

# Glucose and insulin up-regulate the cardiovascular biomarker GDF15 *in vivo* and *in vitro*: effect of meal content and obesity

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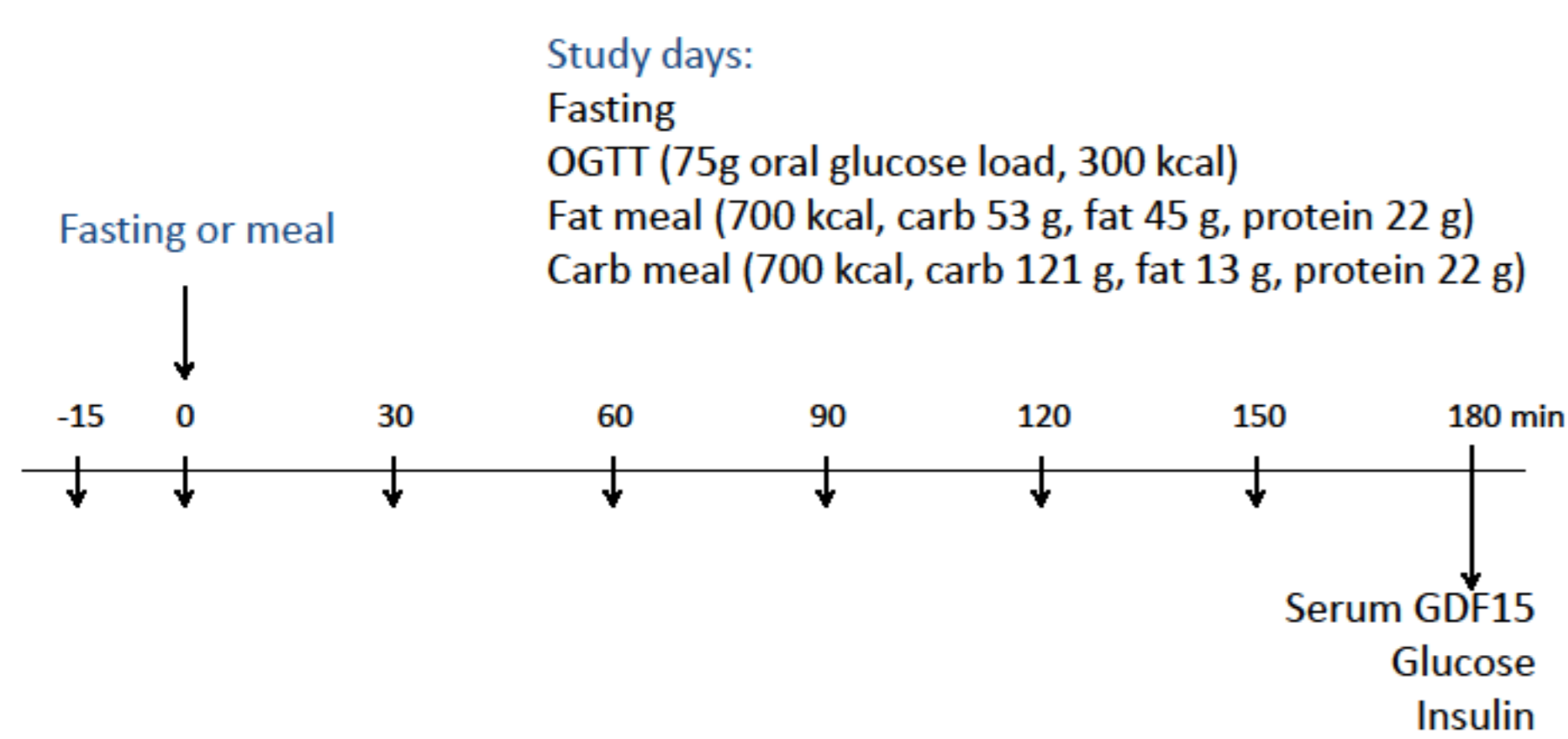
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## Introduction

- Growth differentiation factor 15 (GDF15) has recently been characterized as a cardiovascular risk factor
- GDF15 correlates with insulin and obesity in cross-sectional studies and exerts anorexigenic effects in interventional rodent studies
- GDF15 has been proposed as a possible therapeutic target in the treatment of obesity, however its meal- and nutrient-dependent regulation have not been investigated.

## Methods

- Profiles of GDF15 plasma concentrations were studied in lean and obese individuals in response to carbohydrate-rich and fat-rich meals, a 75 g oral glucose load (OGTT) or fasting.
- Human hepatic HepG2 cells were stimulated with glucose- and insulin, and the effects on GDF15 mRNA levels and protein release in the supernatant were evaluated.



