Metabolic Effects of Fasting
A Two-Edged Sword

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DISCLOSURES

Commercial Interest	What Received	Role
Virta Health Corp	Ownership Interest	Chief Medical Officer Co-founder
Beyond Obesity, LLC	Book Royalties	Author
Atkins Nutritionals, Inc	Honorarium	Science Advisor

Defining the various forms of ‘fasting’

Partial day fasting. Intermittently skipping one or two meals per day, resulting in no calorie intake for periods of 18 hrs (eg, no breakfast) to 24 hrs (no breakfast and lunch) on alternating days. Another version is no food during daylight, as practiced during the Muslim month of Ramadan.

Single day fasting. No food or calories from the evening of day #1 to the morning of day #3 – a span of 36 hours.

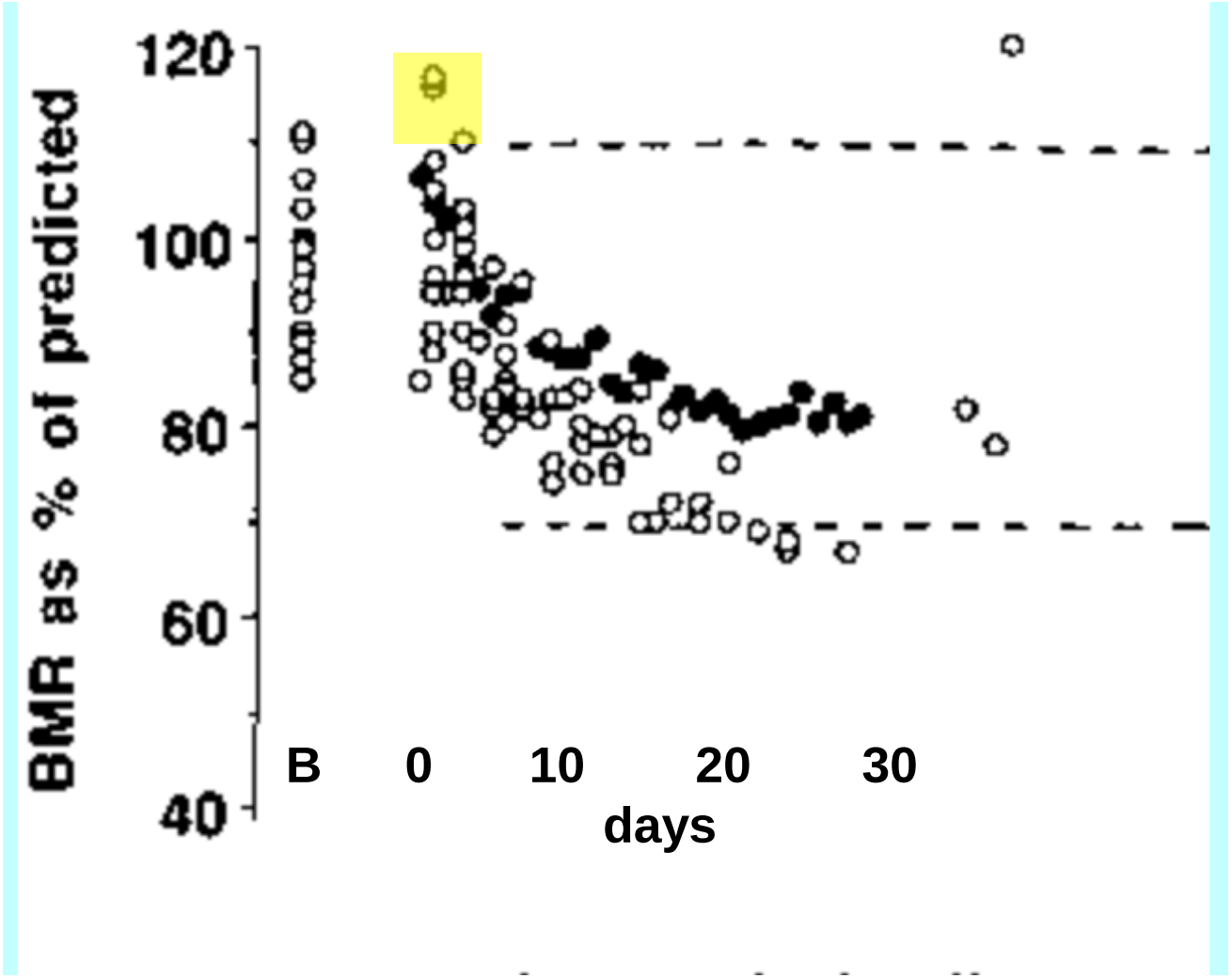
Multiple day fasting. No food or calories for 48 hours or longer.

