

# Regulation of the “Hunger hormone” called Ghrelin &

## Novel metabolic signatures of obesity and diabetes

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Andrea M. Haqq, MD MHS

Associate Professor

Department of Pediatrics, University of Alberta

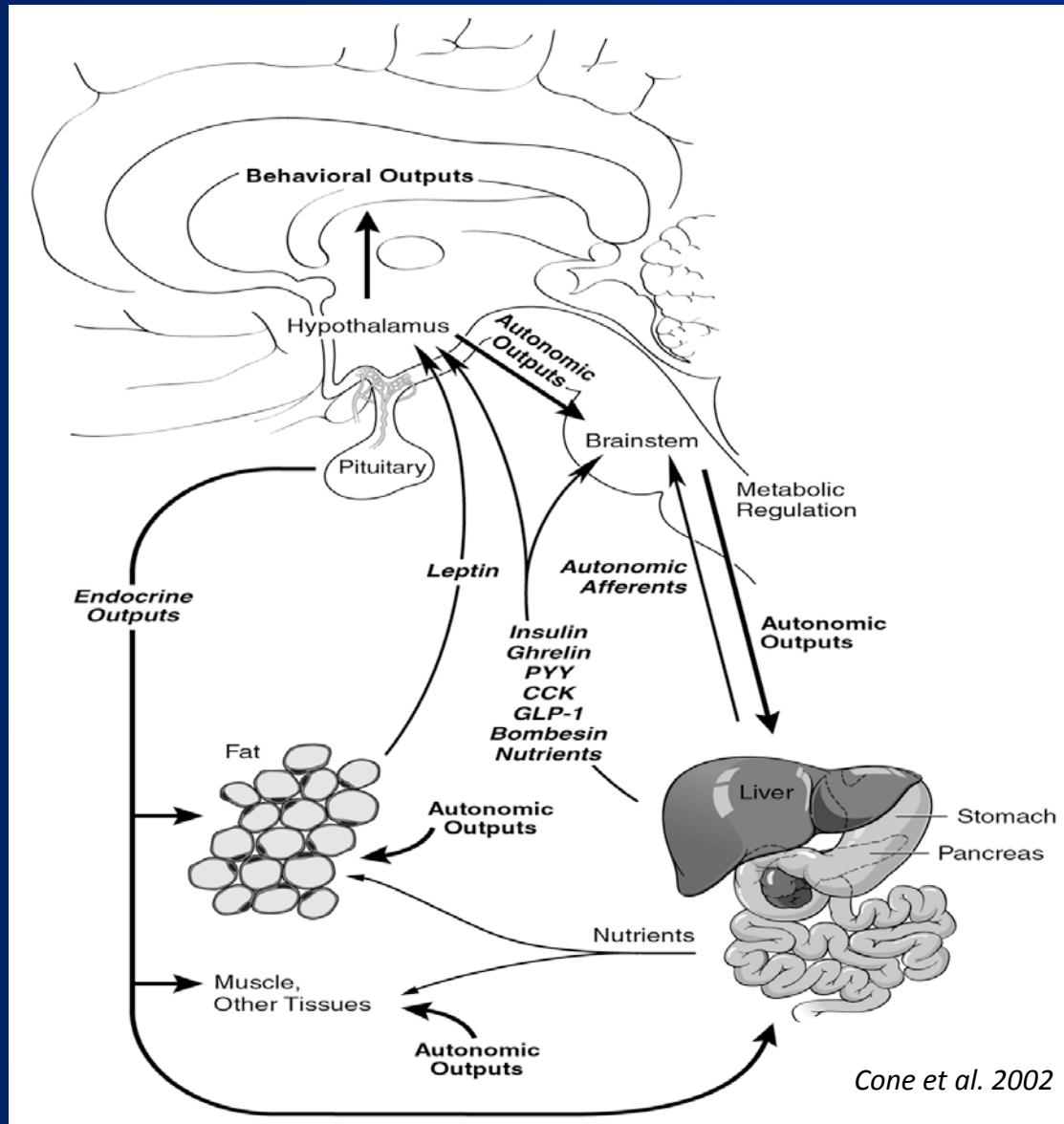
# Disclosures

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  - Alberta Diabetes Institute
  - Foundation for Prader Willi Research (FPWR-Canada)
  - Stollery Children's Hospital Foundation, University of Alberta

