Pain, Metabolism and Weight Management

Michael Veltman
MBBS FANZCA FASE FFPMANZCA

Overview

Epidemiology

Evidence base for diet

Physiology

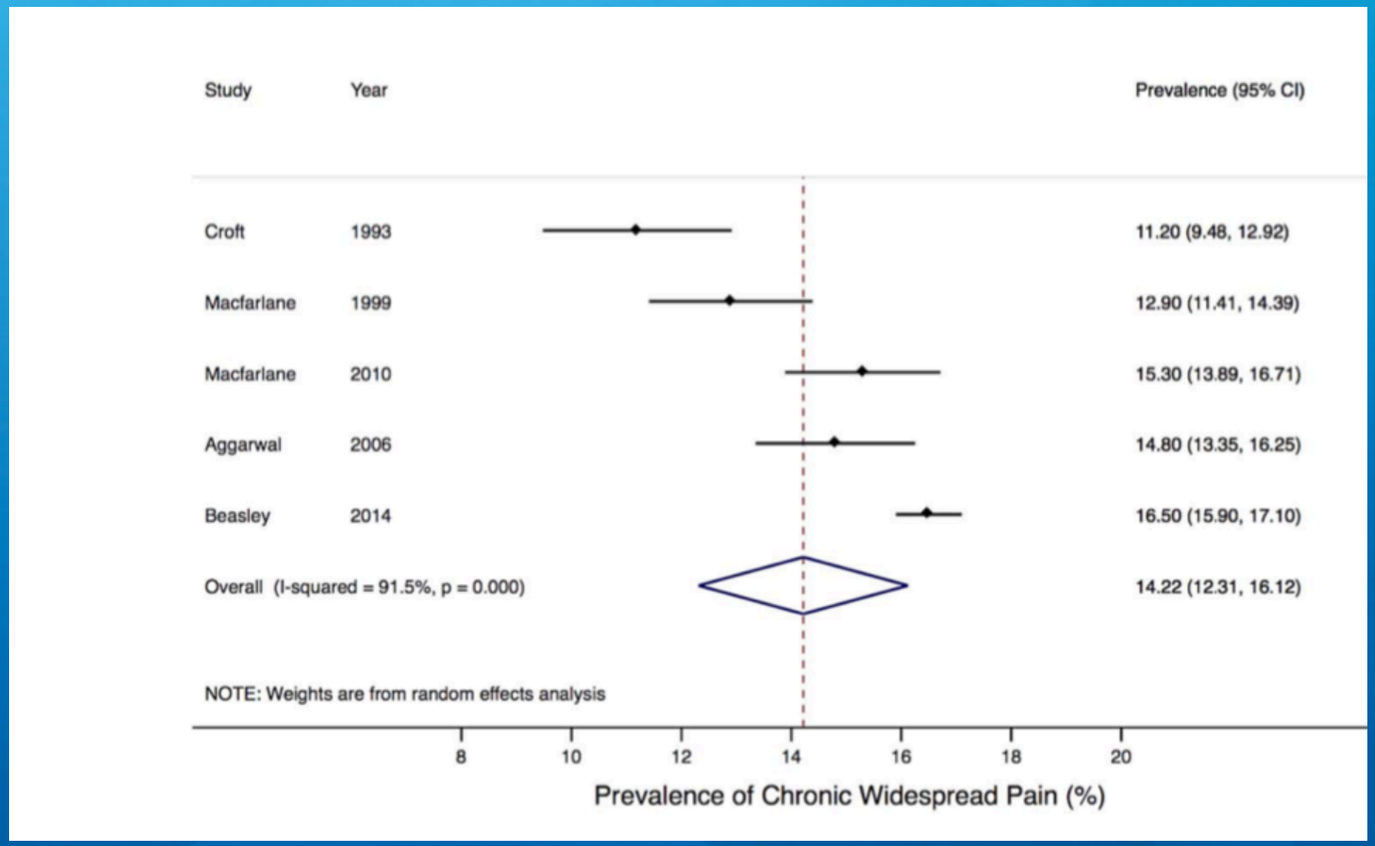
Treatment options

Epidemiology

Epidemiology

Chronic pain is a common condition

- Probably around 20% of the population
- Some estimates are higher (30-50%)
- Associated with age.

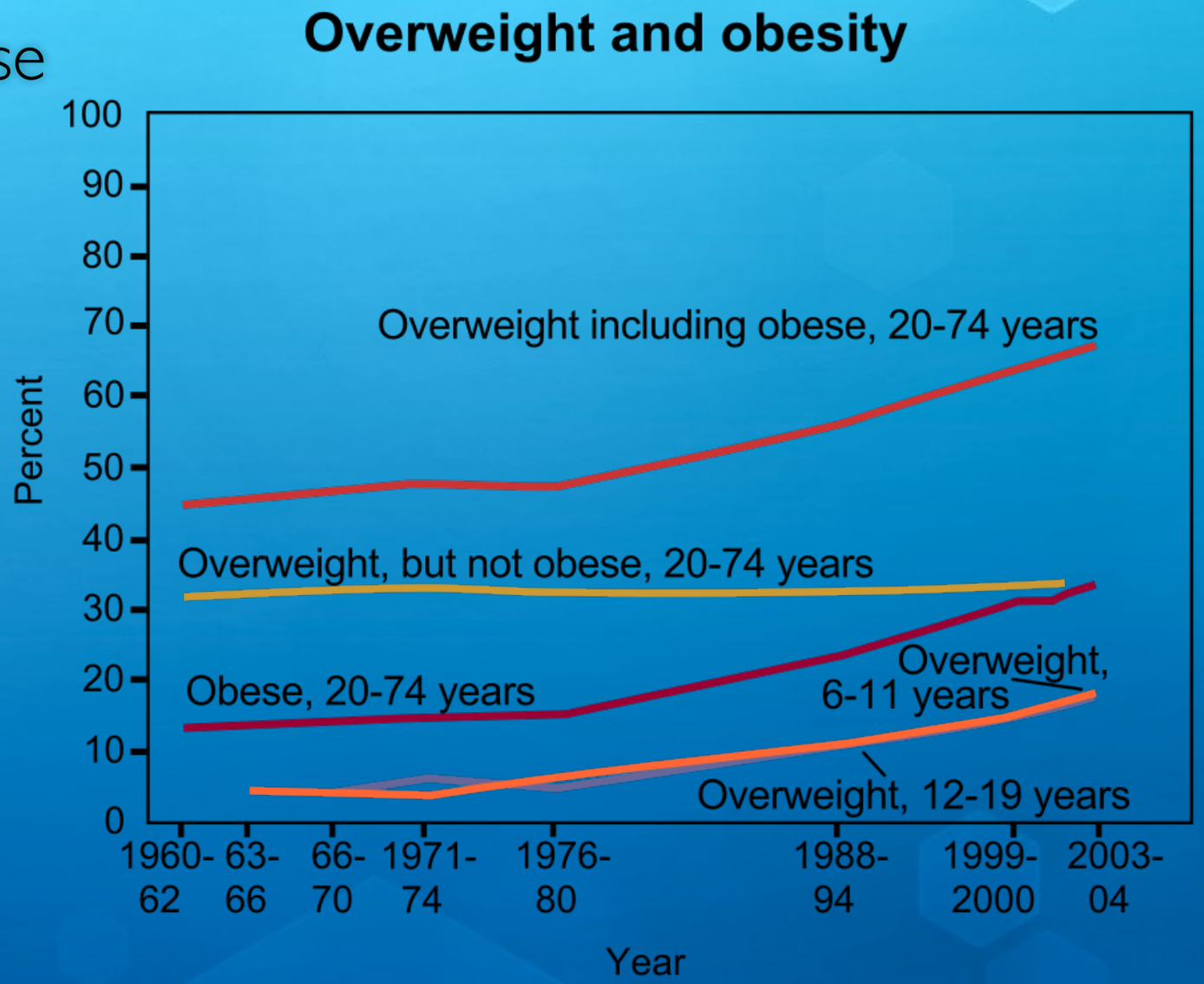


Epidemiology

Incidence of obesity started to rise from around the mid 1970's

Prior to that things were stable.

