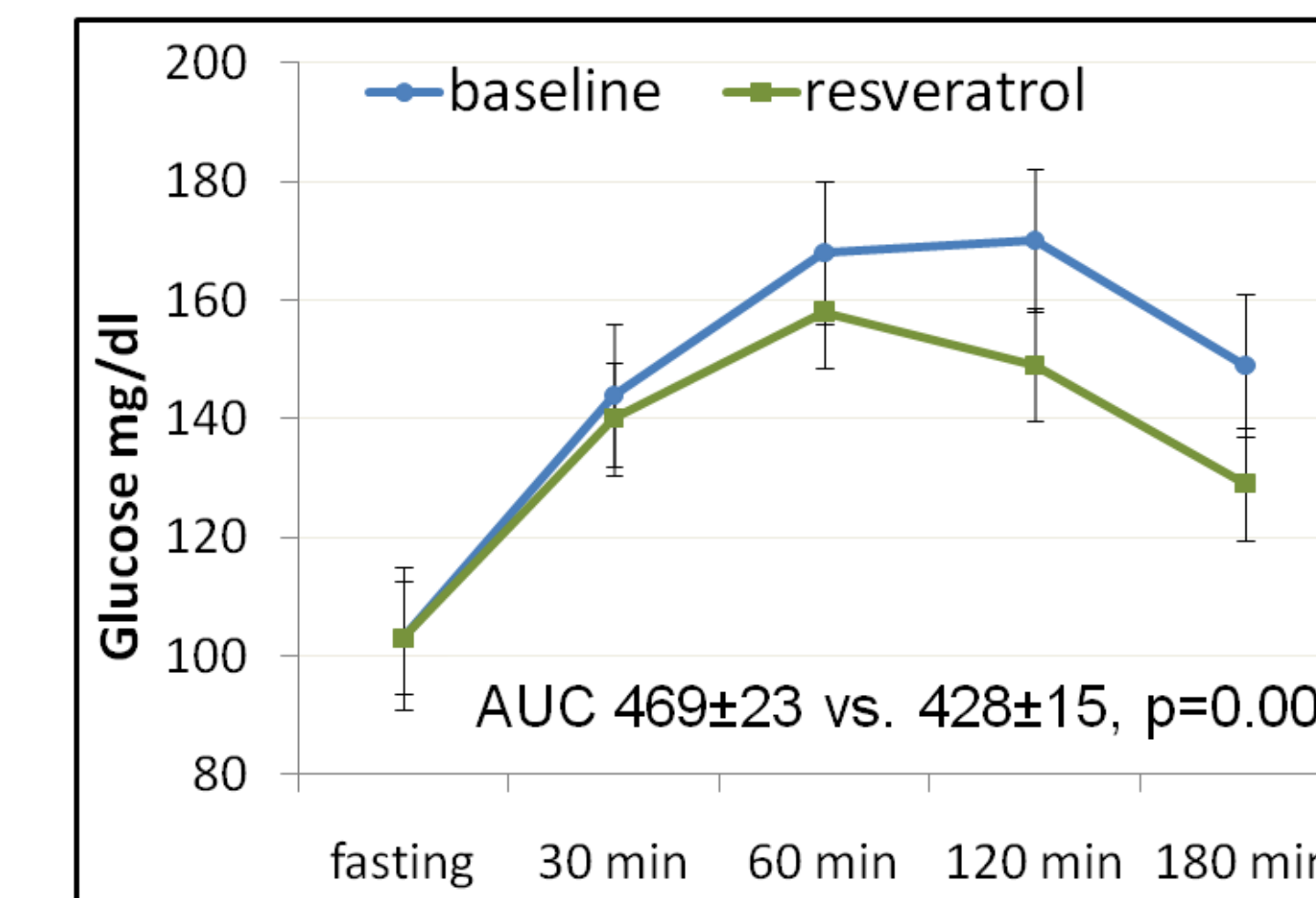
### Resveratrol source

Resveratrol capsules (500 mg) obtained from a commercial source (Biotivia, LLC.)