5:2 intermittent fasting. 2 days per week restricted to 500-600 kcal per day, whether consecutive or separated by one or more days of unrestricted eating.

Key Discussion Points

- Metabolic Rate
- Nitrogen (protein) Losses
- Mineral Issues
- Medication Issues
- Refeeding Syndrome

Changes in Basal Metabolism with Total Fasting



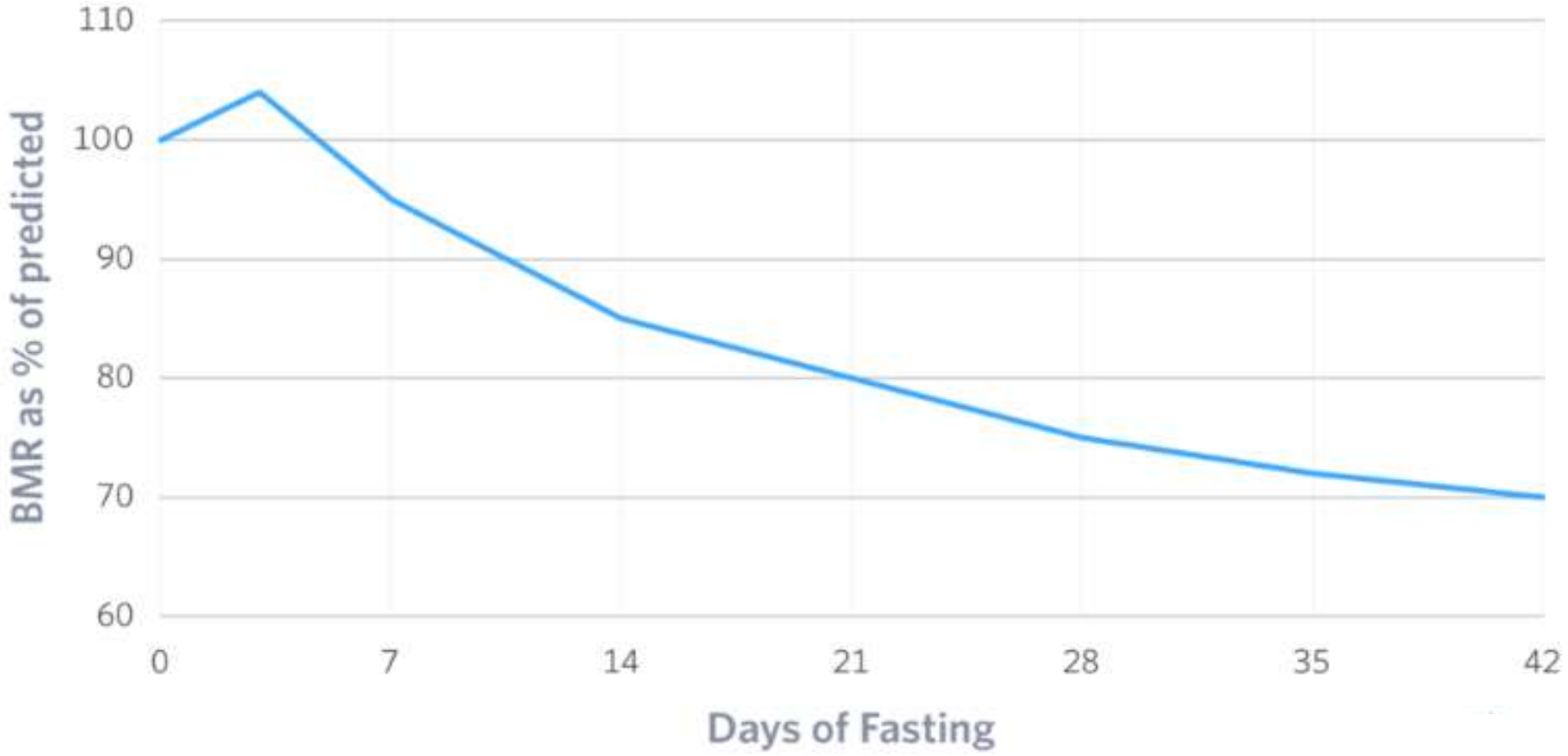
Elia M. 1991. http://archive.unu.edu/unupress/food2/UID07E/UID07E12.HTM