# Outline

- Dietary regulation of ghrelin
- Novel metabolic signatures of obesity and diabetes
  - Role of amino acid metabolism in the pathogenesis of obesity-associated insulin resistance

# Neuroendocrine Regulation of Food Intake and Body Weight



- Many hormones and proteins regulate food intake
- Released from tissues (such as fat tissue, liver, stomach, intestine)
- Circulate in blood
- In brain, signal fullness (satiety) or hunger

# **GHRELIN:**

## **Food Stimulating “Hunger” Hormone**

- Made in the stomach → released into blood → in brain signals need to eat
- In humans, ghrelin injection increases food intake by 28%
- Ghrelin levels in blood increase before meals (hunger) and falls after meals (fullness)

# Prader-Willi Syndrome



4 mo



22 mo



5 1/2 yr

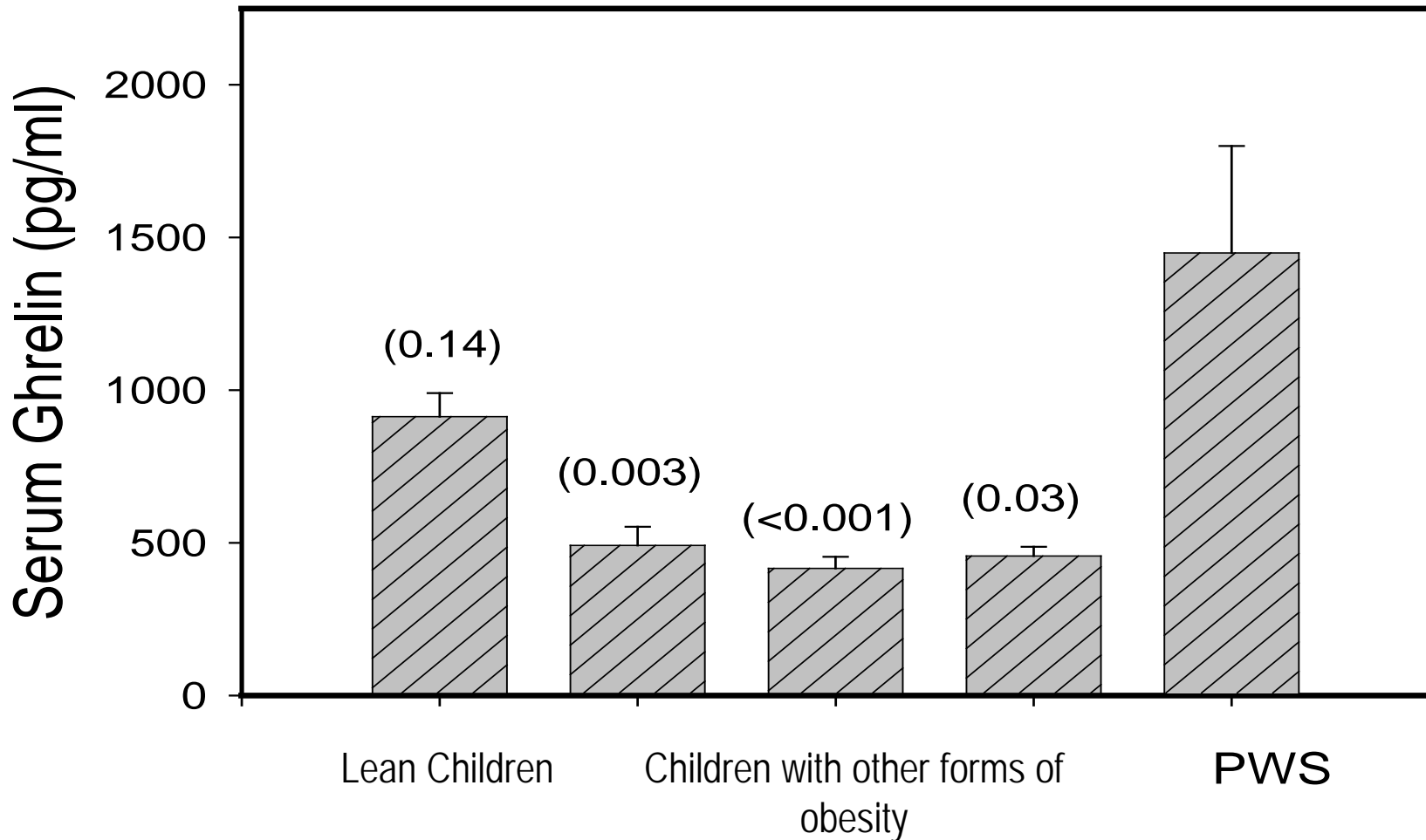


7 yr

Carrel et al. 2002

# Ghrelin Concentrations are Much Higher in Children with Prader-Willi Syndrome (Genetic obesity syndrome)

Haqq, et al. JCEM 88:174-178, 2003