## Baseline characteristics

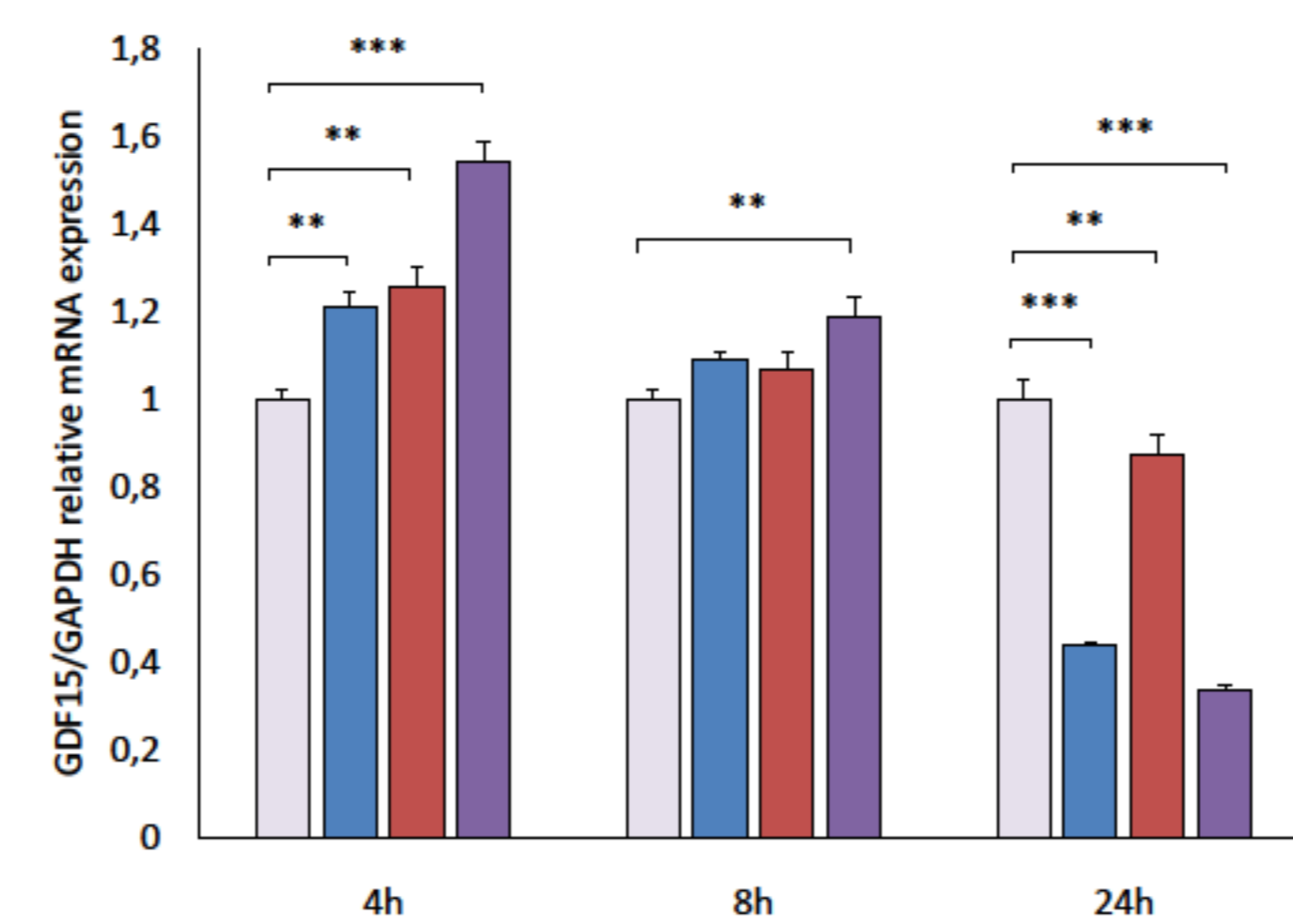
	Lean (n=8)	Obese (n=8)	p
Sex, male/female	5/3	5/3	
Age, years	26.4 (1.1)	26.7 (1.3)	ns
<b>Weight, kg</b>	<b>71.4 (6.4)</b>	<b>119.1 (9.6)</b>	<b>0.001</b>
Height, m	1.80 (0.05)	1.78 (0.06)	ns
<b>BMI, kg/m<sup>2</sup></b>	<b>21.7 (0.9)</b>	<b>34.7 (32.9-44.2)</b>	<b>&lt; 0.001</b>
<b>Waist circumference, cm</b>	<b>79.5 (5.0)</b>	<b>120.3 (5.9)</b>	<b>&lt; 0.001</b>
<b>Hip circumference, cm</b>	<b>88.9 (3.5)</b>	<b>123.0 (4.9)</b>	<b>&lt; 0.001</b>
Waist/hip ratio	0.90 (0.06)	0.98 (0.03)	ns
Fasting glucose, mg/dL	84.0 (2.5)	85.9 (2.6)	ns
<b>Fasting insulin, mU/L</b>	<b>14.6 (1.7)</b>	<b>29.5 (3.3)</b>	<b>0.001</b>
<b>HOMA IR</b>	<b>3.0 (0.3)</b>	<b>6.4 (0.9)</b>	<b>0.003</b>
<b>OGIS</b>	<b>482.0 (23.0)</b>	<b>376.1 (35.7)</b>	<b>0.026</b>
HbA1c, %	5.0 (4.9-5.3)	5.4 (0.1)	ns
Triglycerides, mg/dL	98.9 (18.7)	99.5 (71.3-128.3)	ns
Total cholesterol, mg/dL	182.0 (5.1)	178.8 (9.1)	ns
LDL, mg/dL	103.1 (5.1)	110.4 (9.3)	ns
<b>HDL, mg/dL</b>	<b>59.1 (4.6)</b>	<b>45.9 (3.5)</b>	<b>0.040</b>
<b>CRP, mg/dL</b>	<b>0.04 (0.02-0.11)</b>	<b>0.34 (0.07)</b>	<b>0.001</b>
Serum creatinine, mg/dL	0.97 (0.04)	0.92 (0.04)	ns