So what happened in the 1970's?



SOURCES: Centers for Disease Control and Prevention, National Center for Health Statistics, *Health, United States, 2006,* Figure 13. Data from National Health and Nutrition Examination Survey

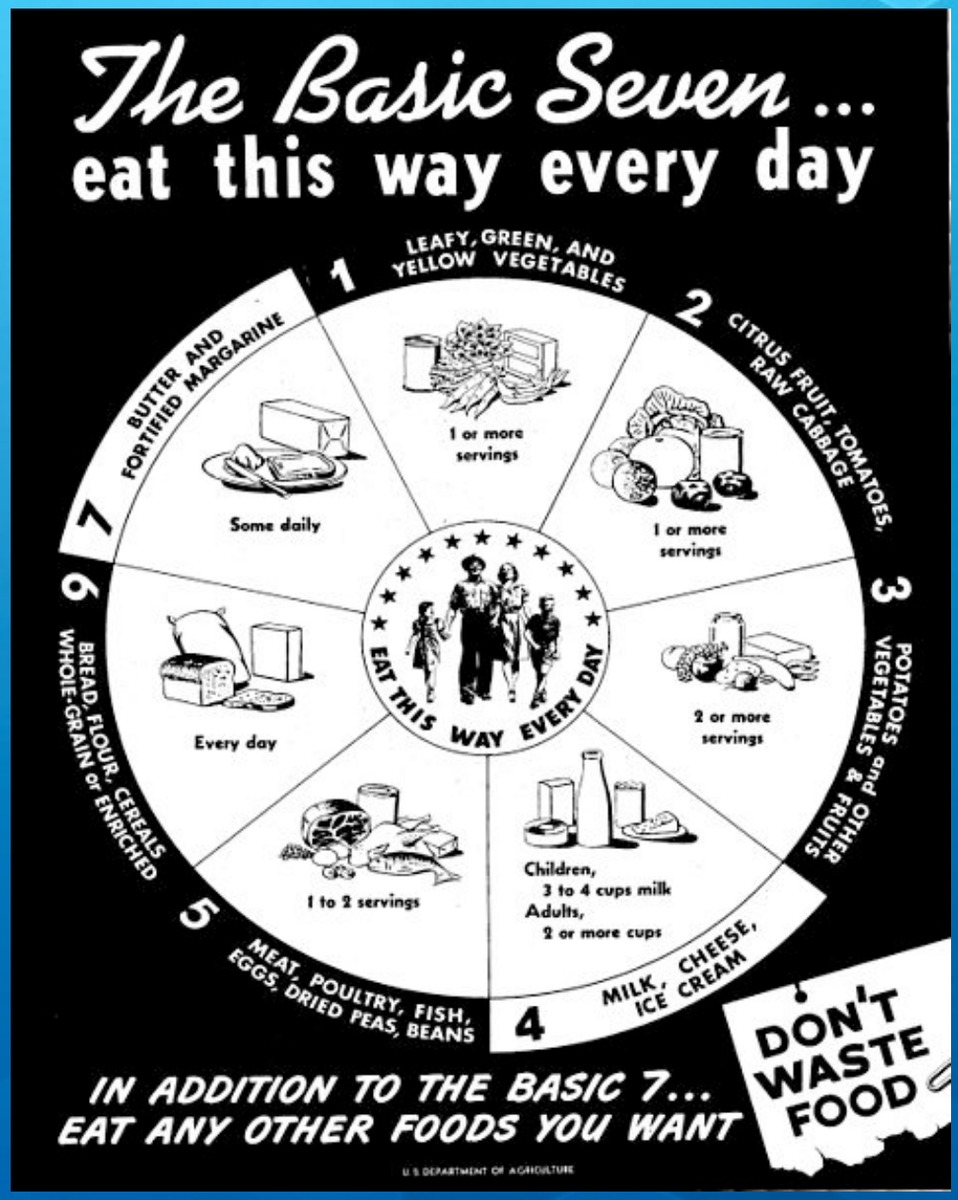
Epidemiology

The idea of "basic foods" was first developed in1972 in Sweden

- "Basic Foods" had to be cheap and nutritious

- "Supplemental foods" added nutrition missing from basic foods.

Rapidly adopted around the world.