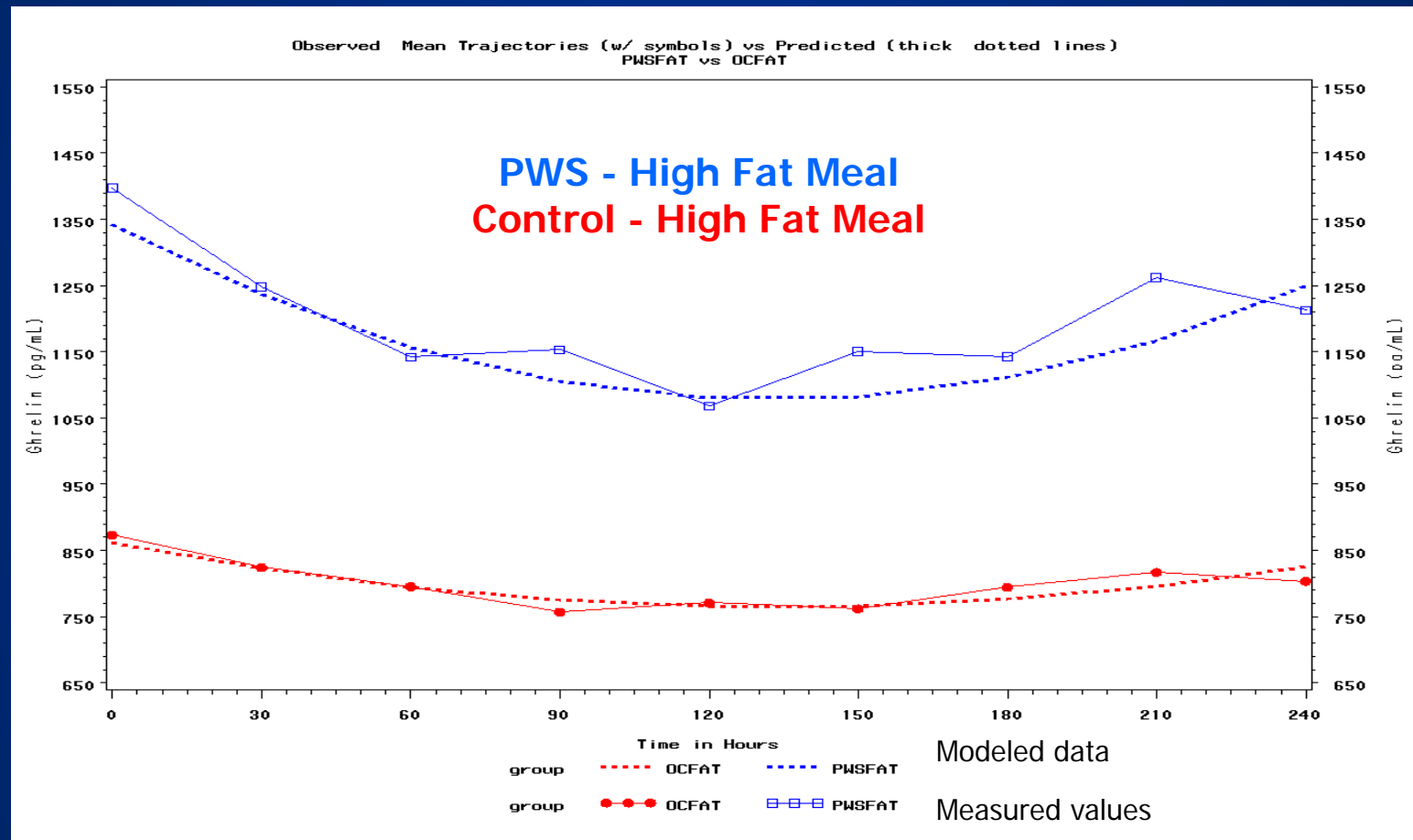
# Postprandial Regulation of Ghrelin

- Circulating levels of ghrelin peak during fasting prior to a meal and are suppressed after meals (reciprocal to insulin), suggesting a possible role in meal initiation (*Cummings, 2001*)
- The postprandial suppression of ghrelin is dependent on the type of ingested macronutrient:
  - Carbohydrate > Fat,  $\uparrow\downarrow$  protein is highly variable (*Erdmann, 2003; Al Awar, 2005; Greenman, 2004*)

# Methods

- 14 children with PWS (n=4 with Uniparental Disomy)
  - median age: 11.35 years   median BMI-Z-score: 2.15
- 14 equally obese children without PWS
  - median age: 11.97 years   median BMI-Z score: 2.35
- Subjects given one of two isocaloric breakfast meals on two separate testing days:
  - 1.) High Carbohydrate
  - 2.) High Fat
- Fasting blood sample and samples every 30 minutes for 4 hours after meal
  - total ghrelin concentration