Thyroid hormone changes in obese subjects during fasting and a very-low-calorie diet.

Rabast U, Hahn A, Reiners C, Ehl M. Int J Obes. 1981;5(3):305-11.

Abstract

Total fasting was compared with VLCD (1.28 MJ, 300 kcal/day; 56 g protein, 12 g CHO) in 14 euthyroid obese patients, selected as matched pairs, **over a period of 28 days**. The weight loss was significantly greater during fasting than during the VLCD (16.5 kg vs. 12.7 kg). **The basal metabolic rate of (BMR) showed a significant decrease (25 per cent) during total fasting,** but was unchanged with the VLCD. With both diets there was a transient increase in T4, FT4 and FT4I, and a tendency for TSH to decrease. There was a decrease in T3 and a transient increase in rT3. Nitrogen balance was attained in five of seven patients on the VLCD after four weeks.



Changes in resting metabolism with short-term and long-term starvation.
Taken from composite data from 5 studies, assembled by Elia, 1991.

- **What we don't know is how quickly (or slowly) the reduced BMR or REE recovers after a prolonged fast**
- To some degree it is associated with recovery of lean tissue
- But the Biggest Loser Study (*Fothergill E, et al. Obesity 2016; 24:1612-19*) implies that extreme negative energy balance can cause a 20% long term reduction in REE -- from 34 kcal/kg LBM at baseline to 27 kcal/kg after 6 years

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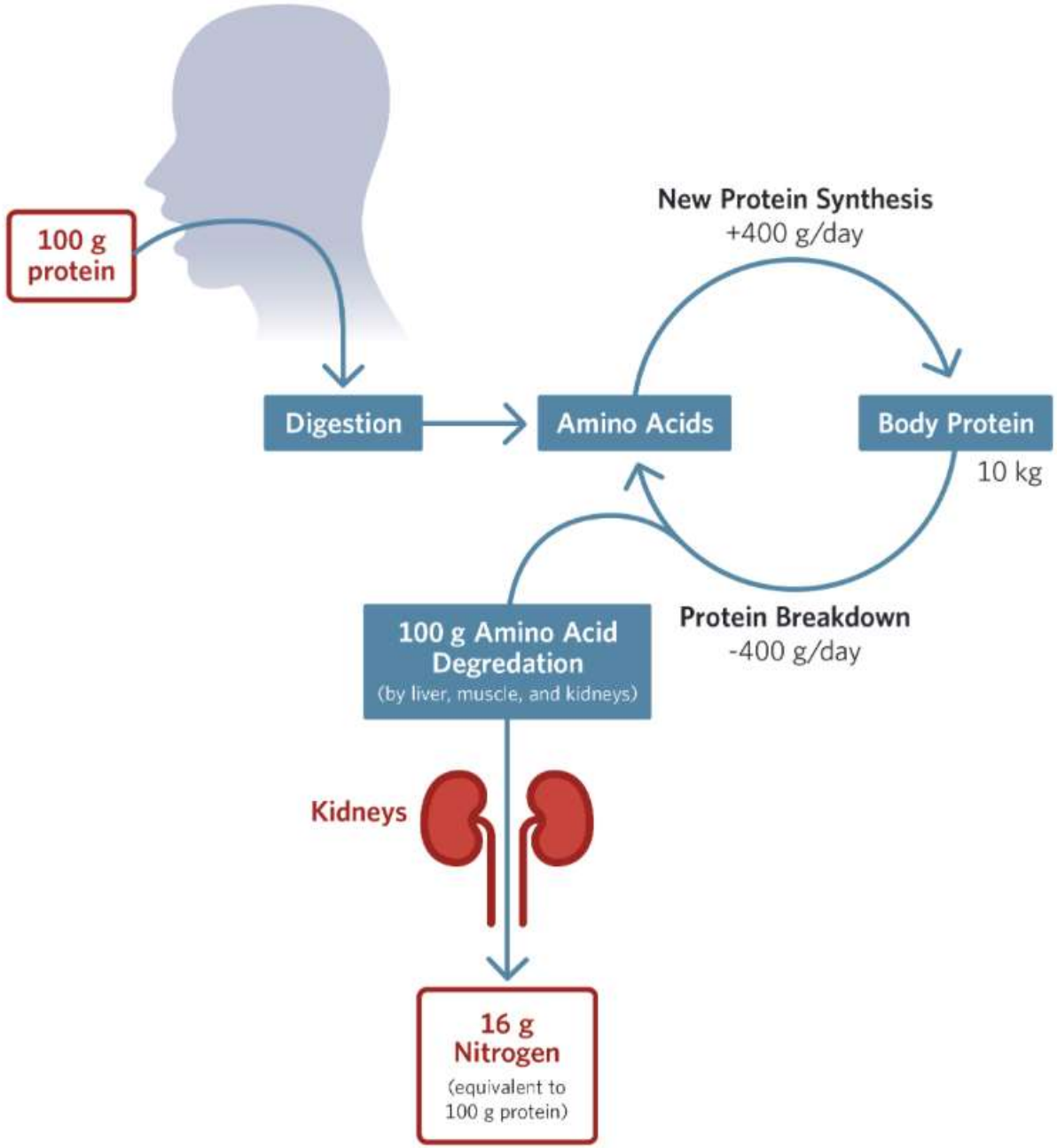
Protein Intake and Turnover



