

Anti-Aging Interventions

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Longevity and Calorie Restriction

- Calorie restriction is healthy and prolongs life.
- A 50% calorie restriction doubles the life-span of *C. elegans* worms, flies, yeast and mice.
- 25% calorie restriction in humans reduces weight 10% in 6 months, reduces metabolic rate and insulin levels and insulin resistance.
- It was once thought that a reduction in metabolic rate was needed to prolong life.

Good RA et al. *Am J Path*, 1976

Calorie Reduction Increases Longevity (Reduced Food Intake in Worms)

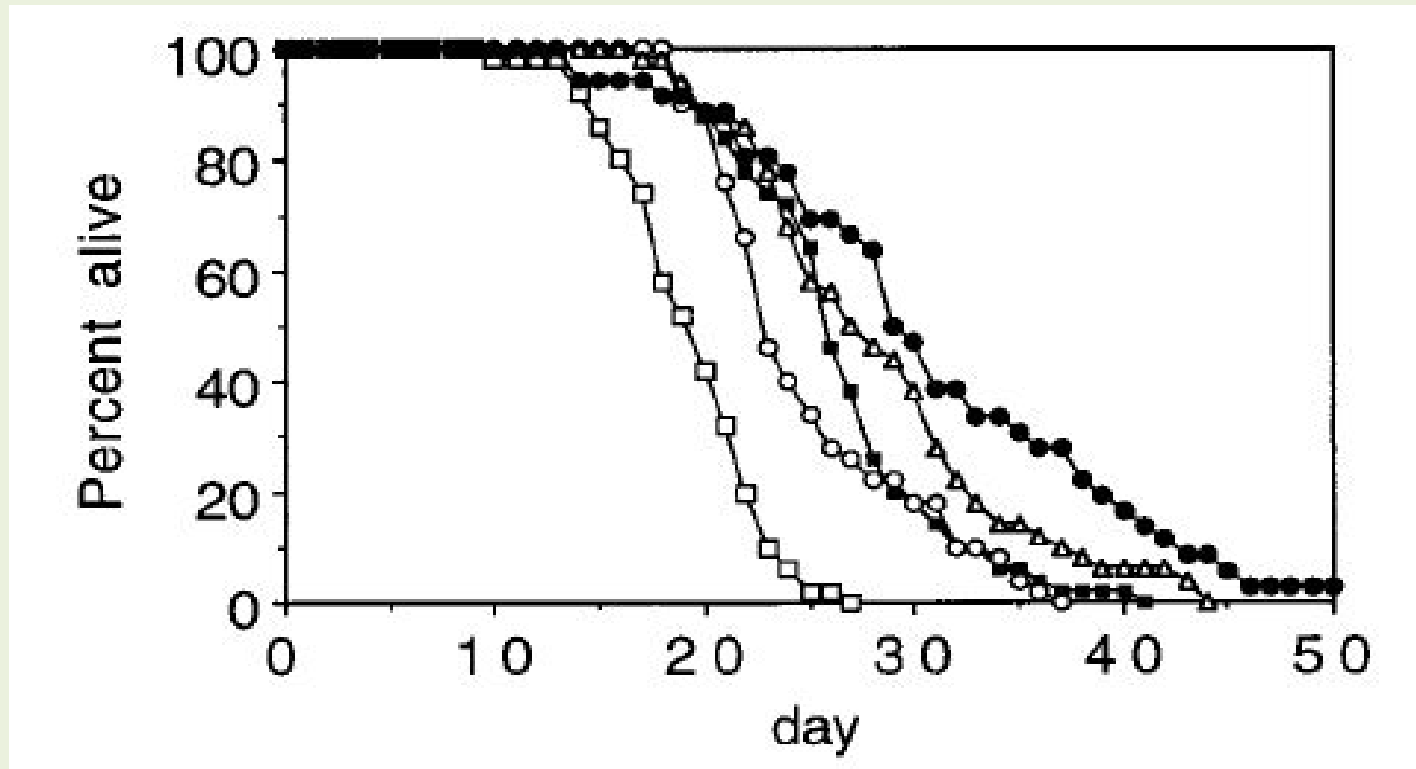


FIG. 1. Four alleles of *eat-2* lengthen life span. The percentage of worms alive on a given day after eggs being laid for a single experiment: N2 (D), *eat-2(ad465)* (E), *eat-2(ad453)* (■), *eat-2(ad1113)* (,), and *eat-2(ad1116)* (F).

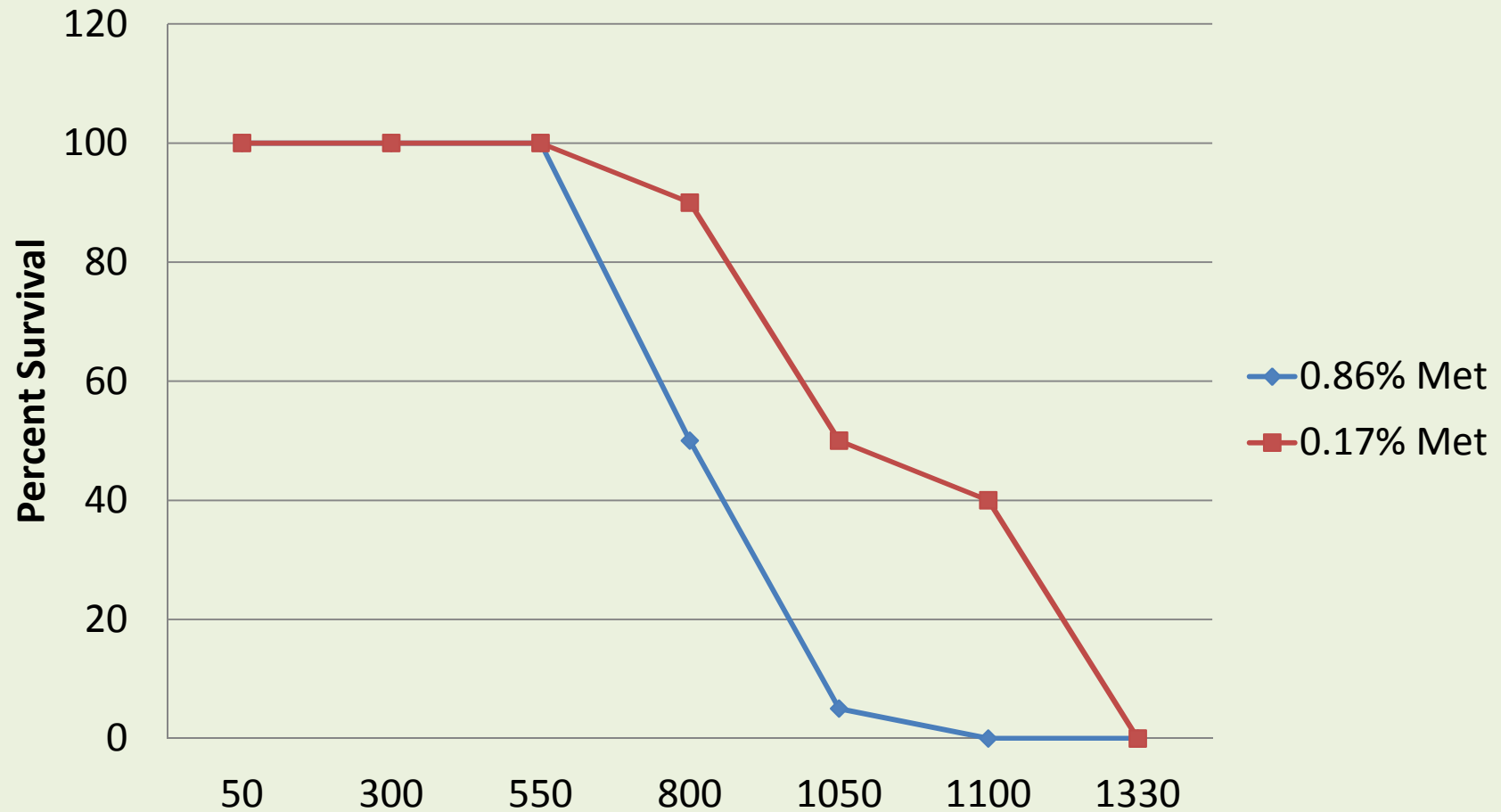
Larsen PL et al. *Genetics*. 1995;139(4):1567-83.