# Comparison of PWS vs. Childhood obese Controls: High Fat Meal

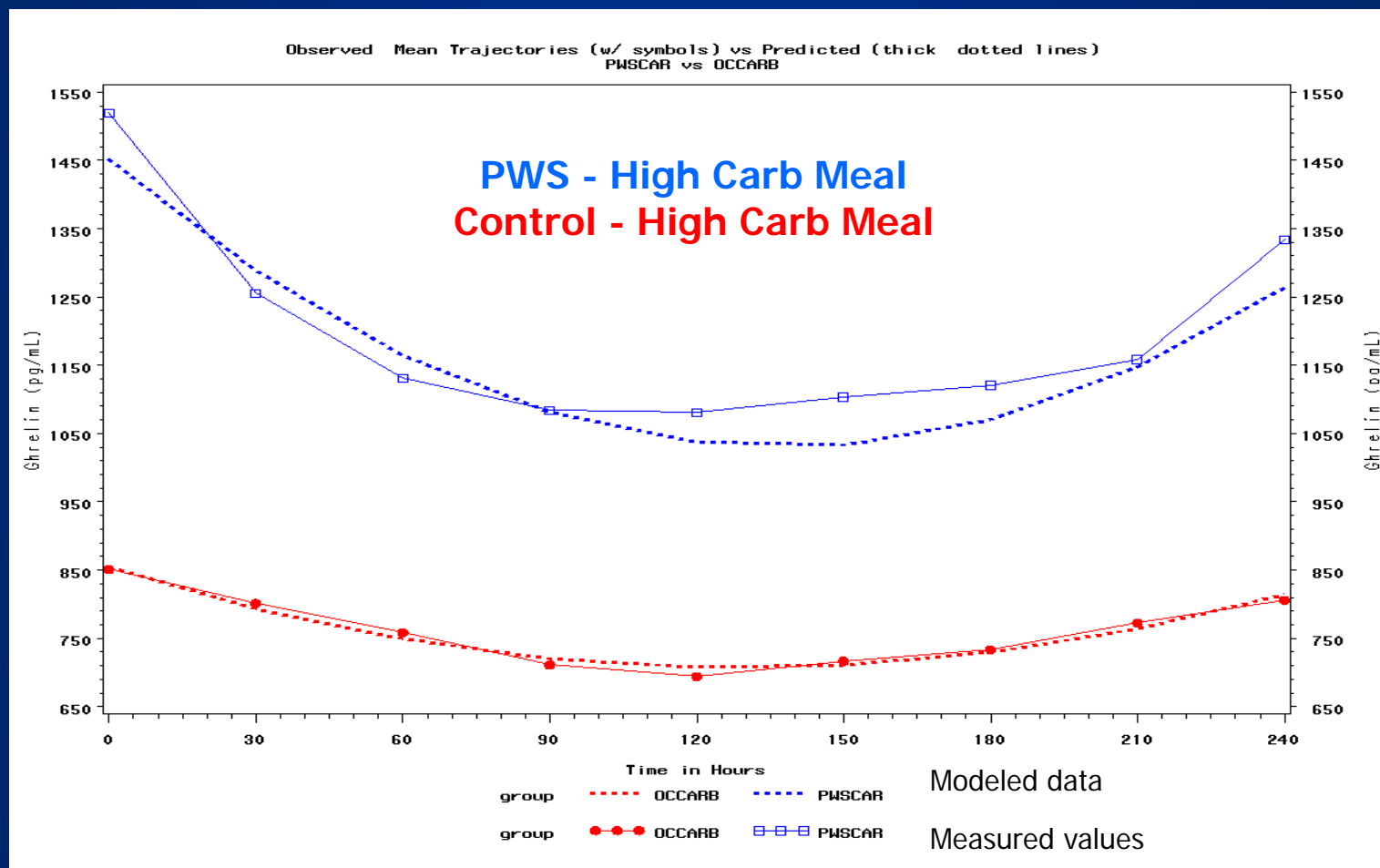


**PWS Baseline > OC Baseline [p<0.0001]**

**PWS rate of ghrelin suppression > OC rate of suppression [p=0.001]**

**PWS rate of rebound in ghrelin post-meal > OC rate of rebound [p=0.0013]**

# Comparison of PWS vs. BMI-Matched Controls: High Carb Meal



**PWS Baseline > OC Baseline [p<0.0001]**

**PWS rate of ghrelin suppression > OC rate of suppression [p<0.0001]**

**PWS rate of rebound in ghrelin post-meal > OC rate of rebound [p<0.0001]**

# Conclusions I

- Ghrelin in the children with PWS is lowered by feeding either a high carbohydrate or high fat meal (high carbohydrate lowered ghrelin more than high fat)
- The rebound in ghrelin levels after the meal is more rapid in the children with PWS than in controls
- This ghrelin rebound may promote food craving after meals in children with PWS, thereby facilitating progressive weight gain
- Not known how high protein meals would effect ghrelin levels in children with PWS

# Novel Metabolic Signatures of Obesity: Role of amino acid metabolism in pathogenesis of insulin resistance

Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, Haqq AM, Shah SH, Arlotto M, Slentz CA, Rochon J, Gallup D, Ilkayeva O, Wenner BR, Yancy WE, Eisenson H, Musante G, Surwit R, Millington DS, Butler MD, and Svetkey LP

*A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance Cell Metabolism 9: 311–326, 2009.*