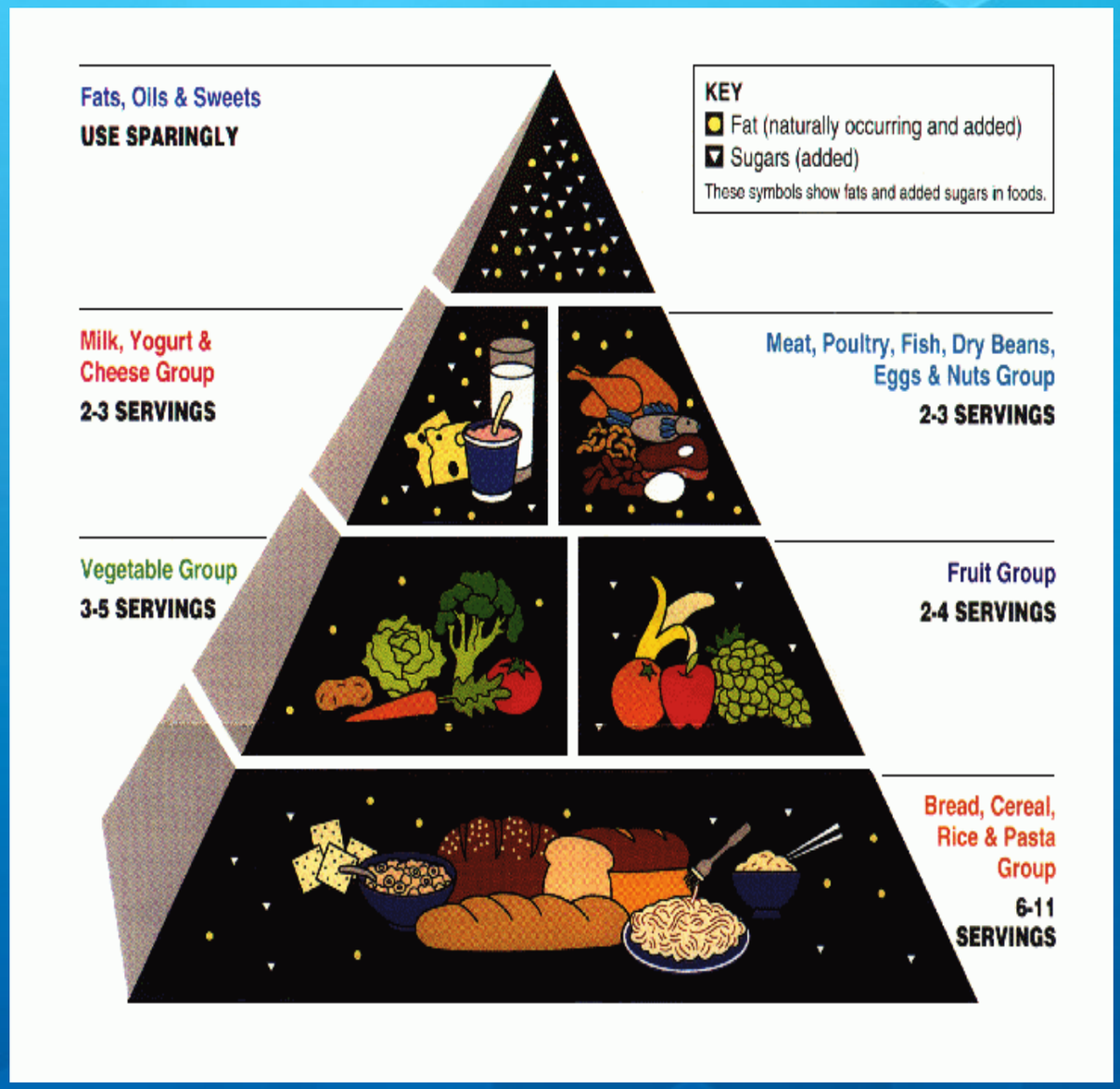


Epidemiology

Food pyramid evolved

- Often driven by agriculture.

- Really no evidence base.



Pain and Obesity - Relationship?

Prospective population based cohort study

- 78 973 people in Nord-Trøndelag County

- 11 years follow up

  - 1995-6 (Hunt 2)
  - 2006-2008 (Hunt 3)

37 071 had complete data

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 17, No 11 (November), 2016: pp 1246-1256
Available online at www.jpain.org and www.sciencedirect.com

Long-Term Changes in Musculoskeletal Pain Sites in the General Population: The HUNT Study

Ingunn Mundal,[*,†] Johan Håkon Bjørngaard,[‡,§] Tom I. L. Nilsen,[‡] Barbara I. Nicholl,[¶] Rolf W. Gråwe,[*,||] and Egil Andreas Fors[‡]

*Departments of *Neuroscience, and [‡]Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway.*
[†]Psychiatric Out-Patient Unit, Kristiansund Hospital, Møre and Romsdal Hospital Trust, Kristiansund, Norway.
[§]Forensic Department and Research Centre Bröset, [||]Department of Research and Development, Clinic of Substance Use and Addiction Medicine, St. Olav's University Hospital, Trondheim, Norway.
[¶]Institute of Health and Wellbeing, University of Glasgow, Scotland, United Kingdom.

What factors predated pain?

Increases in number of pain sites independently predicted by:

- Anxiety
- Depression
- Sleeping problems
- Obesity

For each 3 points of BMI increase, one extra painful site 11 years later.

Table 4. Mean Change in Number of Pain Sites in HUNT2 (1995–1997) and HUNT3 (2006–2008) According to Change in Different Risk Factors

	Within-Subjects N = 26,875 Individuals in 48,669 Observations	
Risk Factor	*Mean Change**	*95% CI*
HADS score		
No anxiety or depression	Reference	
Depression, not anxiety	.17	.06–.28
Anxiety, not depression	.23	.15–.32
Anxiety and depression	.46	.34–.57
Sleeping difficulties		
No sleep problems	Reference	
Sleep problems	.31	.25–.38
Smoking status, never smoking	Reference	
Ex-smoker	.11	−.04 to .26
Current daily smoker	.11	−.05 to .26
BMI normal (18.5–24.9)	Reference	
Underweight (<18.5)	−.09	−.45 to .27
Overweight (25–29.9)	.08	.01–.14
Obese (≥30)	.14	.04–.25
Alcohol, monthly use, 0 times a month	Reference	
1 to 7 Times a month	.05	−.02 to .11
≥8 Times a month	−.04	−.14 to .06
Abstainer	−.03	−.16 to .10
Physical activity		
Inactive	Reference	
Active	.03	−.08 to .01
Pain sites from HUNT2 to HUNT3	−.07	−.11 to −.04

NOTE. Within-individual fixed effect linear regression.
*Adjusted for age, physical activity, and chronic disease when these variables were not the main variable of interest.

Evidence Base

Its simple, right?

$$WeightGain(kg) = (Intake - Expenditure)/7000$$

Doing the math over 40 years:

120 Kg versus 80 Kg (1 kg /year)

19 calories per day difference.

So that should be really easy to fix.

Evidence Base of standard treatment?

Diet does work

- Hirsch published in 1950's using diet control

- Showed that limiting portions caused weight loss

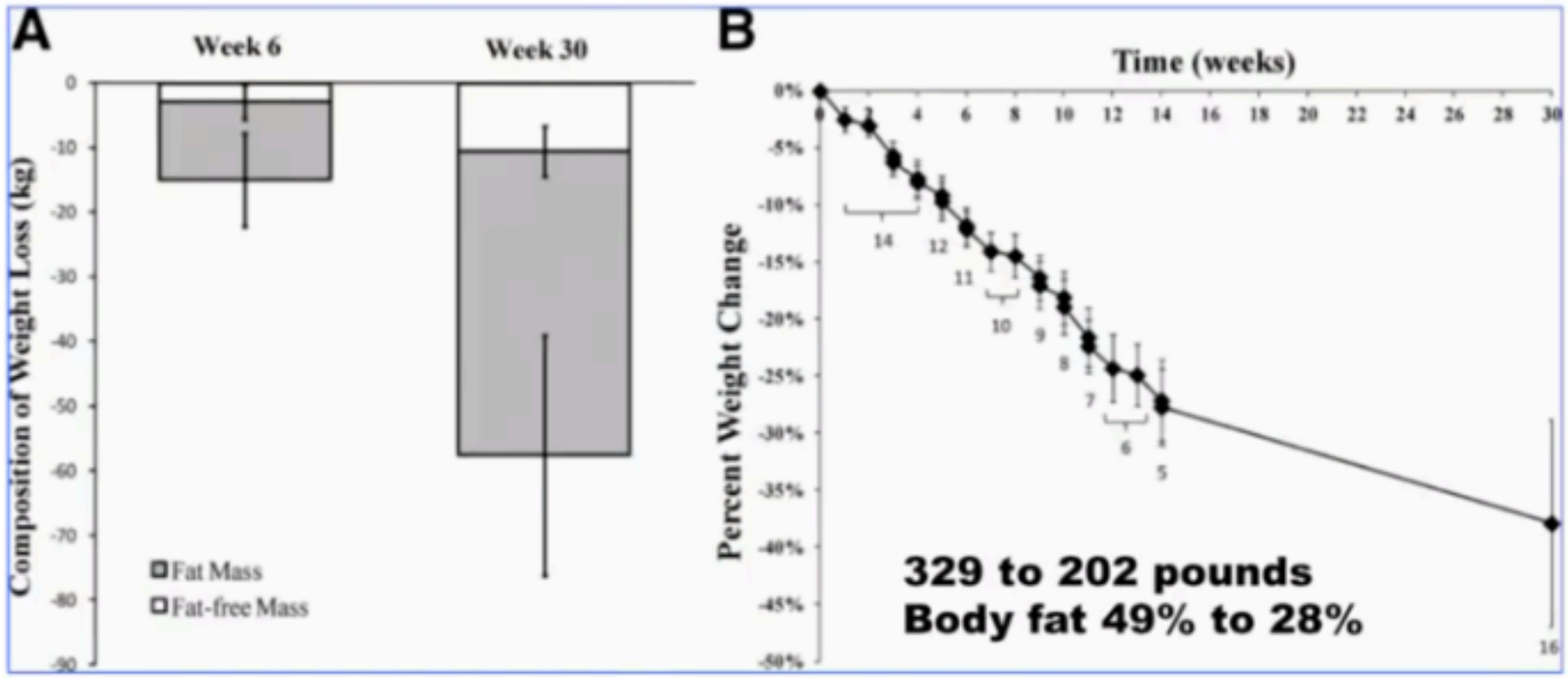
- Showed that metabolism slowed with 10% reduction in weight