Longevity and Methionine Restriction

- Methionine restriction is healthy and prolongs life.
- Methionine restriction increases food intake, and metabolic rate, but decreases insulin, insulin resistance and body weight.
- Longevity may be associated with a reduction in insulin and an increase in insulin sensitivity

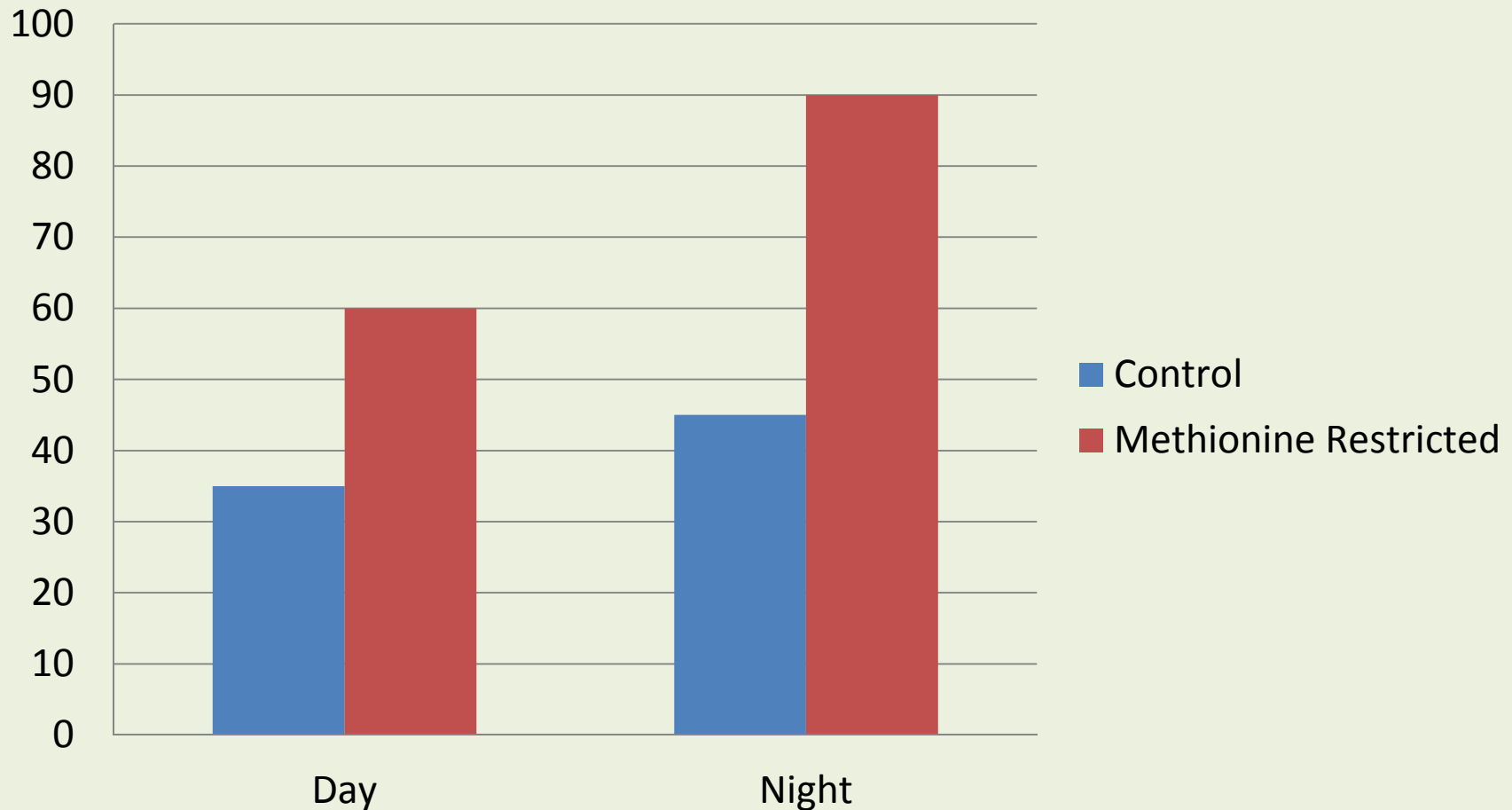
Orentreich et al. J Nutr, 1993

Methionine Restriction Extends Life in Rats



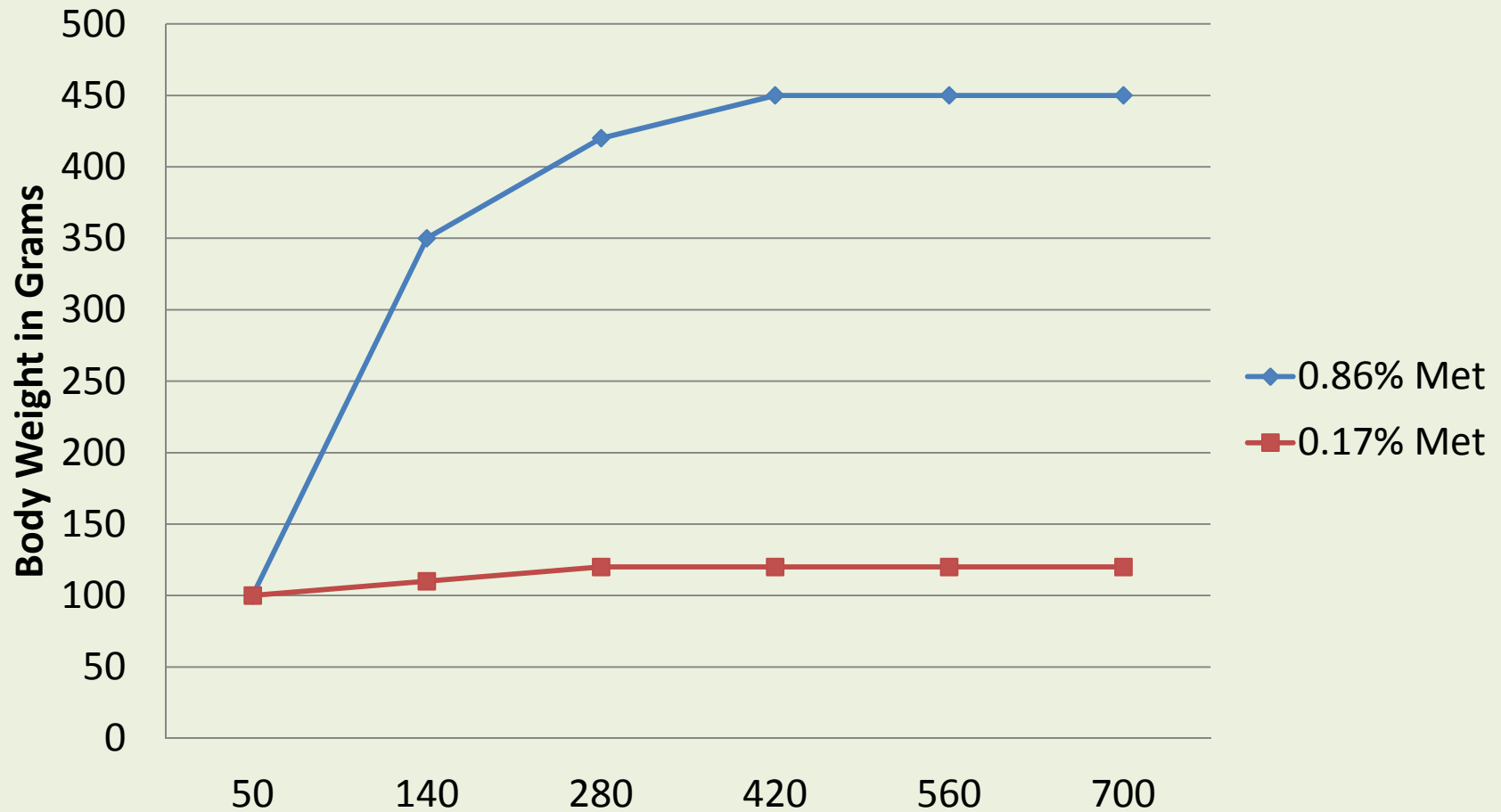
Orentreich et al. J Nutr, 1993

Methionine Restriction Increases Metabolic Rate More When Awake



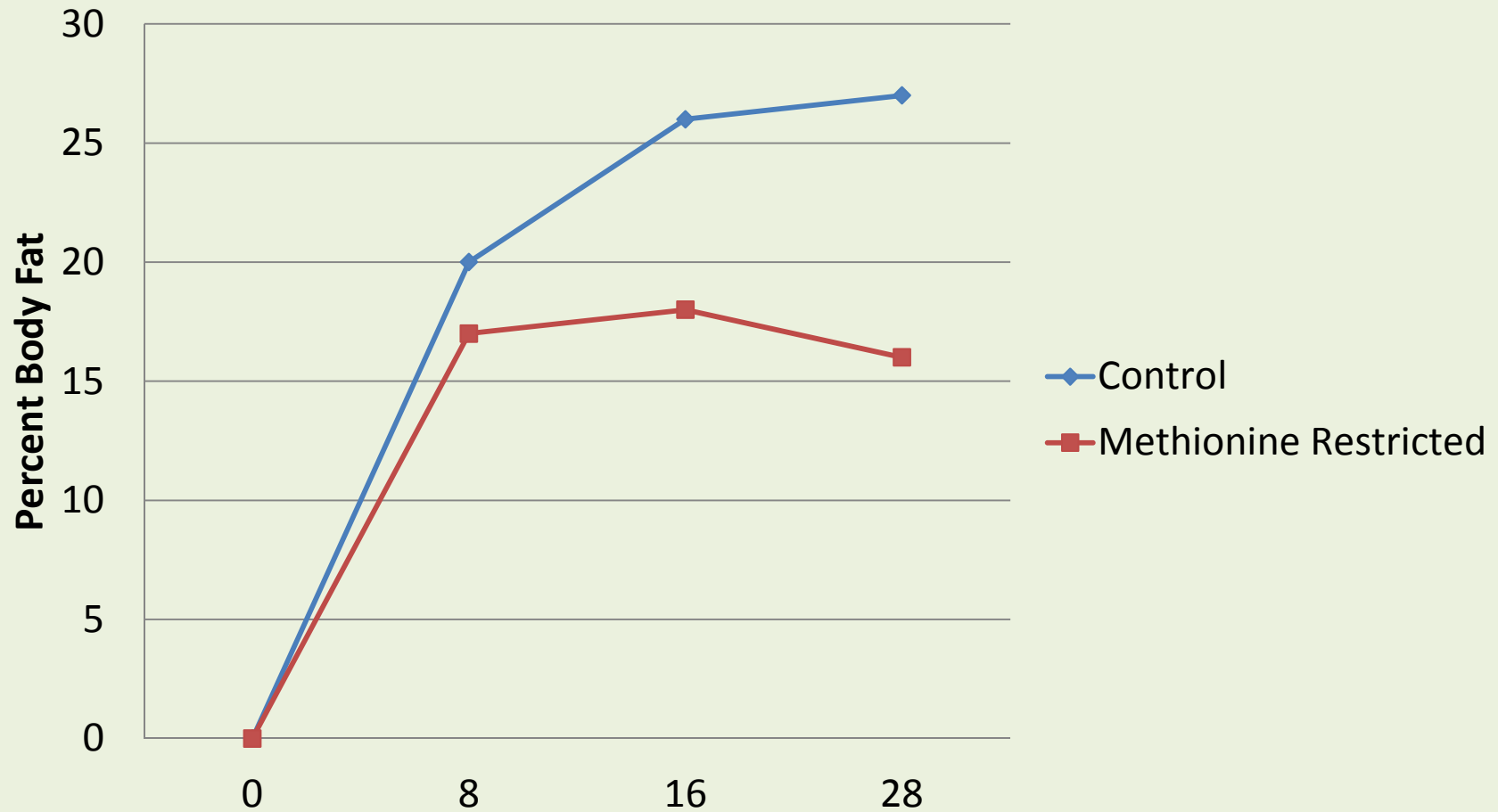
Malloy VL et al. Aging Cell. 2006;5(4):305-14