## Conclusions

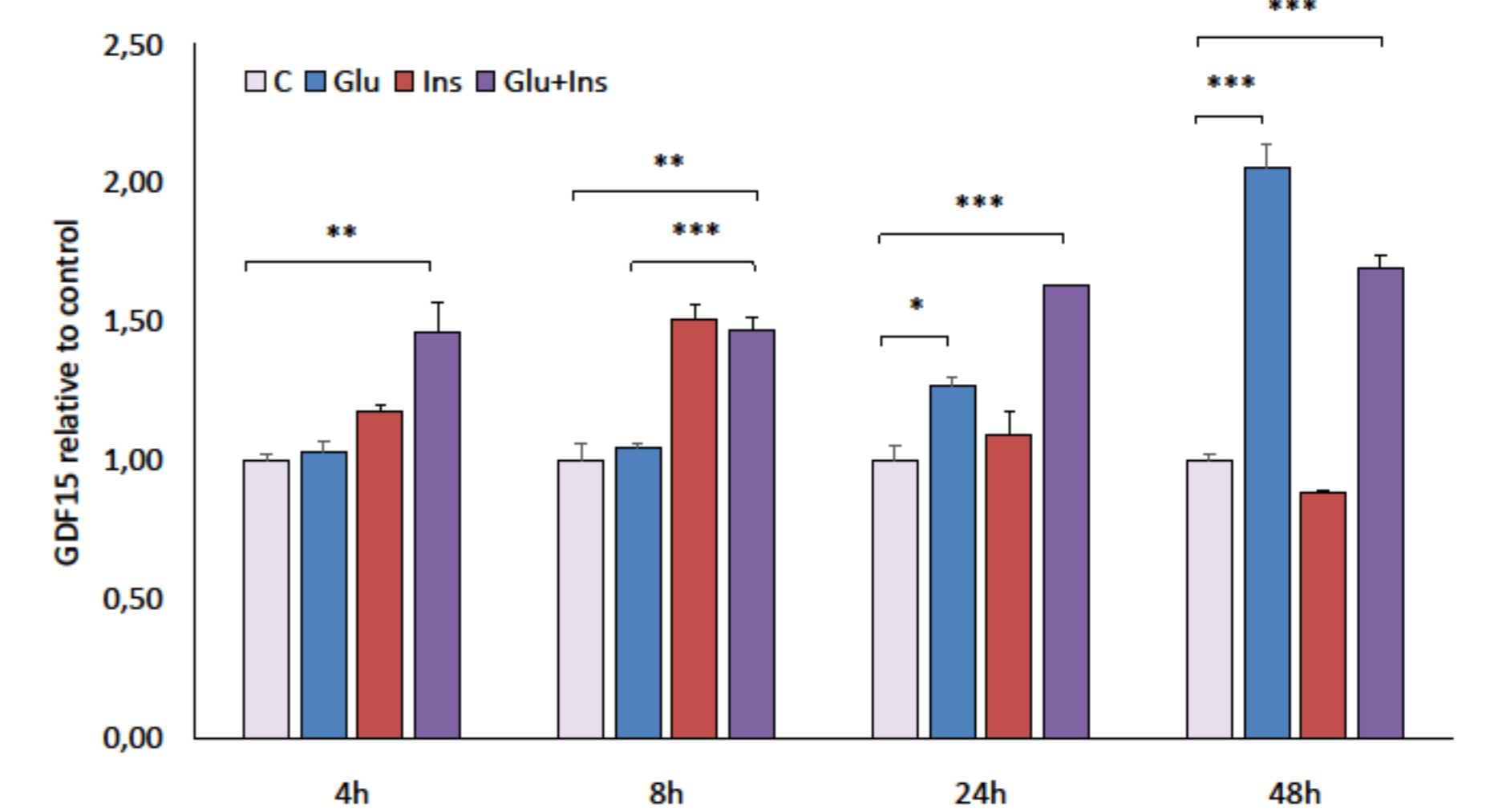
- GDF15 decreases during fasting and increases in response to high peaks in glucose and insulin concentrations following oral glucose ingestion in men.
- These changes are, at least in part, mediated via direct effects of glucose and insulin on GDF15 transcription and release.
- These data provide the first evidence on nutrient-related changes in GDF15 concentrations in humans.