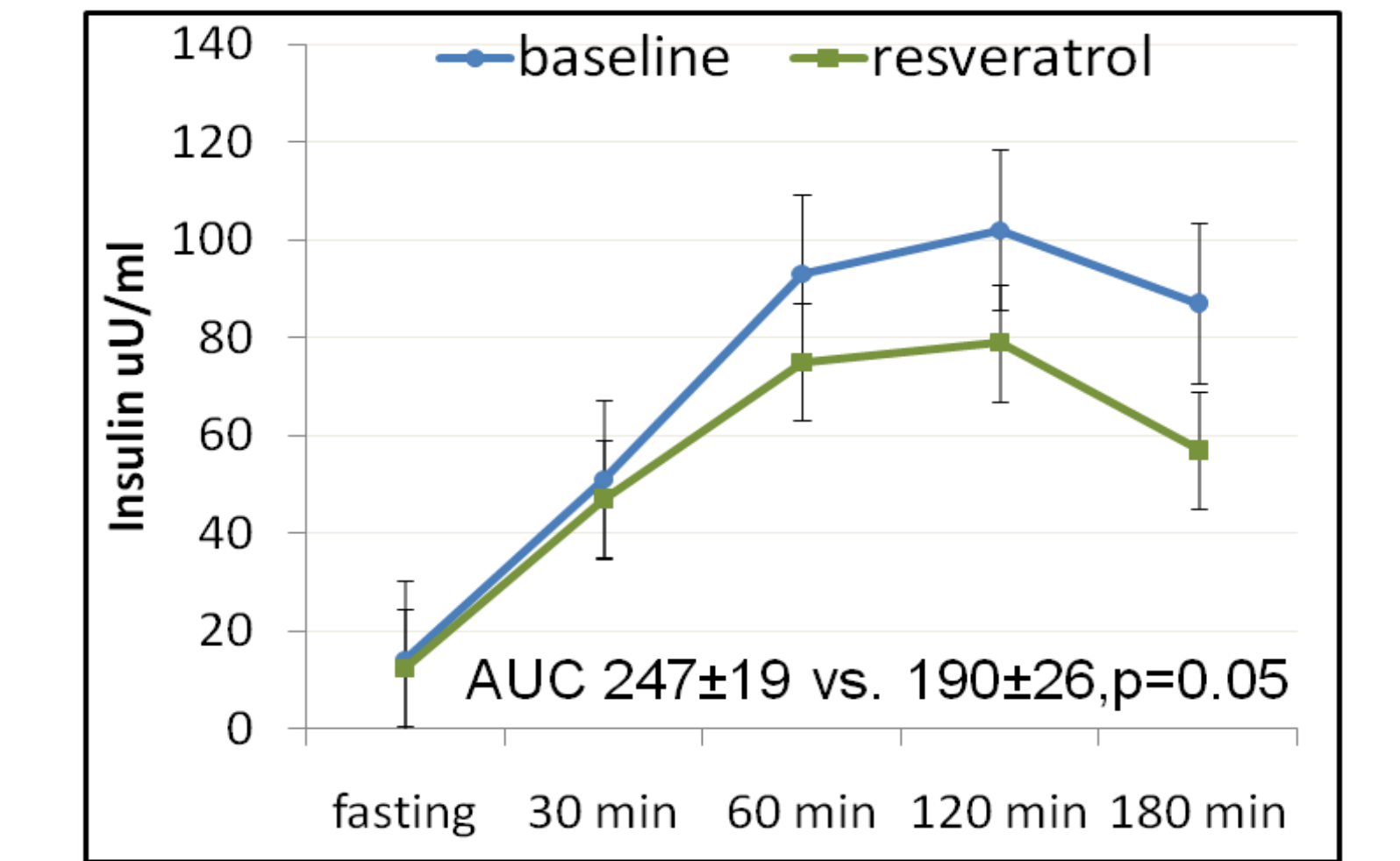
Resveratrol content independently confirmed by mass spectrometry, performed by W. Wu, PhD and R. Shen, PhD, Proteomics and Analytical Biochemistry Unit, National Institute on Aging (NIH)