Change in Body Weight



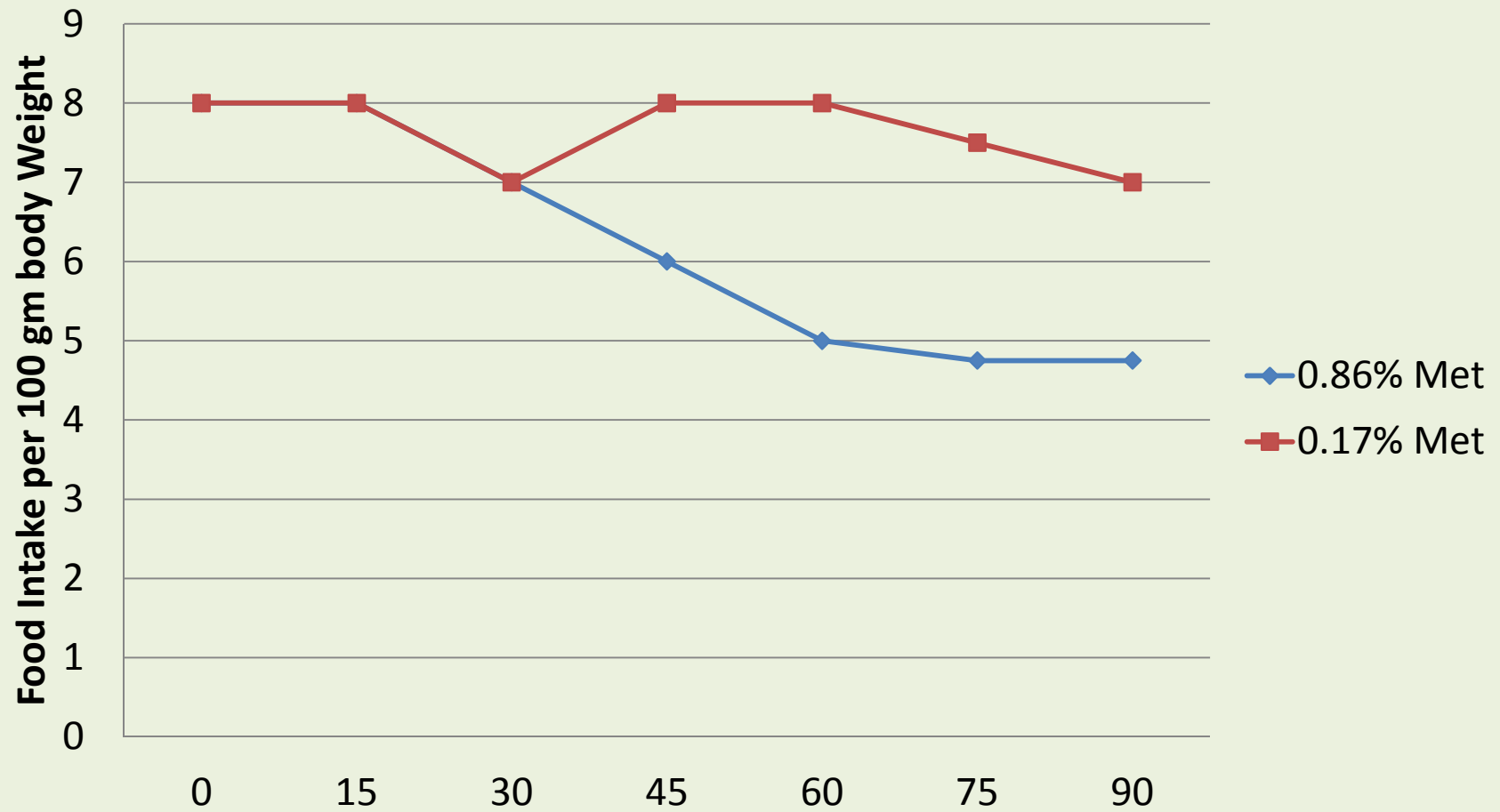
Orentreich et al. J Nutr, 1993

Change in Percent Body Fat



Orentreich et al. J Nutr, 1993

Change in Food Intake



Orentreich et al. J Nutr, 1993

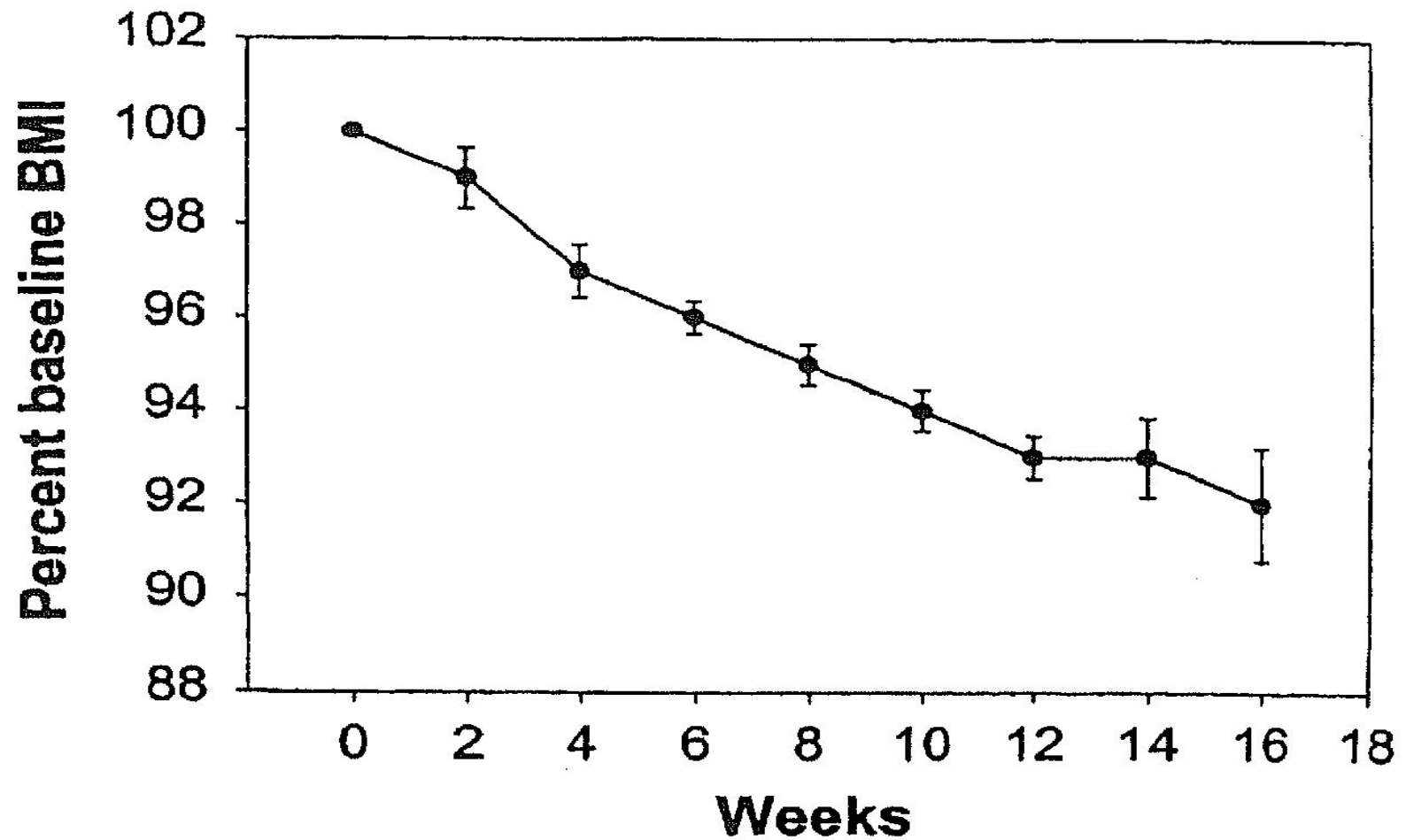
Methionine, Cancer and Humans

- Methionine restriction is harmful to cancer cells.
- Normal cells can re-methylate homocysteine for the methionine they need but cancer cells are deficient in this function