Admitted to hospital and controlled what people ate.

Better in this regard than most published studies on nutrition.

The biggest loser
Eat less, move more

The Biggest Loser Diet



J Clin Endocrinol Metab. 2012 Jul;97(7):2489-96

Evidence for Diet

Real world diet programs usually get about six months:

Eat less, move more.

The Biggest Loser Diet

- Reduce Calories
- Increase Exercise

- Eat Less, Move More
- 2015 Rankings
  - #3 Weight Loss
  - #11 Overall

BEST DIETS
U.S.News & WORLD REPORT
RANKINGS

The Biggest Loser

"NBC never does a reunion. Why? We're all fat again"

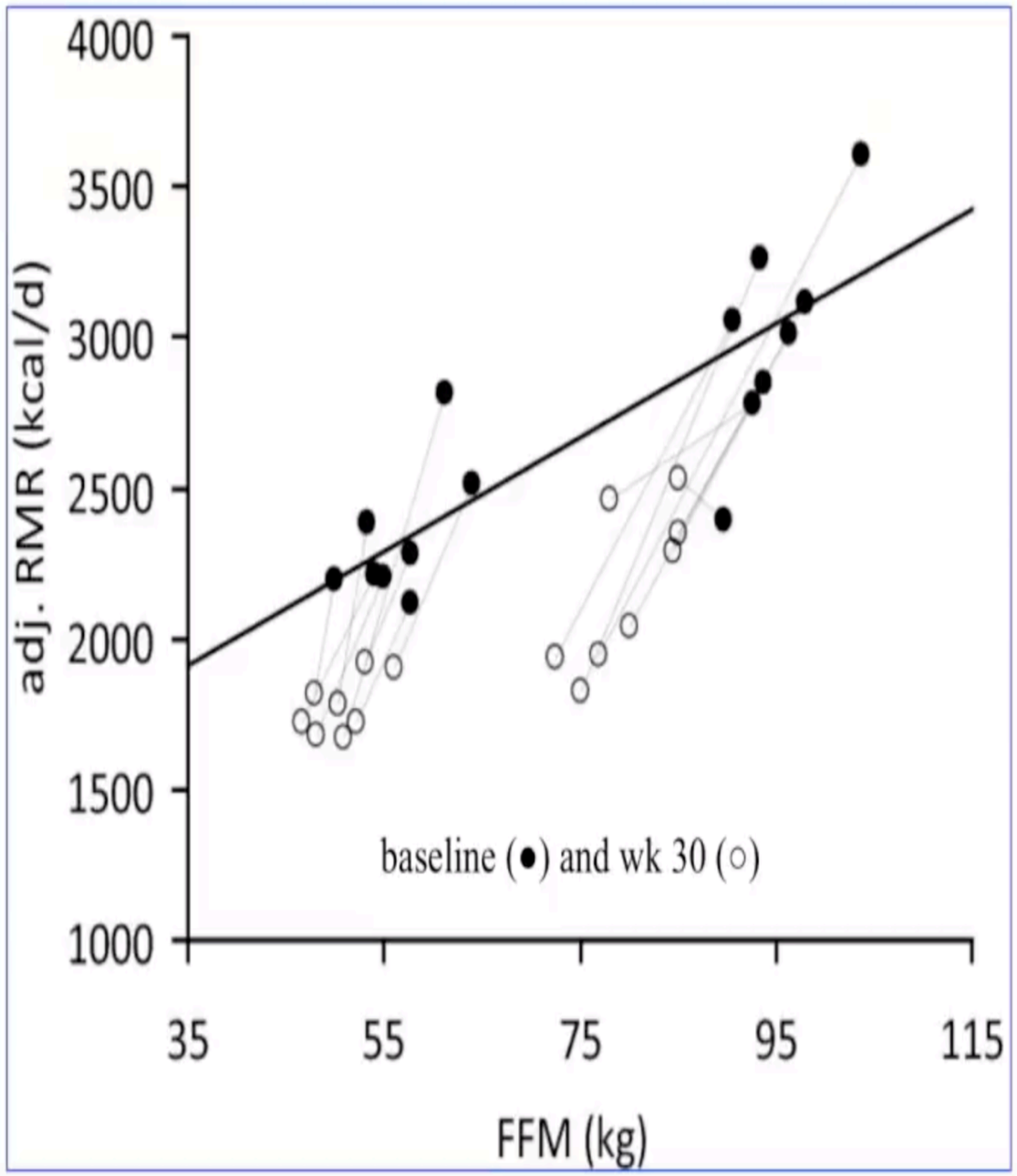
Metabolism slows down

Every single person who entered the biggest loser slowed their metabolism

Average was 700 cal/day reduction.

Everyone feels awful.