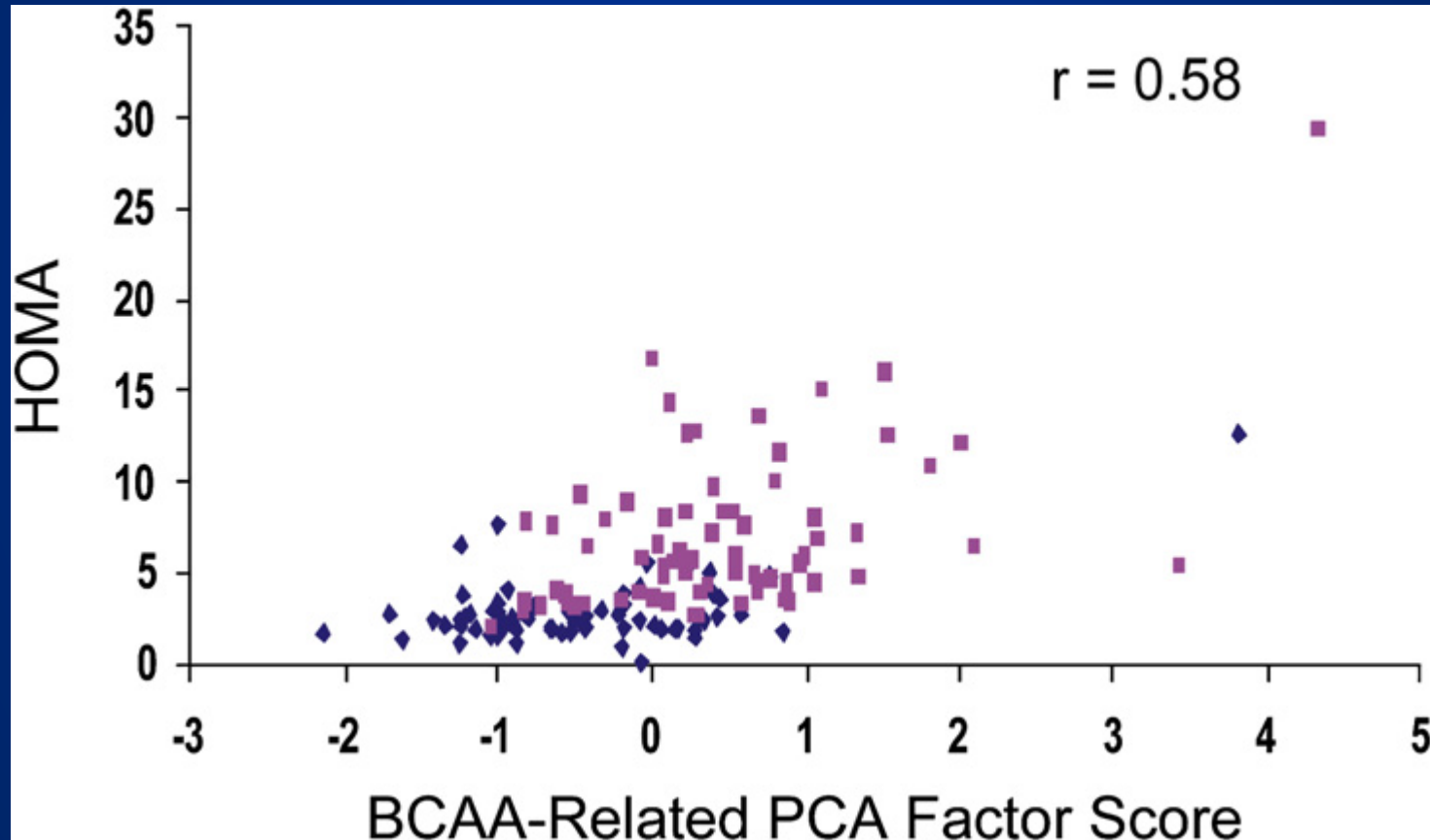
Laferrere B, Arias S, Swerdlow N, Gorroochurn P, Bose M, Bawa B, Teixeira J, Stevens RD, Wenner BR, Bain JR, Muehlbauer MJ, Haqq A, Lien L, Shah S, Svetkey LS, Newgard CB

*Differential metabolic impact of gastric bypass versus dietary intervention in obese diabetic persons despite identical weight loss. (Sci Transl Med. 2011 Apr 27;3(80):80re2).*

# Branched chain amino acids

- Amino acids are the building blocks of proteins
- BCAAs (branched chain amino acids) consist of leucine, isoleucine, and valine, and are “essential” amino acids
  - the body cannot synthesize them from precursors so they must be obtained directly from the diet
  - Homeostasis of BCAAs is determined largely by catabolism in the liver, brain or muscle

# Branched Chain Amino acids (BCAAs) and Insulin Resistance



Diamonds, lean subjects (n = 67);  
Squares, obese subjects (n = 74)