- A safety study to evaluate methionine restriction in humans was done in cancer patients without cachexia over 17 weeks

Safety

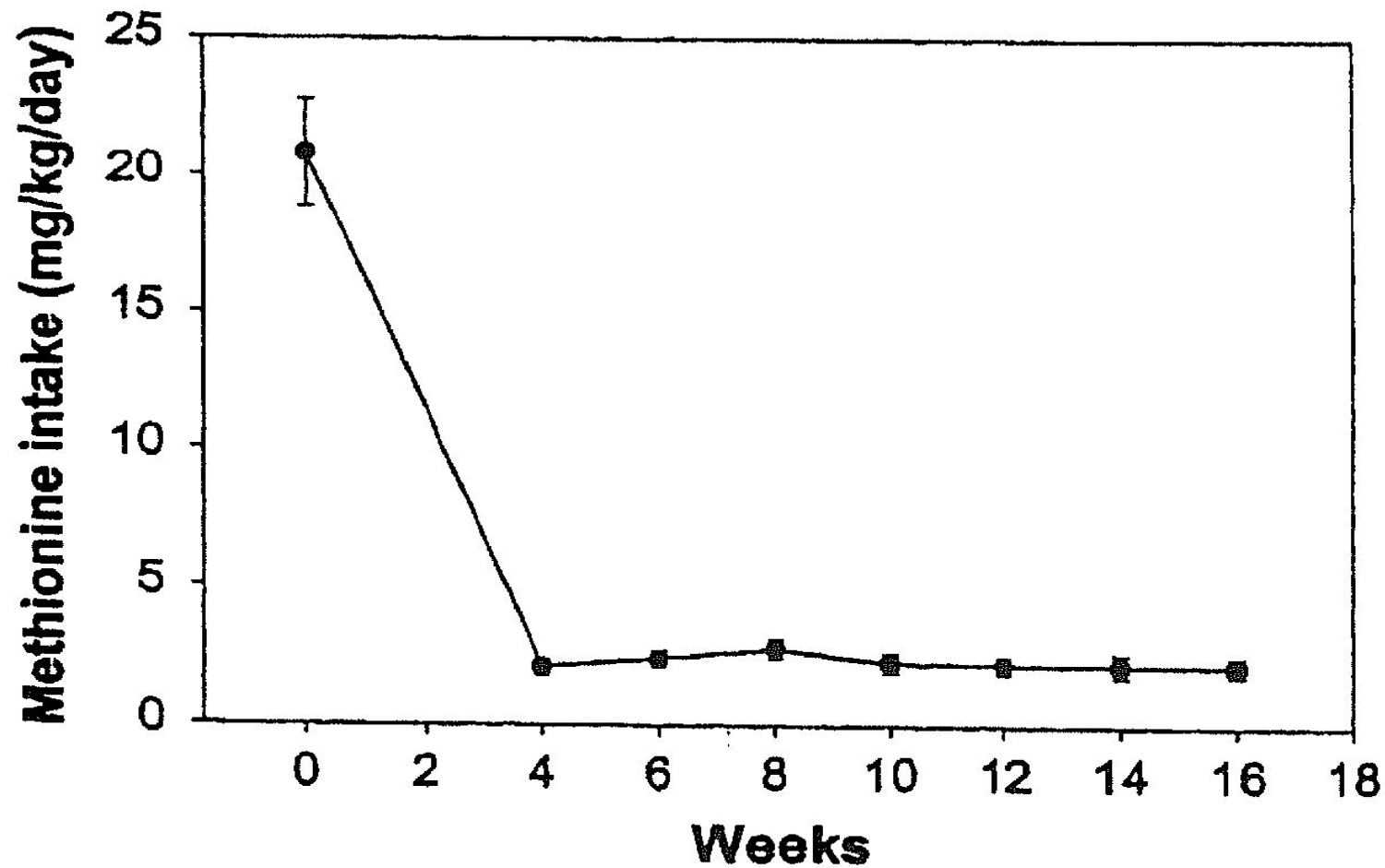
- Methionine restricted methionine to 2mg/kg per day in 8 cancer patients
- The cancer patients lost 0.5% of their body weight/week
- Methionine fell 58%
- Albumin and pre-albumin did not decrease
- Calorie intake increased and methionine restriction was safe for 17 weeks.