Classic Cahill Human Starvation Experiment 1970

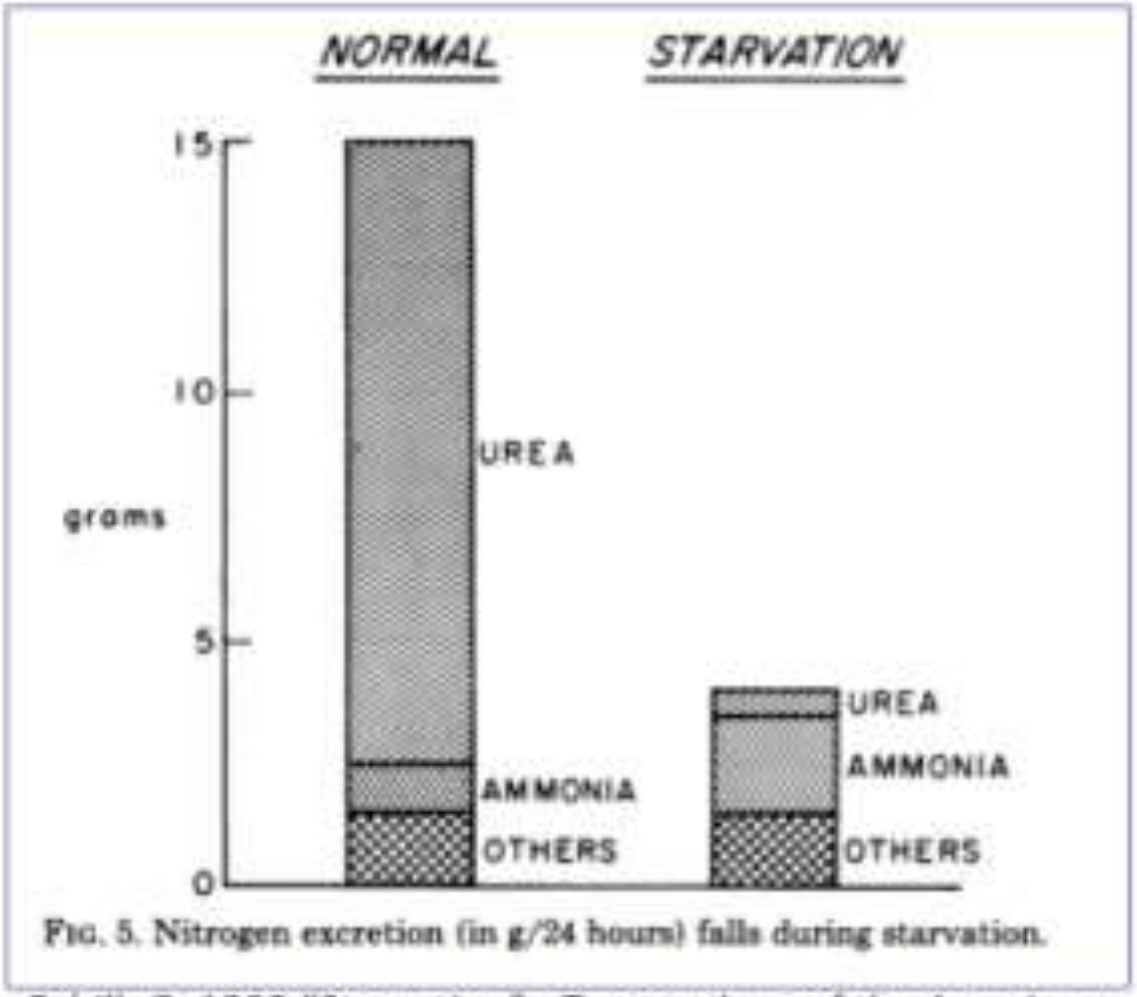


FIG. 5. Nitrogen excretion (in g/24 hours) falls during starvation.

Cahill, G. 1983 "Starvation" - Transactions of the American Clinical and Climatological Association 02/1983; 94;1-21

An important point of science that is missed by popular bloggers:
This ‘starvation’ rate of nitrogen excretion (4 g/d) is following **28 days** of fasting adaptation.