## RESULTS

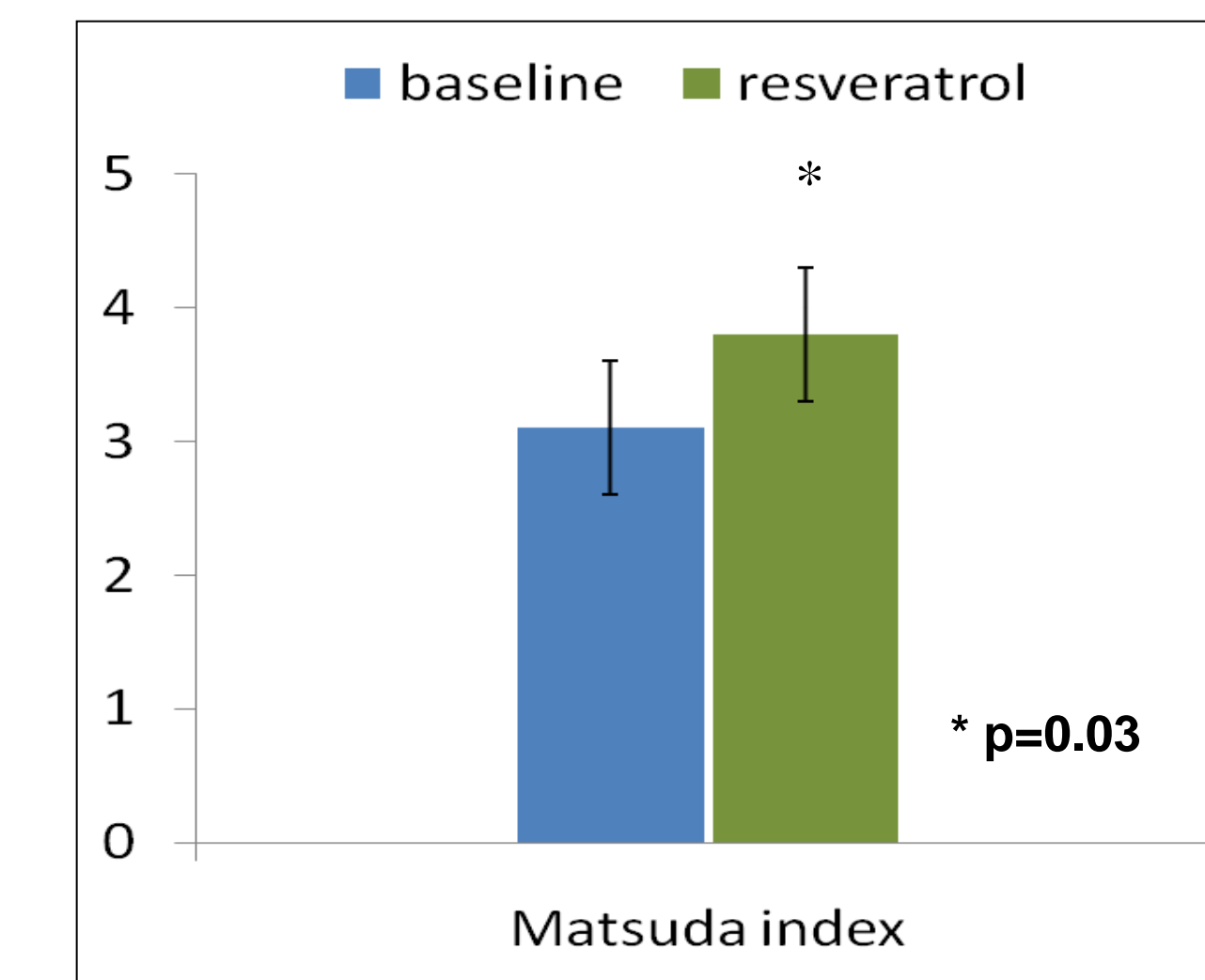
### Fasting and post-prandial glucose during SMT