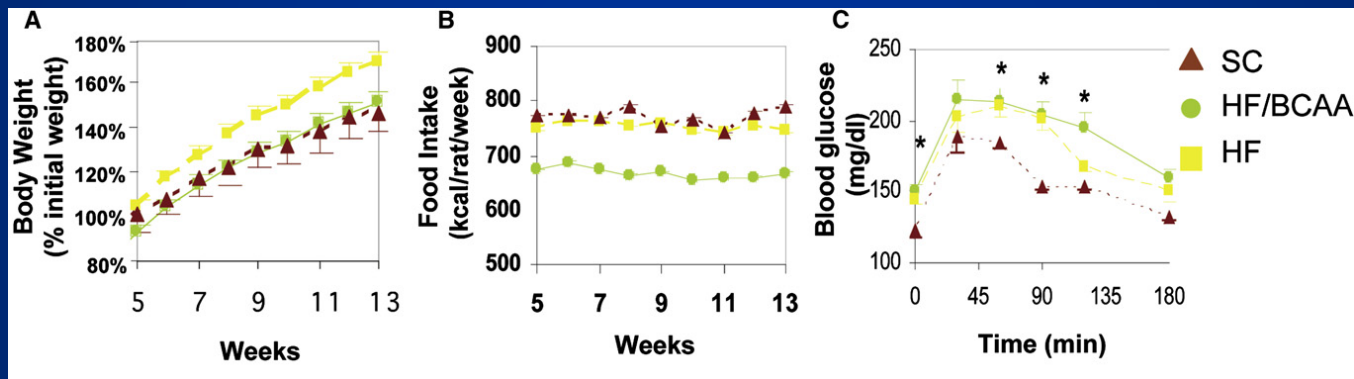
# Obese individuals have higher BCAAs than Lean individuals

**Table 4. Amino acids, uM.** All results presented as medians (25th, 75th percentile).

	<b>Obese (n=74)</b>	<b>Lean (n=67)</b>	<b>p-value</b>
Valine	281.4	235.3	< 0.0001
Leucine/Isoleucine	170.0	149.0	< 0.0001
Glutamate/Glutamine	118.4	81.2	< 0.0001
Glycine	282.6	328.4	0.0007
Alanine	433.4	367.3	< 0.0001
Phenylalanine	72.6	61.6	< 0.0001
Tyrosine	79.5	67.1	< 0.0001
Aspartate/Asparagine	20.1	16.5	< 0.0001
Arginine	135.2	115.3	0.0007