Losses in the first week are 12-15 g/d.

Loss of body nitrogen on fasting[1,2]

Gilbert B. Forbes, M.D. and Ernst J. Drenick, M.D.

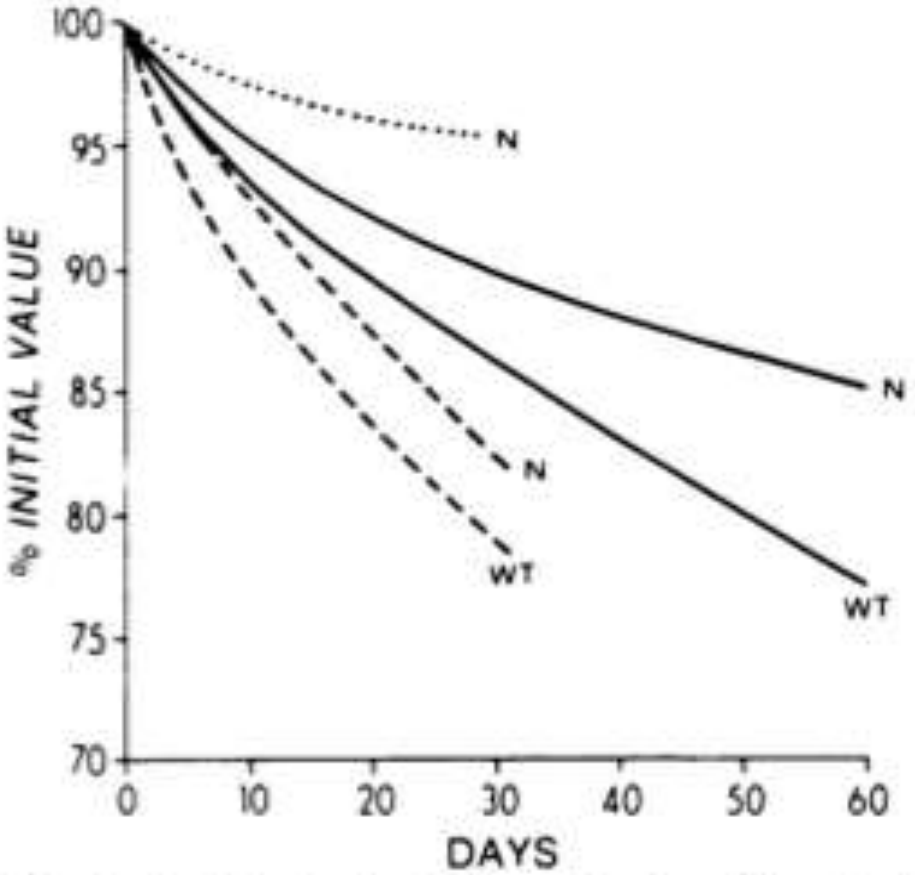


FIG. 1. Decline in body N and body weight (both as percentage of initial values) during fasting: (——), nine obese subjects; (----), four nonobese subjects; (. . . . . .), one subject on protein-free diet.