Weight Loss of 0.5% of Body Weight per Week



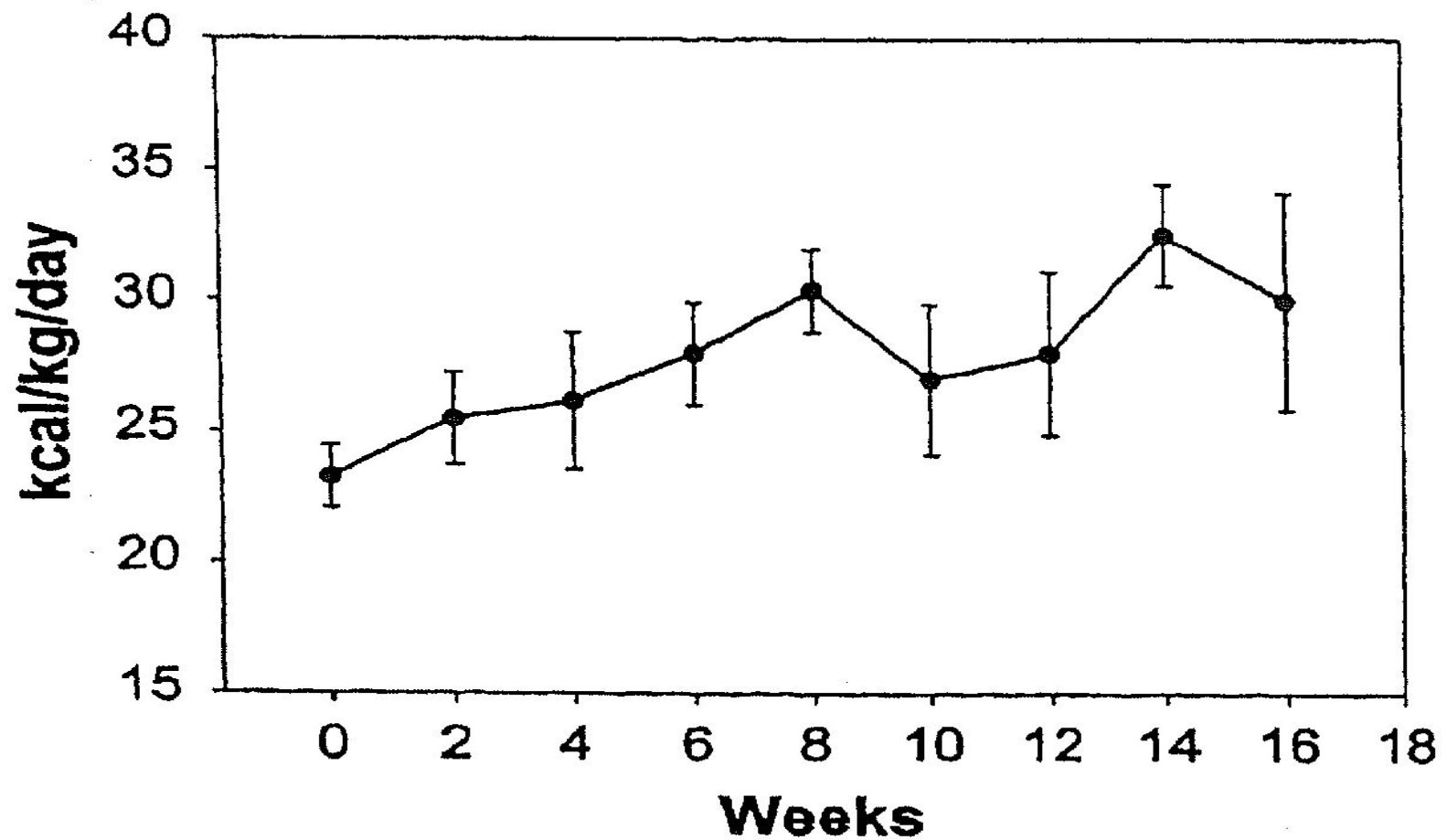
Epner DE et al. Nutr and Cancer. 42(2):158-66, 2002