## Regulation of GDF15 transcription and secretion

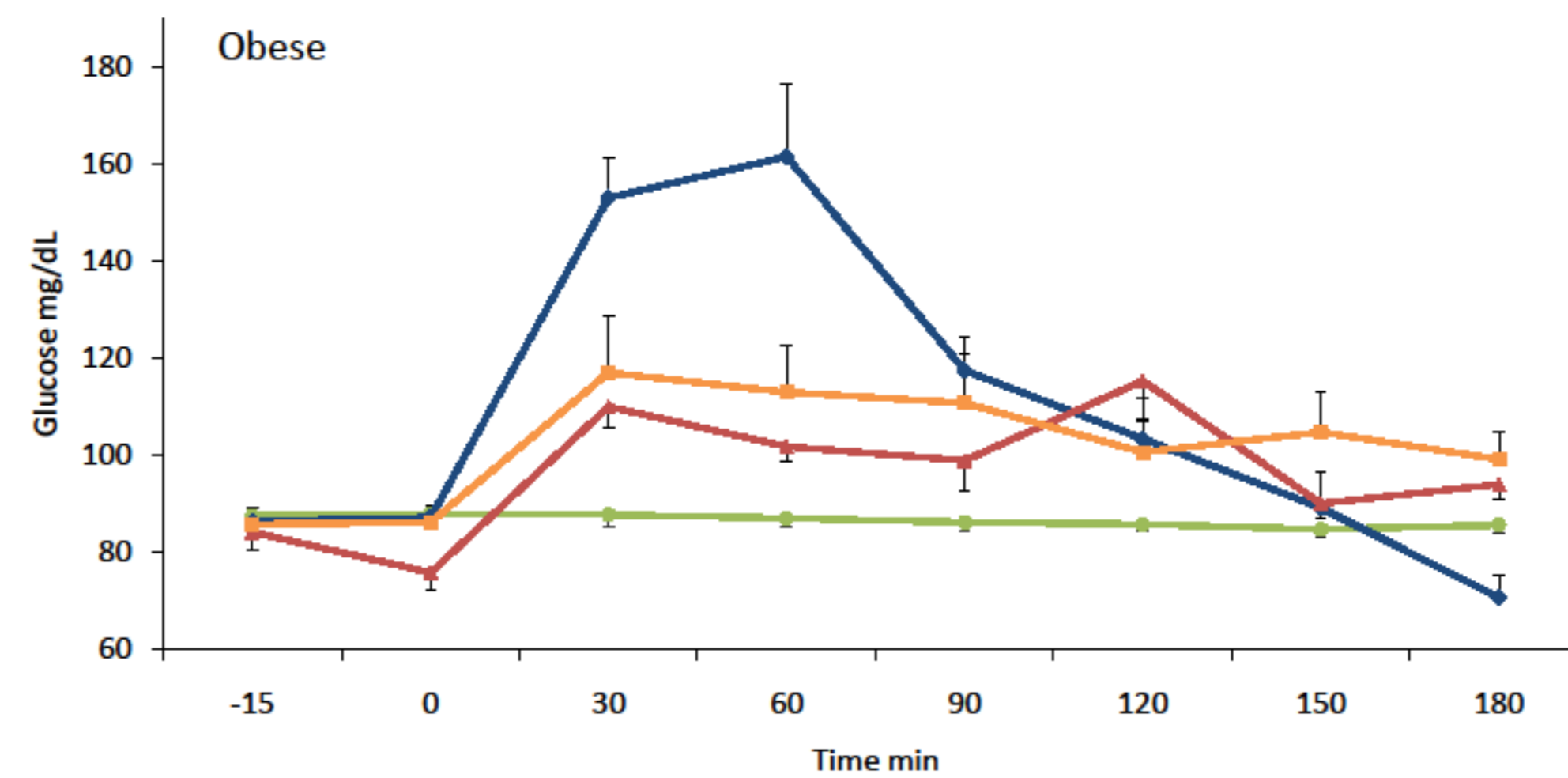