Median values shown in table

# Supplementation of a high fat diet with BCAAs promoted Insulin resistance in rats

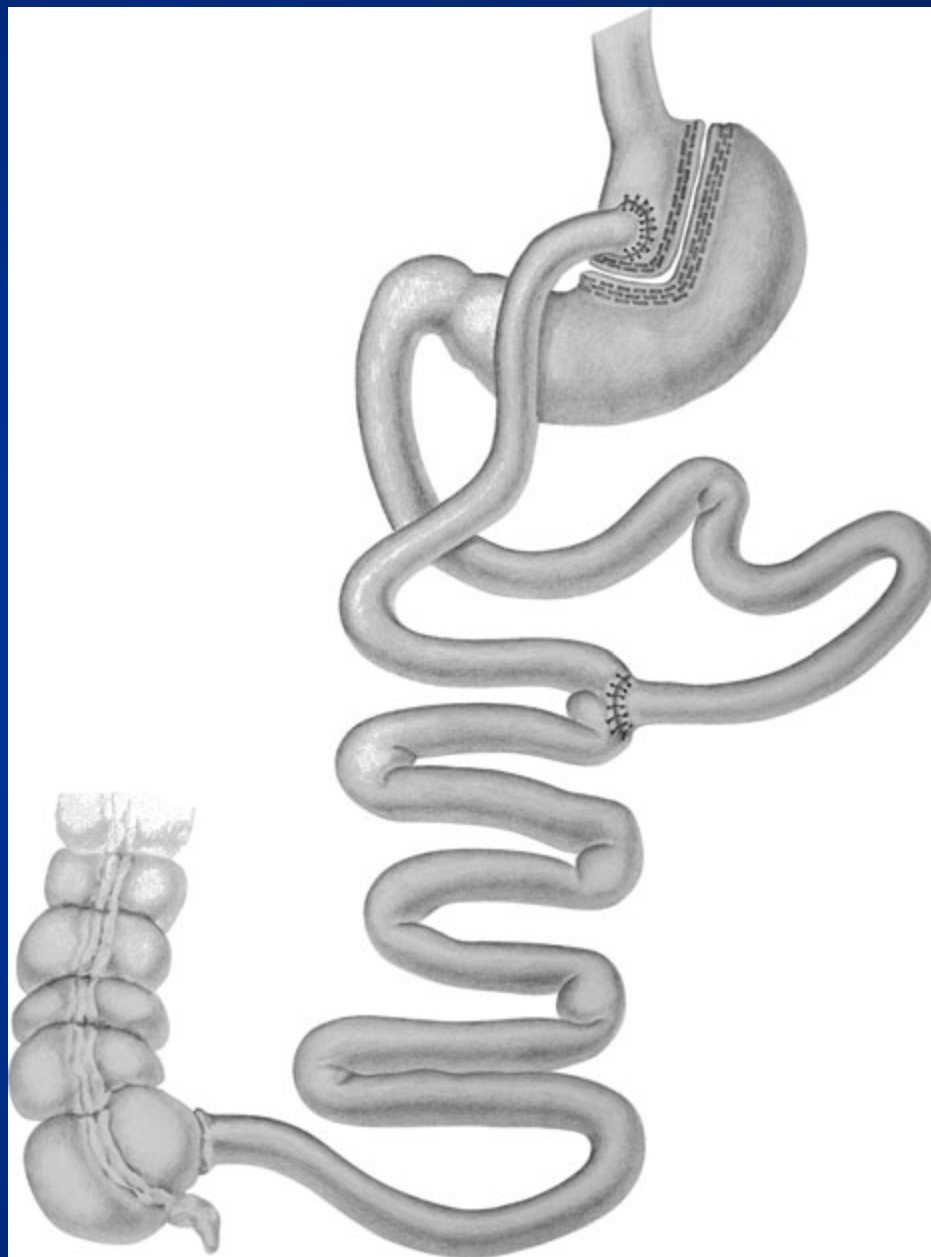


- Circulating amino acids may promote insulin resistance via disruption of insulin signaling in skeletal muscle

# Elevation in BCAAs are associated with increased risk in development of T2DM

- Nested Case-control (189 cases and matched age, BMI, sex controls) study of the Framingham Offspring study
  - Baseline elevations in BCAAs (Leucine, Val, Isoleucine) and Phenylalanine and Tyrosine → ~4 fold risk for development of T2DM
  - Individuals in the top quartile of amino acid score (for isoleucine, Phe and Tyr) had 5-7 fold higher risk for development of diabetes compared with individuals in lowest quartile
  - Findings now replicated in an independent prospective cohort
  - Suggests a hyperaminoacidemia “biomarker” can identify early insulin resistance preceding clinical diabetes by years

- RYGB is performed by dividing the stomach and creating a small reservoir (30 ml) anastomosed to the distal end of the jejunum, which is divided at about 75 cm from the ligament of Treitz.
- The proximal end of the transected bowel is then sutured in an end to the side of the jejunum at about 100 cm from the gastro-jejunal anastomosis.
- T2DM resolves in approx 85% of RYGB cases within days prior to significant weight loss!



# Improvement in glucose tolerance in obese subjects post-gastric bypass is associated with decline in BCAAs



- Despite equivalent 10kg wt loss, GBP only results in significant decrease in total AA and BCAAs
- BCAAs and related metabolites were uniquely correlated with degree of insulin resistance (HOMA-IR)
- Mechanism remains unclear but perhaps related to increased catabolism of BCAAs

# Conclusions II – BCAA Story

- BCAAs and related metabolites are associated with obesity, insulin resistance and diabetes
- Further studies are required to understand the genetic and environmental contributions to elevations in BCAAs
- These elevations in BCAAs might be responsive to therapeutic interventions to improve insulin resistance and future diabetes risk

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## Contact Information

Andrea M. HAQQ

Email: [haqq@ualberta.ca](mailto:haqq@ualberta.ca)

Michelle Mackenzie

Phone: **780-407-7241** or  
***michelle.mackenzie@ualberta.ca***