Decreased Metabolism



J Clin Endocrinol Metab. 2012 Jul;97(7):2489-96

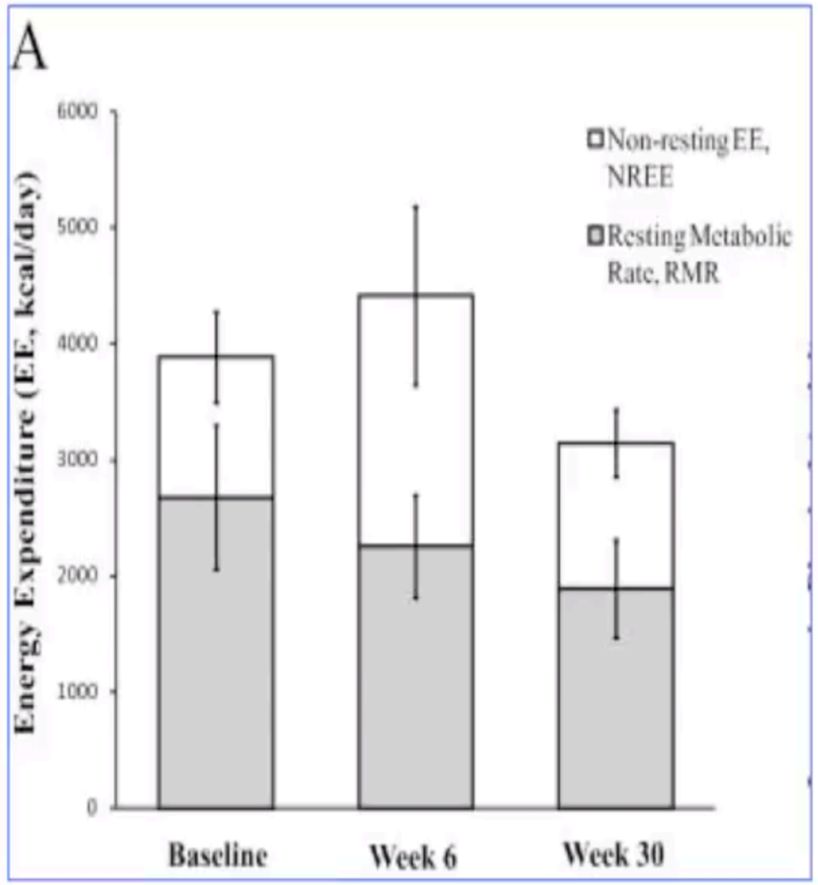
So how do we manage obesity?

We tell everyone to eat less and exercise more

We know that the evidence base is that this will fail

Then we blame the patient for failing a treatment we have prescribed that lacked evidence for long term efficacy.

Decreased Metabolism

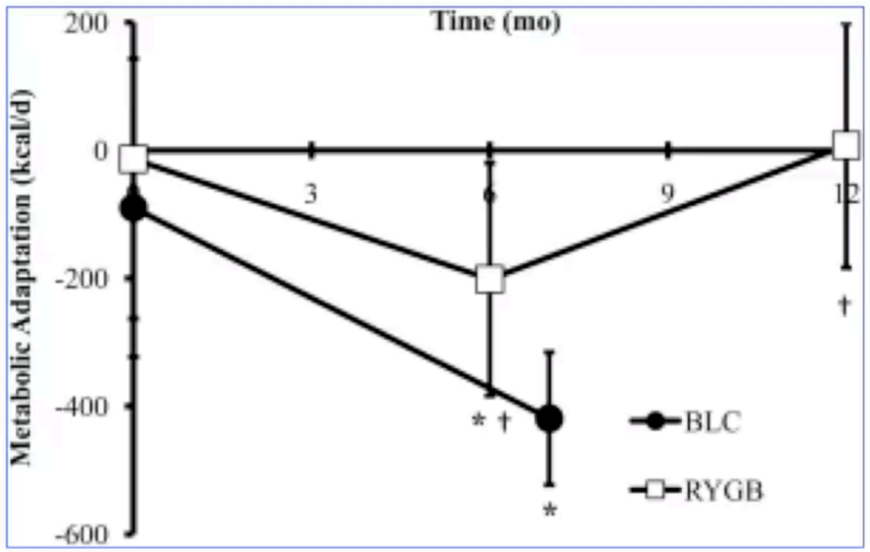


J Clin Endocrinol Metab. 2012 Jul;97(7):2489-96

Does this always happen?

So why is bariatric surgery different?

Biggest Loser vs Bariatrics



Metabolic Adaptation following Massive Weight Loss

Long Term Effect of Bariatrics

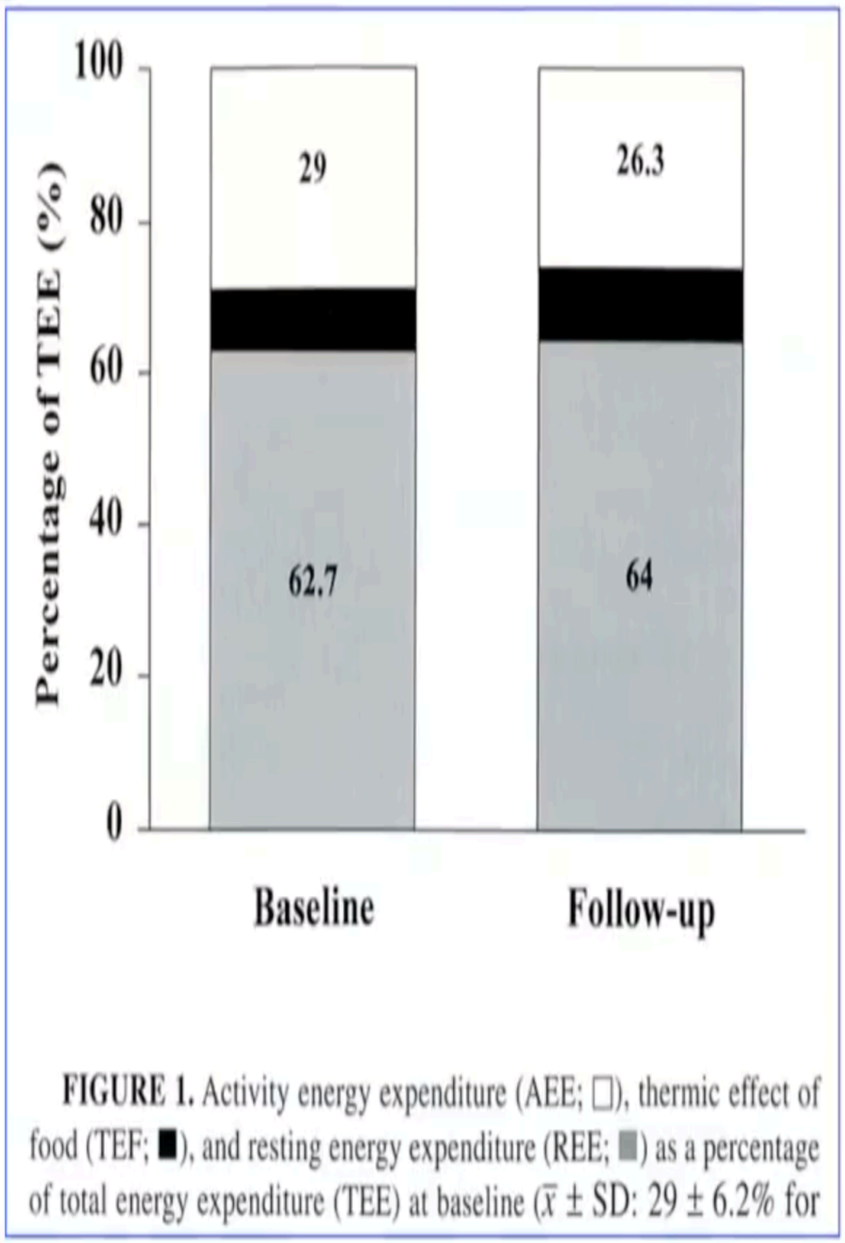


FIGURE 1. Activity energy expenditure (AEE; □), thermic effect of food (TEF; ■), and resting energy expenditure (REE; ■) as a percentage of total energy expenditure (TEE) at baseline ($\bar{x}$ ± SD: 29 ± 6.2% for

Am J Clin Nutl' 2003;78:22- 30.