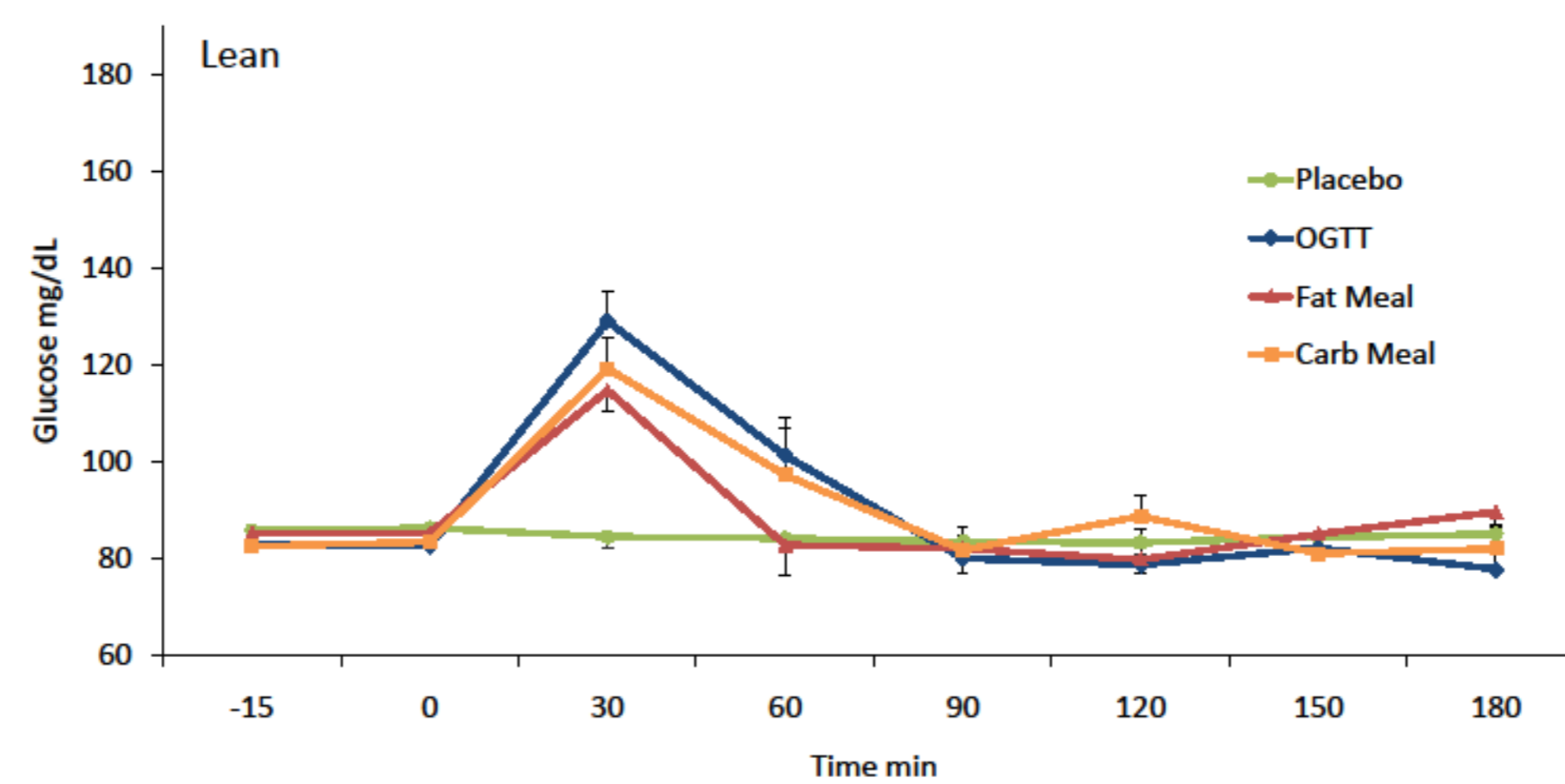
GDF15 transcription