Methionine Intake was Dramatically Reduced



Epner DE et al. Nutr and Cancer. 42(2):158-66, 2002

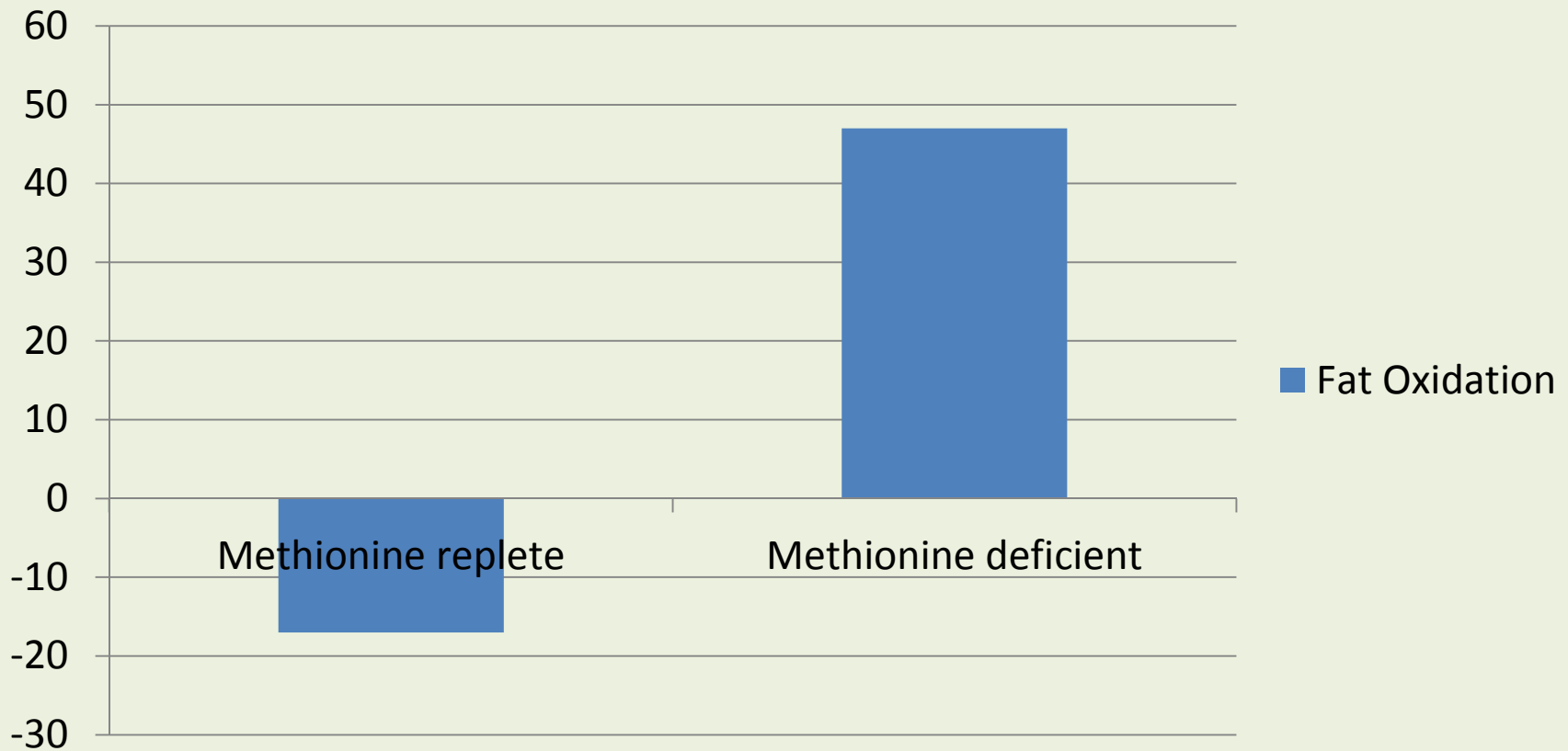
Food Intake Increased



Epner DE et al. Nutr and Cancer. 42(2):158-66, 2002

Change in 24 hour Fat Oxidation 16 wk Methionine Restriction PBRC

Fat Oxidation, $p < 0.05$



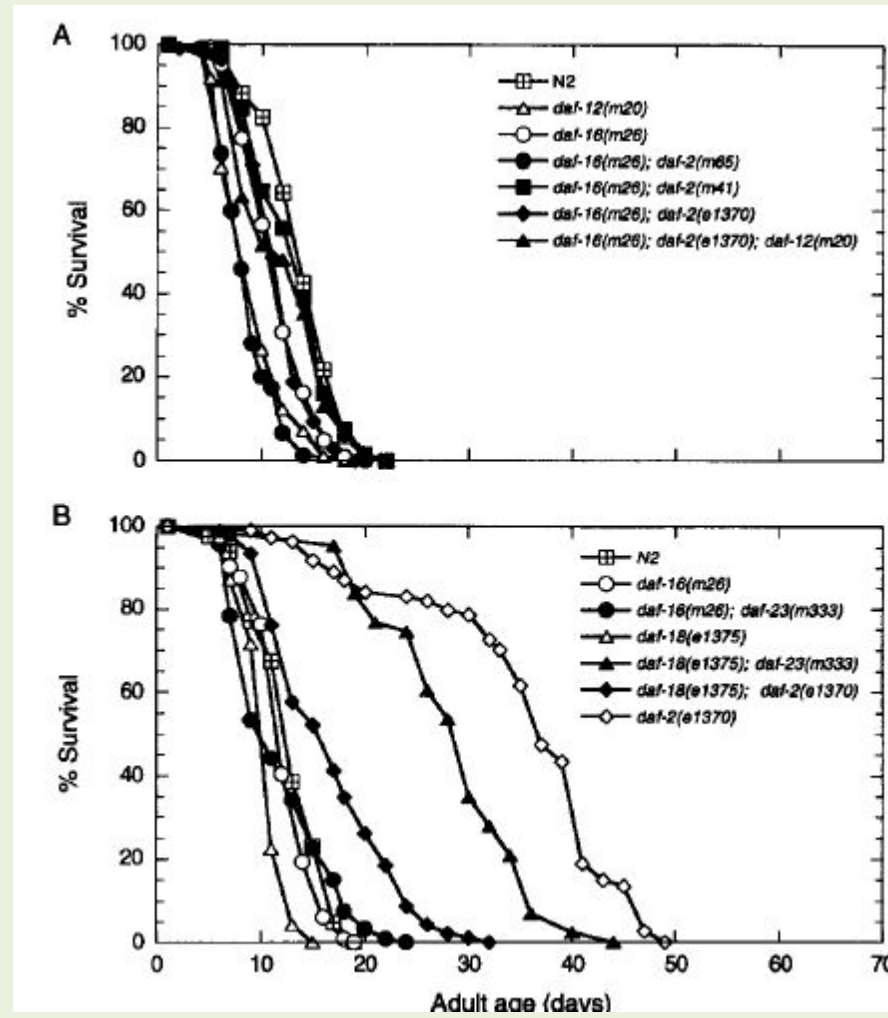
Longevity and Reproduction

- Diet restriction extends life and reduces fecundity decreasing normal egg production
- Longevity and decreased fecundity are reversed by essential amino acids.
- Methionine alone can restore fecundity without reversing longevity.
- With proper balance of nutrients one can have both fecundity and healthy longevity

Aging and Caloric Restriction

- Caloric restriction extends lifespan for yeast, *C. elegans* worms, drosophila flies and rodents
- In *C. elegans* worms, the Daf-2 gene is the homolog of the insulin receptor. When this gene is knocked out, longevity is increased. Suggesting that reductions in insulin signaling is involved in aging.
- Mannoheptulose from avacados is an inhibitor of glucokinase and inhibits insulin secretion.