Other things regulate weight

Insulin regulates weight

- Type 1 DM presents with weight loss

Insulin causes weight gain.

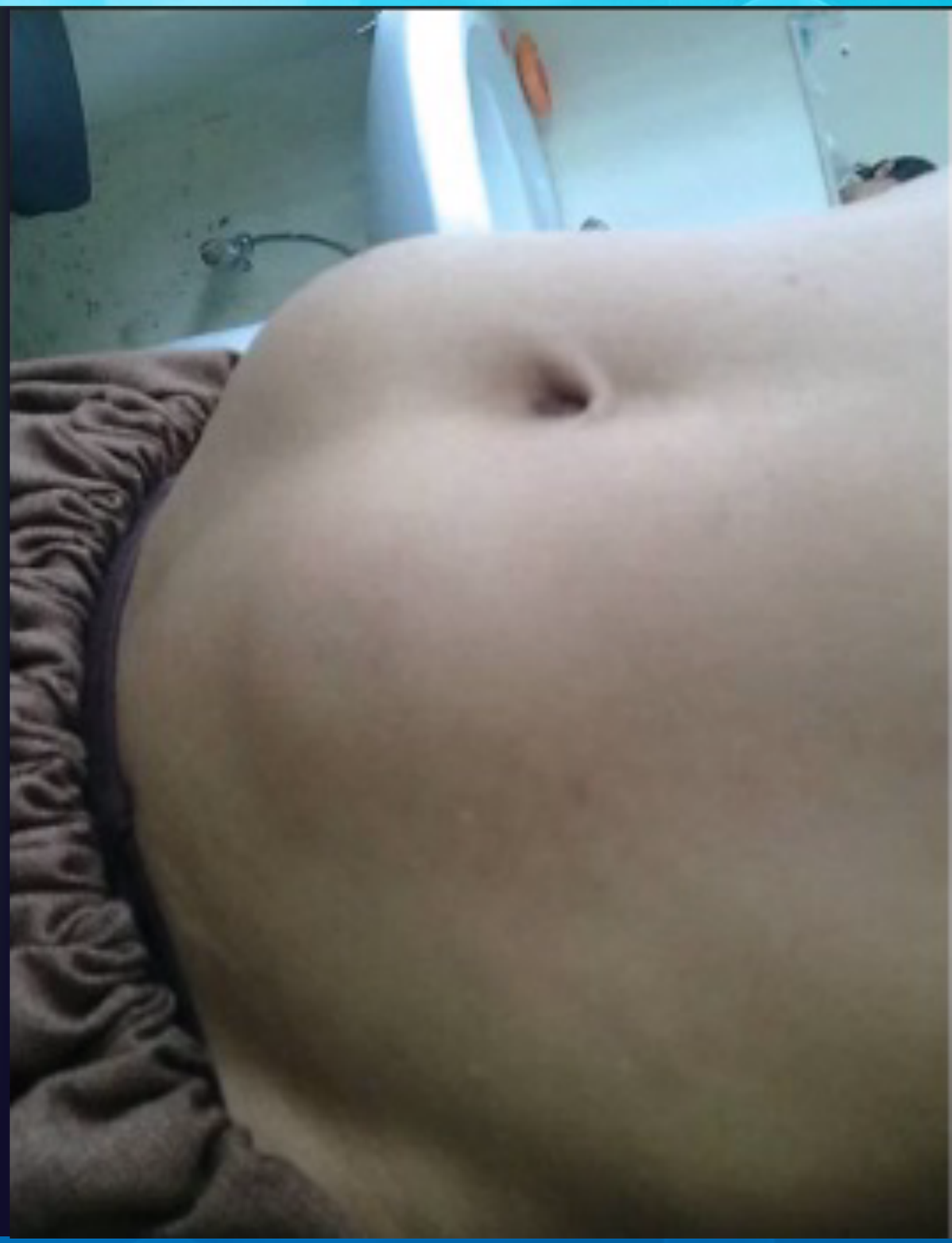
- Subcut insulin => lipohypertrophy

Insulin causes GLT-4 expression

-> Glucose uptake into muscle and fat

-> Enhances lipogenesis

-> Blocks lipolysis



Physiology

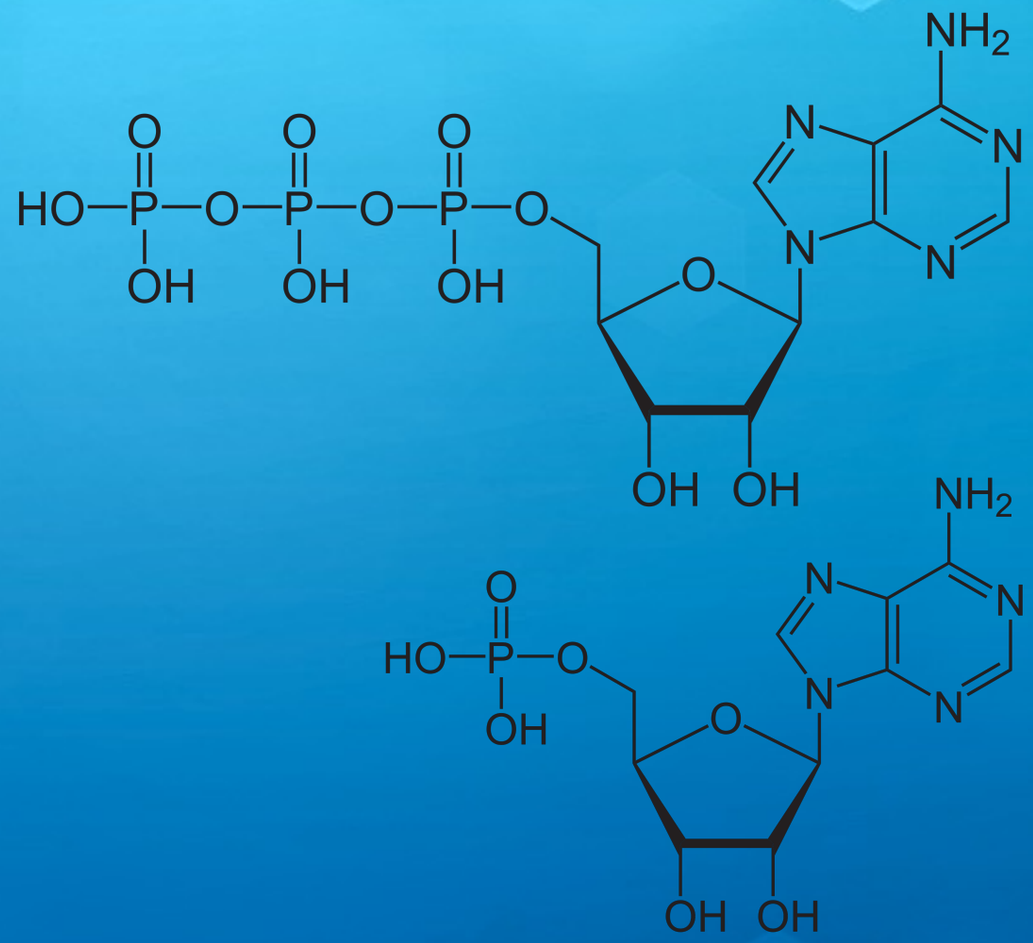
Adenosine - Phosphate

Adenosine is found in all cells

- Part of DNA

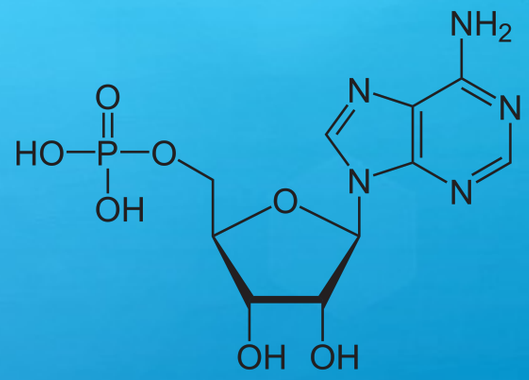
- Used as an energy store

Phosphate ions are added on to hold energy



AMPK, mTOR, HBP

Hexosamine biosynthetic pathway (HBP) => Energy sensor

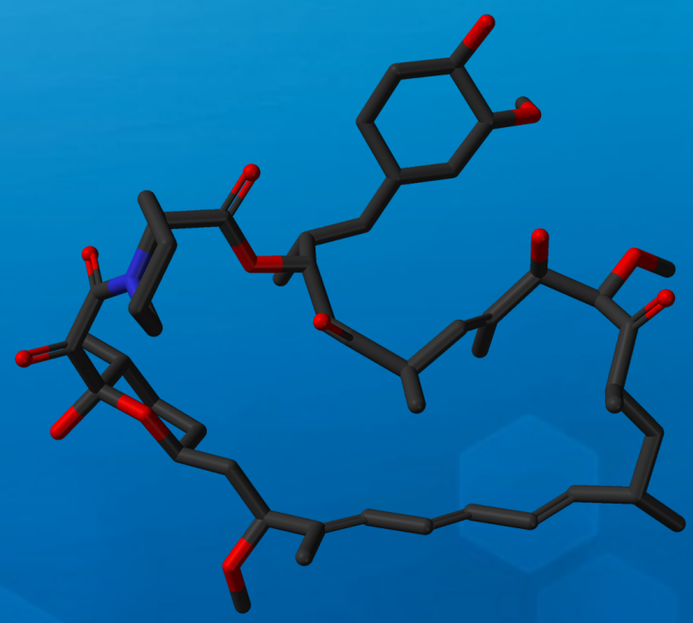


AMP Activated Protein Kinase => low energy response

-> Activated when ratio of ATP:AMP falls.

mammalian Target Of Rapamycin => high energy response

-> Activation of this leads to cell growth, division and inflammation



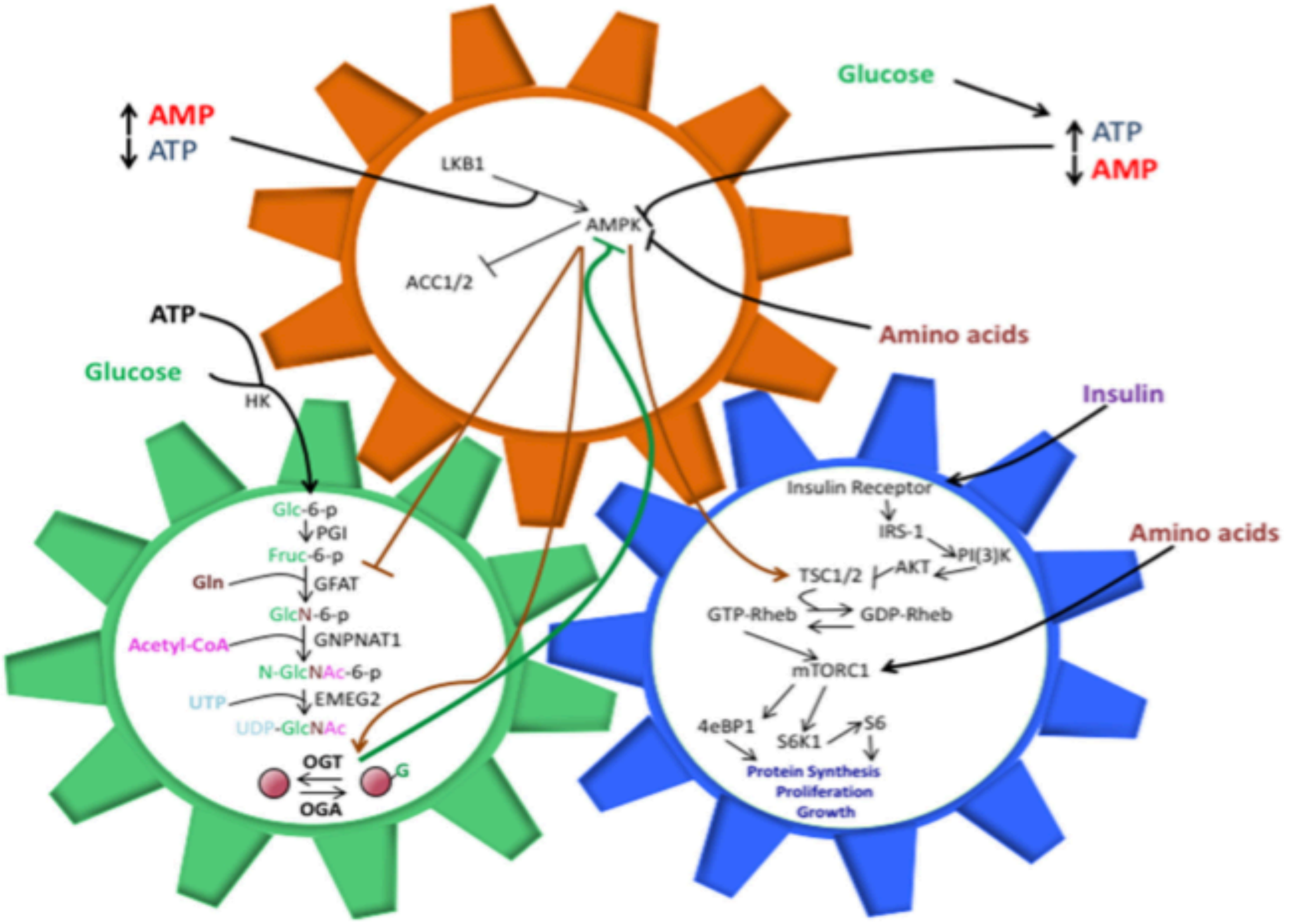


FIGURE 1 | The shared components between the HBP, AMPK, and mTOR pathways allow them to work in a synchronized manner to direct cell activity, but perturbations in these interactions can also drive pathology. O-GlcNAcylation of AMPK inhibits its ability to phosphorylate TSC1/2 and repress mTORC1 activation. This, in turn, can lead to unchecked cell proliferation, a hallmark of cancer and other diseases. The balance of nutrient intake also plays a pivotal role in guiding the interactions between these pathways. Increased glucose levels can bolster ATP production, both of which are necessary components for the HBP. Along with heightened UDP-GlcNAc levels, the ATP:AMP ratio shifts, thus hindering AMPK activation. Increasing amino acid intake contributes to AMPK suppression and direct/indirect mTORC1 activation, though the exact mechanisms behind these phenomenon are not entirely understood.