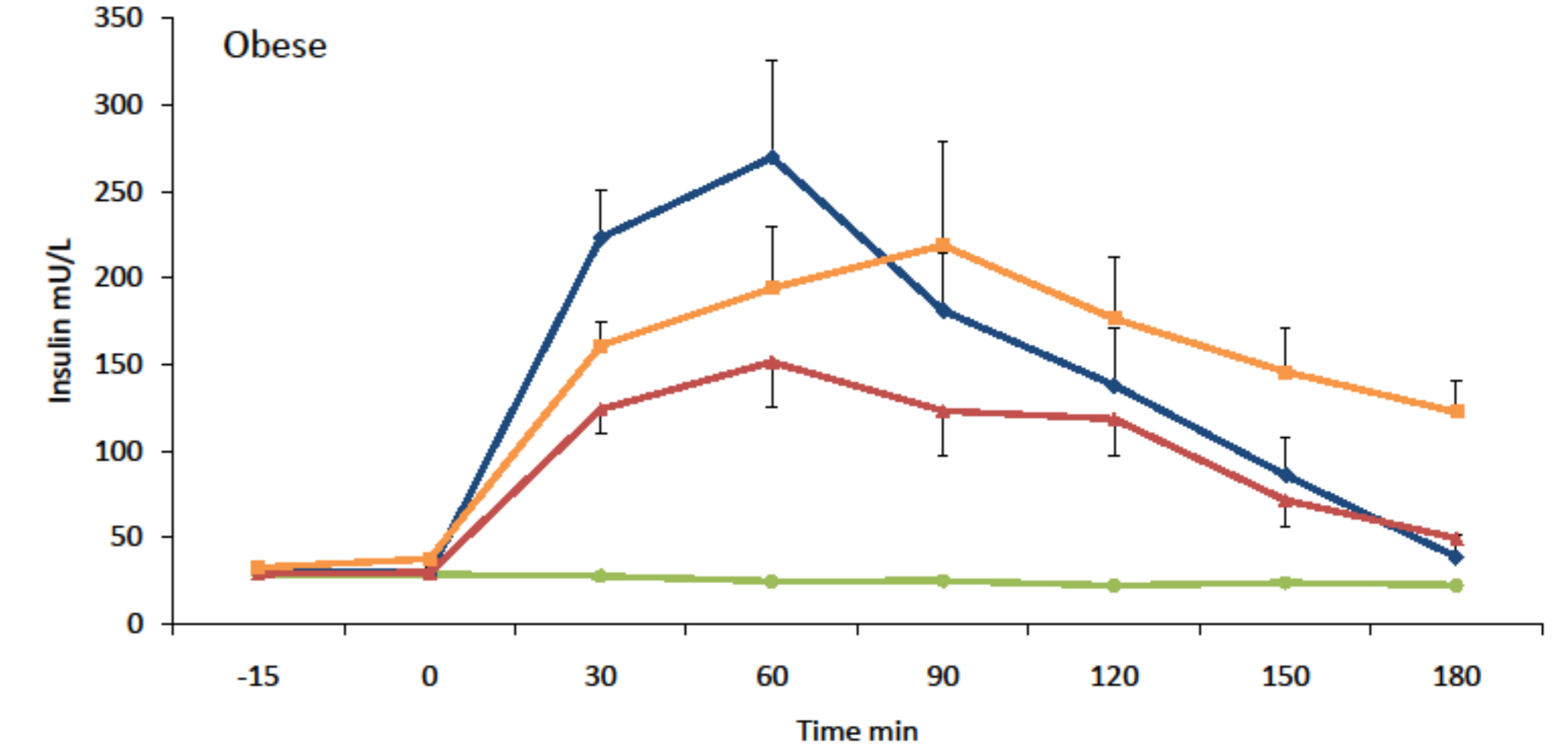
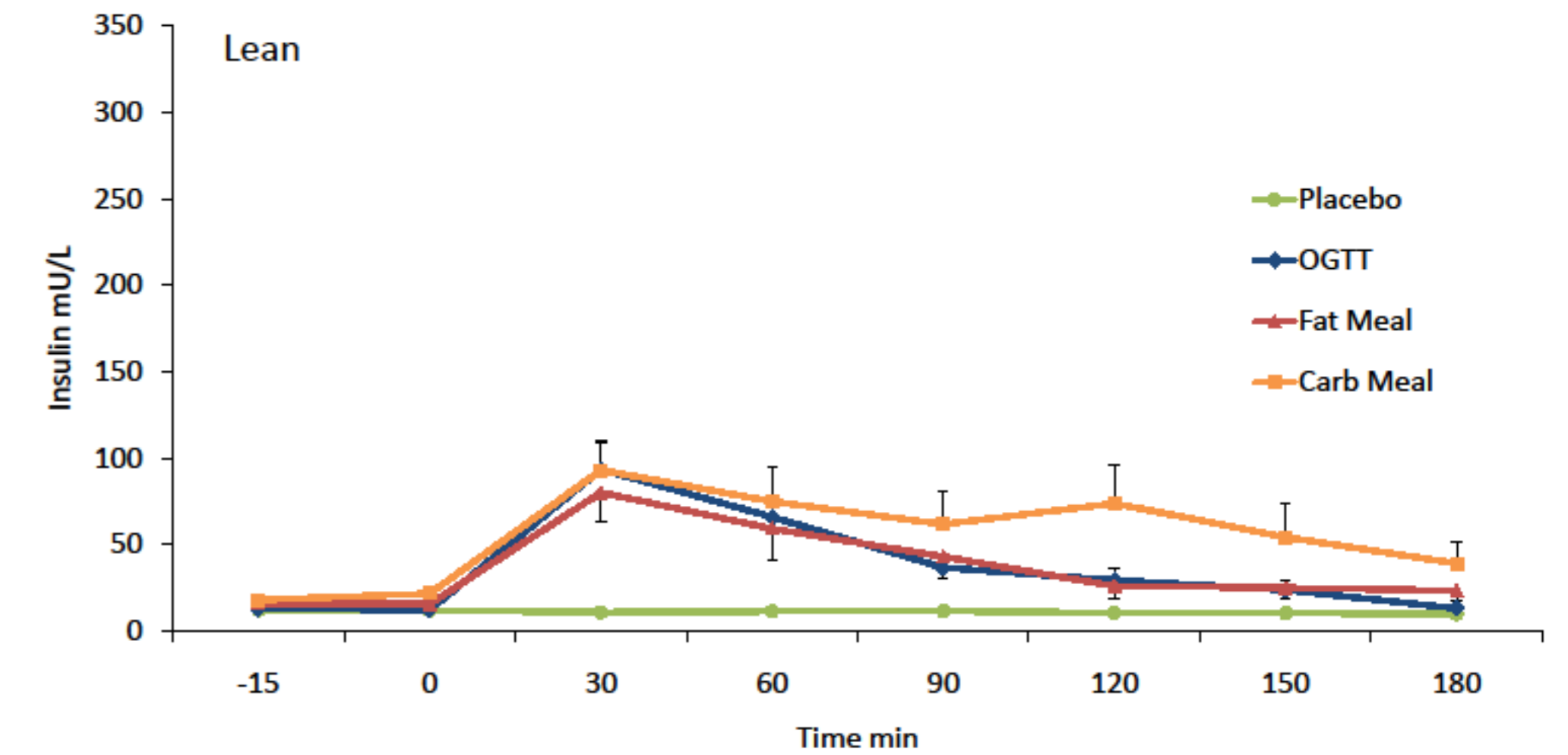
GDF15 release (ELISA from culture supernatants)