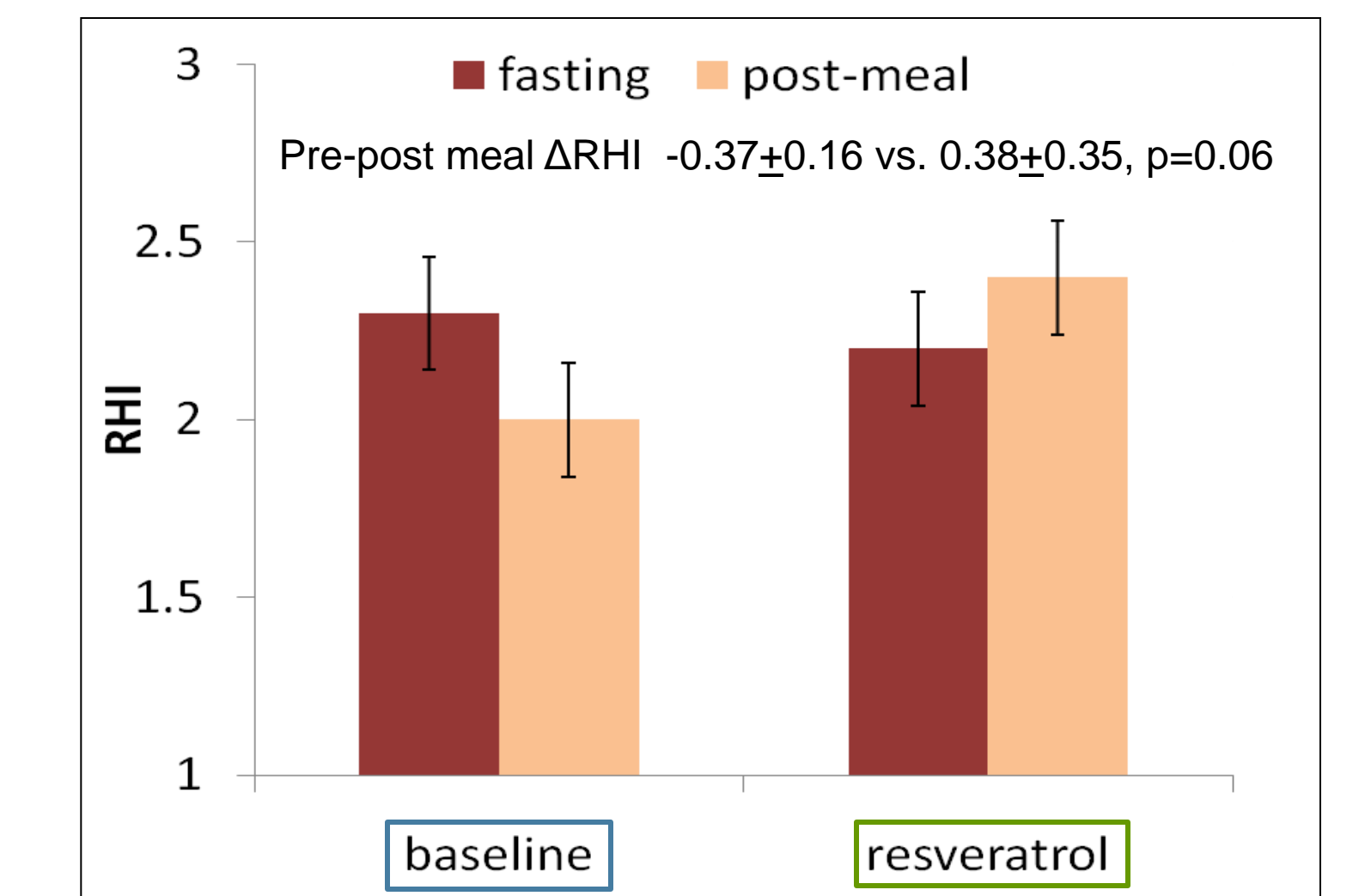
### Fasting and post-prandial insulin during SMT



### Matsuda Index at baseline and after 4 weeks of resveratrol



### Pre- and post meal RHI at baseline and after 4 weeks of resveratrol



### Other parameters at baseline and after 4 weeks of resveratrol

	Baseline	Resveratrol	P
Weight (kg)	74.0 (4)	73.6 (4)	0.3
Systolic blood pressure	129 (6)	126 (5)	0.5
Diastolic blood pressure	72 (3)	70 (3)	0.7
hs-CRP (mg/dl)	2.3 (0.6)	2.2 (0.8)	0.5
HDL-cholesterol (mg/dl)	51 (3)	50 (4)	0.8
LDL-cholesterol (mg/dl)	104 (9)	111 (11)	0.6
Triglycerides (mg/dl)	103 (13)	112 (13)	0.6
CIR <sub>30</sub>	0.6 (0.1)	0.5 (0.1)	0.4
Peak post-meal glucose (mg/dl)	185 (10)	166 (9)	0.003

### Additional results:

- There was no apparent dose-response effect of resveratrol at the doses studied (results combined for this analysis).
- All subjects completed the study and there were no changes in safety parameters (chemistries, CBC, urinalysis, EKG)
- Medication was well-tolerated and compliance was nearly 100% by pill count.

## RESULTS

### Subject characteristics (n=10)

	Mean (SEM)
Sex	7F/3M
Age (yr)	72 (1)
BMI (kg/m <sup>2</sup> )	29 (2)
Body fat (%)	35 (5)
Waist circumference (cm)	87 (5)
Weight (kg)	74(5)
BP systolic (mm Hg)	129 (6)
BP diastolic (mm Hg)	72 (3)
Fasting plasma glucose (mg/dl)	110 (5)
OGTT 2 hr glucose (mg/dl)	183 (11)
HOMA-IR	5.1 (0.7)
hs-CRP (mg/dl)	2.3 (0.6)

## CONCLUSIONS

- In older adults with IGT, resveratrol treatment was associated with:
  - Lower plasma glucose and insulin after a high-carbohydrate meal
  - Improved insulin sensitivity
  - A trend toward higher post-meal reactive hyperemia index (RHI), suggestive of improved microvascular endothelial function
- There was no clear dose-response effect in the 1-2 g/day range
- Resveratrol treatment was well-tolerated and no toxicity was observed
- These preliminary data support the conduct of larger studies to further investigate the effects of resveratrol on glucose metabolism and vascular function in humans.