Energy sensing mechanisms

Low energy - AMPK activates.

- Cellular function slows down

High energy mTOR activates

- Cells grow and divide. (Normal and cancer cells)
- Inflammatory effects

This is seen in every cell in every complex (multicellular) organism.

What about higher functions?

Hypothalamic AMPK is a major mediator of energy balance.

Activation leads to:

- Induced appetite

- Decreasing thermogenesis and basal metabolic rate

Hypothalamic neurons in the arcuate nucleus release

Neuropeptide Y (hunger)
Pro-opiomelanocortin (saiety)

Decreasing Hypothalamic AMPK

Leptin (made in fat cells)

Depolarises POMC neurons, stimulates β-endorphin and α-MSH

Adiponectin

Promotes glucose uptake and FFA oxidation in muscles, reduces hepatic gluconeogenesis, increases brown adipose tissue thermogenesis

Has anti-inflammatory properties.

Reduced levels of this in obesity and T2DM

Decreasing Hypothalamic AMPK

GLP-1

Produced by neurons in nucleus solitary tract. suppresses appetite.

Inhibits AMPK activation with fasting

Insulin

Central administration of insulin produces satiety.

Insulin resistance in the brain leads to hyperphagia.

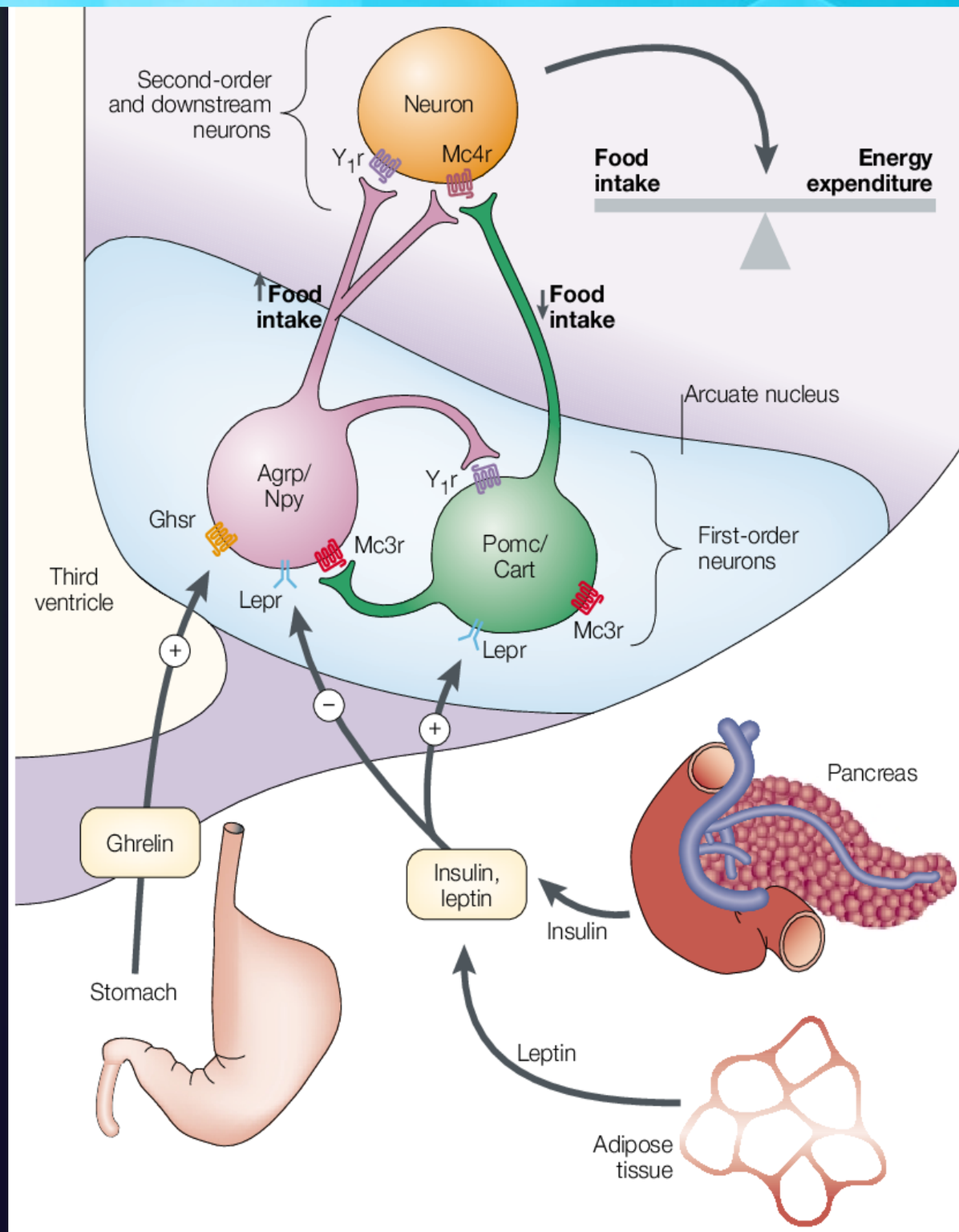
Increasing Hypothalamic AMPK

- Ghrelin

Made in stomach

Stimulates appetite via hypothalamic neuropeptide Y

Upregulates AMPK in the hypothalamus.



Treatment options

Medications

Phentermine (Duromine) - similar to amphetamine

- releases dopamine, typically 5-10% body weight loss

Significant side effects

hypertension, tachycardia

rarely stroke, angina, cardiac failure

pulmonary hypertension, cardiac valve disease

CNS overstimulation

GI effects - Nausea and vomiting

Bupropion/Naltrexone (Contrave)

Combination therapy 6-8% body weight loss (360mg/32mg)

- Causes activation of POMC neurons, safety

Side effects

- Excitatory effects, risk of seizures.
- Hypertension, arrythmias
- Mood elevation (bipolar disease contraindicated)

GLP-1 Receptor Agonists
Liraglutide

Satiety via reduction in hypothalamic AMPK.

5-10% weight loss (up to 13% in some studies)

Dosage: 0.6 - 3.0 mg/day subcutaneous injection

Side effects

- Slowing of GI tract function. Reflux, nausea and vomiting.

- Constipation (Rarely diarrhoea)

- Flu like symptoms, headache, dizziness.

- Hypoglycaemia, rare in non-diabetics

Surgery

Still the gold standard for reducing total body weight

Very strong positive effect on diabetic control

Gastric bands 20%

Gastric sleeve 40%

RY bypass 50%

Summary

Epidemiology

Evidence base for diet

Physiology

Treatment options