Am J Clin Nutr 32; 1570-4, 1979

72 Obese and Lean Men and Women Fasted from 7-28 days (1975)

Their key findings:

- At equal weight greater nitrogen losses were found in men than in women, in both normal and obese subjects.
- In spite of much higher weight and larger energy expenditure the nitrogen loss in obese subjects however was not higher than in normal ones.
- Mean daily nitrogen losses varied from 14.5 g (normal and obese men early in starvation) to 3.0 g (obese women after a 4-weeks fast).

Implications:

- Fasting men lose lean tissue more rapidly than women, **BUT**
- Both lose around ¾ lb of lean tissue daily in the first week
- After 28 day, both men and women are still losing > ¼ lb/d lean tissue
- **Extra adipose tissue (aka 'obesity') does not protect against lean tissue losses**

Göschke H, Stahl M, Thölen H. Nitrogen loss in normal and obese subjects during total fast. Klin Wochenschr. 1975; 53:605-613.

Daily Urea Nitrogen Losses During Total Fasting

- 1 gm of nitrogen excretion = 1 oz of lean tissue loss
- In addition to urea, humans lose about 2 gm/d nitrogen as ammonia and 1 gm from skin & stools
- Thus lean tissue losses start at ¾ lb/d and decline to ½ lb/d after 2 weeks