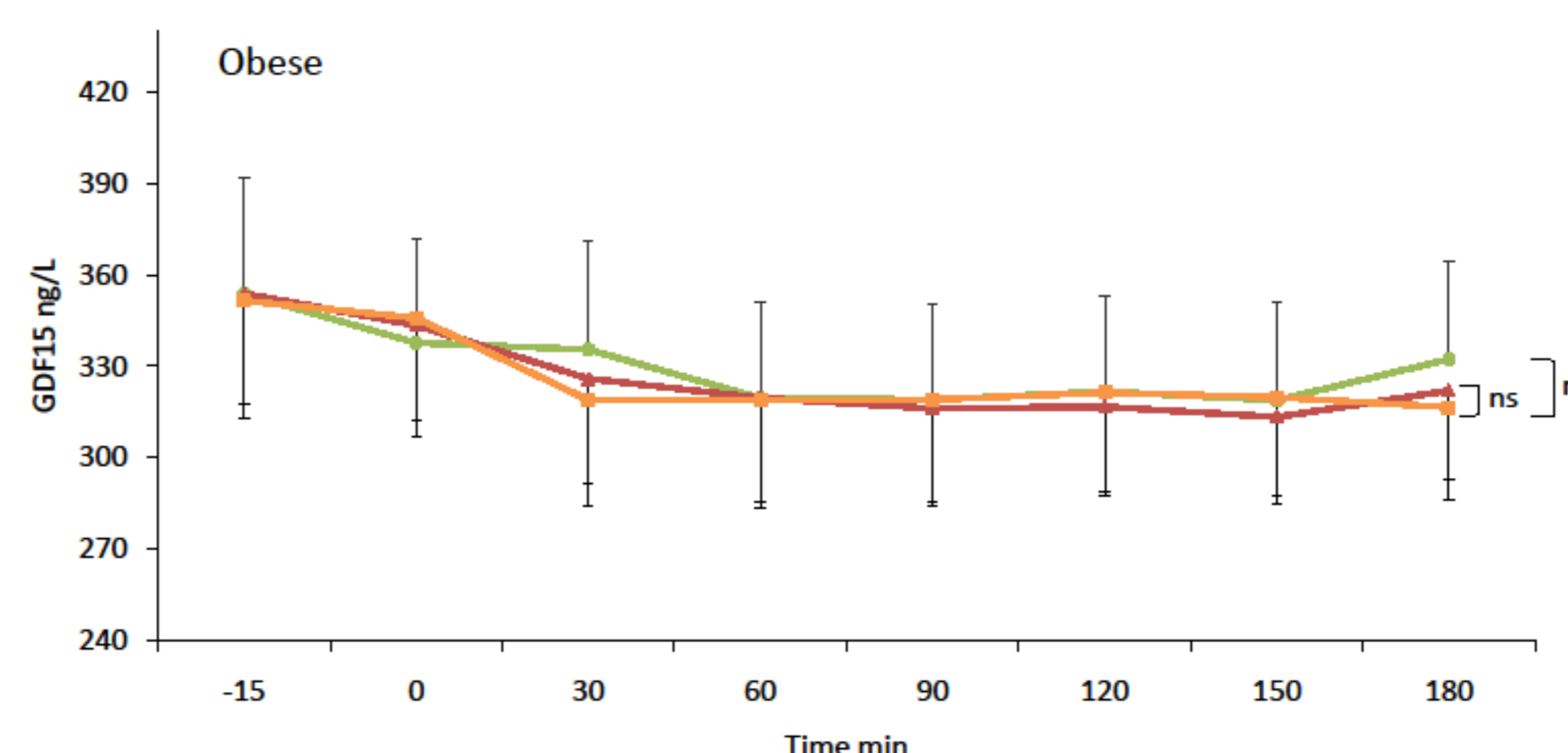
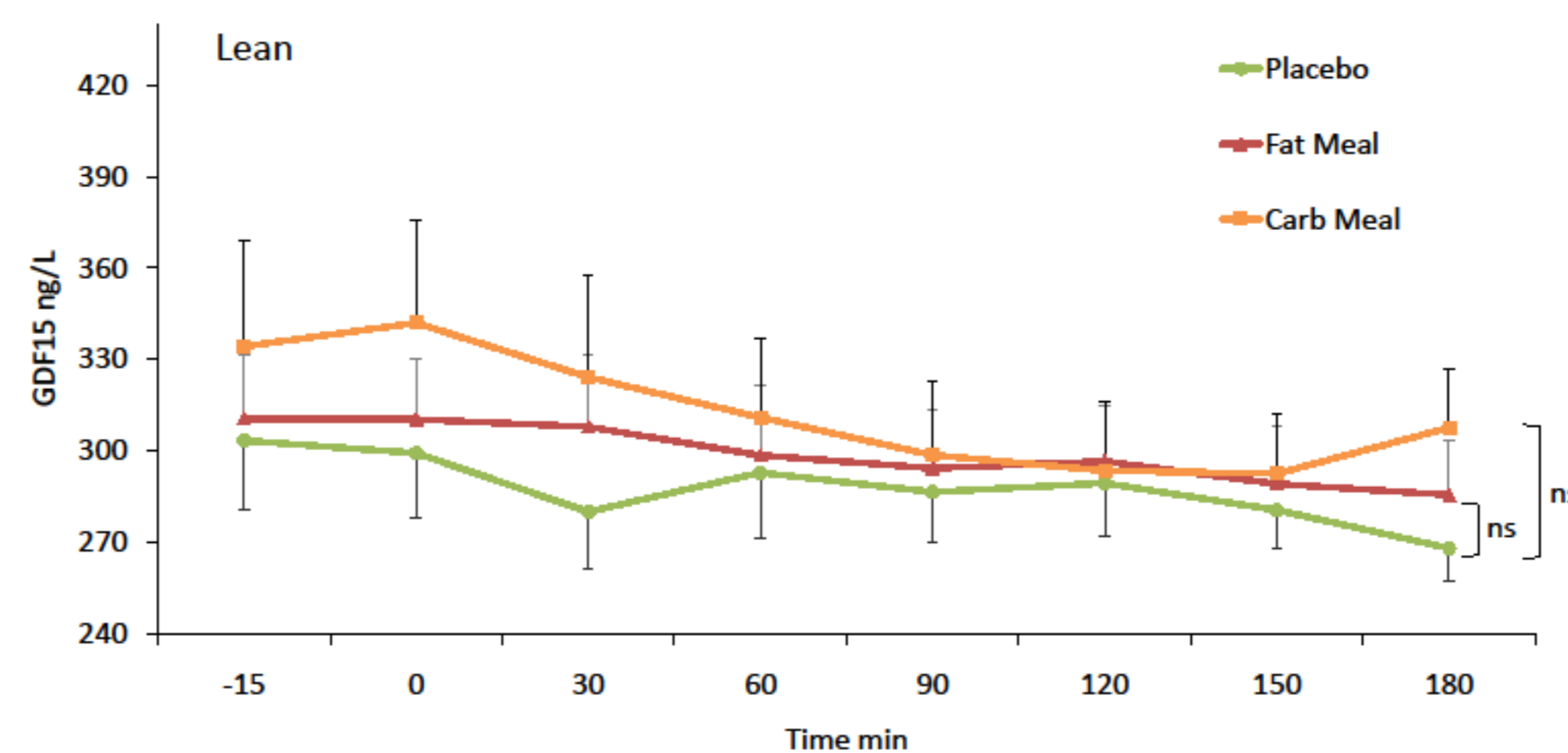
## Profiles of plasma glucose levels



## Profiles of plasma insulin levels



## Profiles of plasma GDF15 levels: Different meals



## Profiles of plasma GDF15 levels: Oral glucose load