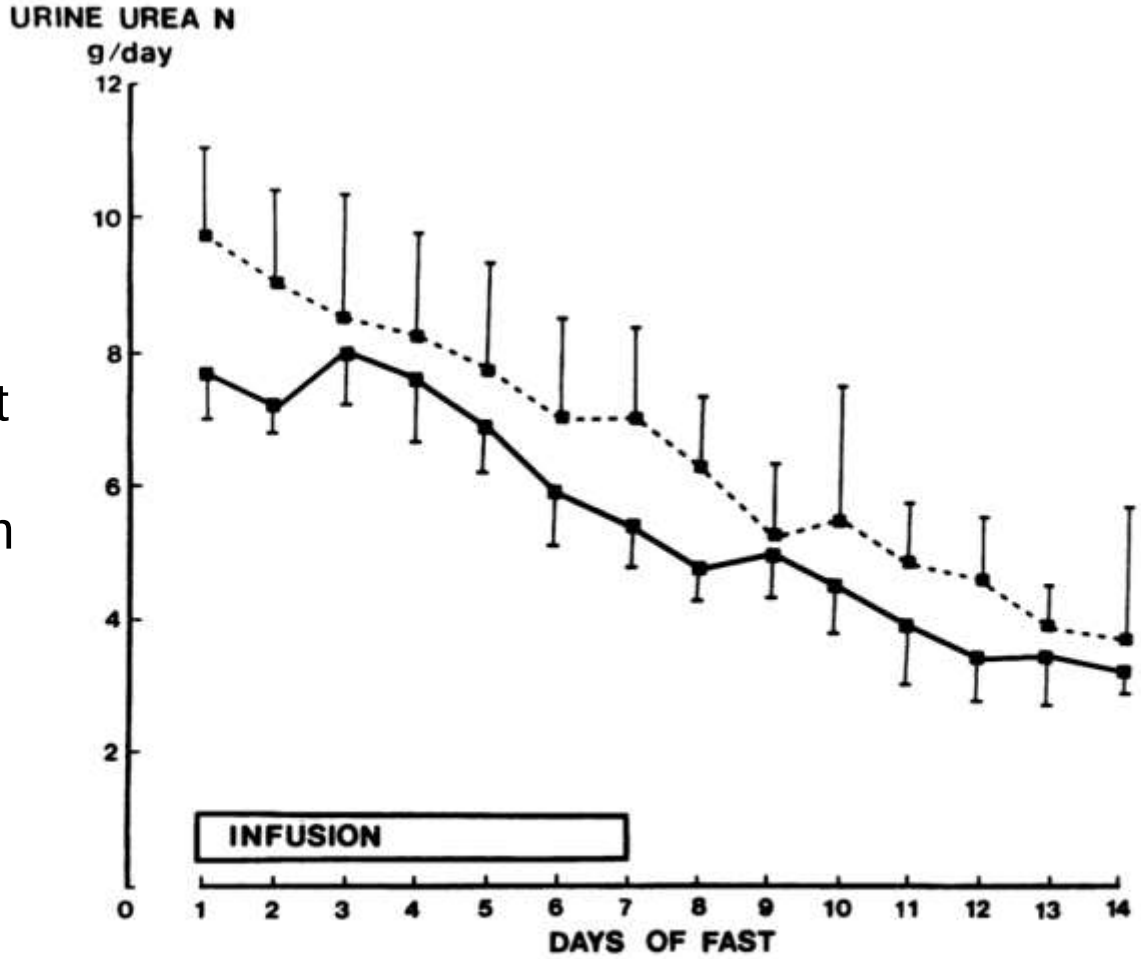


FIGURE 3 The effects of infusing 11 mmol α-ketoisocaproate (——) daily during the first 7 d of a fast on daily urinary urea nitrogen excretion compared with daily urinary urea nitrogen excretion during a control fast (– – –). The vertical bars represent ±1 SEM.

Mitch WE, Walser M, Sapir DE. Nitrogen Sparing Induced by Leucine Compared with That Induced by its Keto Analogue, a-Ketoisocaproate, in Fasting Obese Man. J Clin Invest. 1981; 67:553-62.

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Mineral Losses with Fasting

- Accelerated sodium excretion – the ‘natriuresis of fasting’
- As circulating plasma volume is reduced, increased aldosterone stimulates potassium exchange to preserve sodium
- Reduced potassium inhibits muscle protein synthesis
- Magnesium is lost commensurate with shrinking lean body mass
- Prolonged fasting causes major mineral deficits that need to be repleted after cessation of the fast
- With intermittent fasting, minerals lost on the fasting days need to be recovered during fed days

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Fasting or Carbohydrate Restriction Rapidly Change Glycemic Control
This is a powerful but dangerous tool in managing type 2 diabetes

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Research Article

Intermittent fasting in Type 2 diabetes mellitus and the risk of hypoglycaemia: a randomized controlled trial

B. T. Corley ✉, R. W. Carroll, R. M. Hall, M. Weatherall, A. Parry-Strong, J. D. Krebs

Accepted manuscript online: 6 February 2018 Full publication history

DOI: 10.1111/dme.13595 View/save citation

- Non-blinded randomized parallel group trial of intermittent fasting in adults with T2D on hypoglycemic medication(s)
- Fasting consisted of ~500 kcal per day 2 days per week, consecutive or non-consecutive
- Medications were reduced on fasting days
- **Fasting increased the relative risk of hypoglycemia to 2.05 (95% CI 1.17 to 3.52)**

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Refeeding Syndrome

- First reported in WWII starvation survivors
- 60 deaths reported to CDC following 'Liquid Protein Diet' – deaths due to dysrhythmia
- Likely cause due to rapid shifts into muscle of K^{+}, M^{++}, and nitrogen along with glycogen
- Occurs with rapid refeeding following prolonged starvation
  - not uncommon in hospitalized patients on TPN
- Associated with reduced lean body mass, not prevented by residual adiposity

Refeeding syndrome: what it is, and how to prevent and treat it. HM Mehanna, J Moledina J Travis. BMJ. 2008; 336:1495–1498. doi: 10.1136/bmj.a301

Summary
The Case Against Prolonged Fasting

- Early and ongoing loss of lean tissue (starting at 3/4 lb per day and continuing at ¼ lb per day over 28 days)

- Progressively reduced metabolic rate:
  - 8% 1st week
  - 15% 2nd week
  - 25% 4th week

- Progressively ‘diminishing returns’ of weight loss increases drive to continue and/or limit protein and mineral intakes

- Risk of death from ‘refeeding syndrome’ after prolonged fasting