Less Insulin Signaling Increases Lifespan



Mannoheptulose 15mmol/L Reduces Insulin Secretion

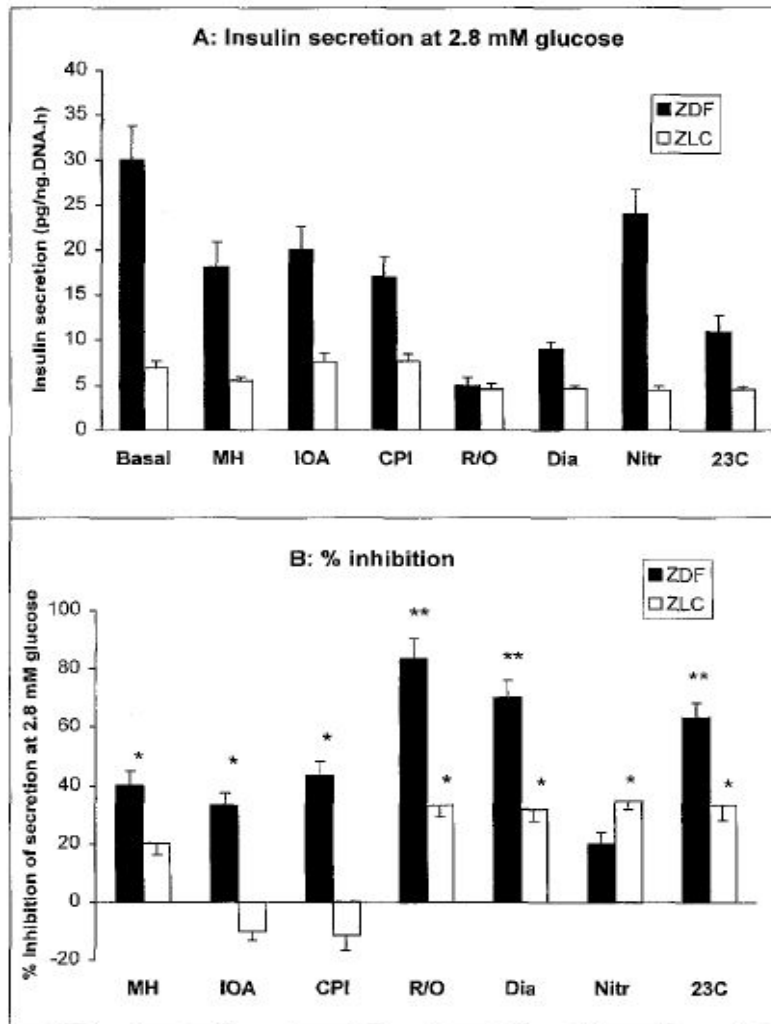
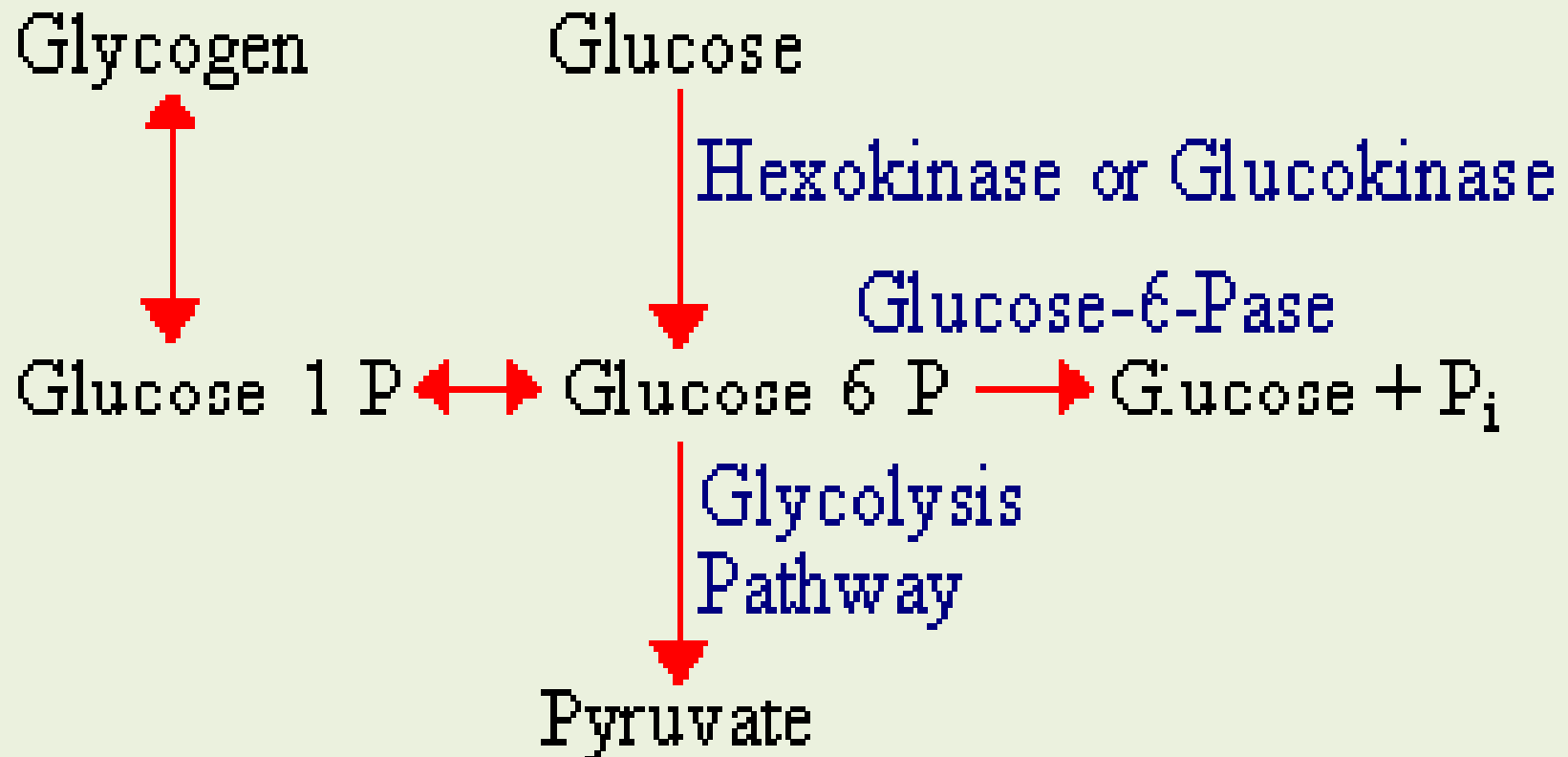


Fig 2. Effects of inhibitors of membrane depolarization and fuel metabolism on basal insulin secretion in islets from ZDF and ZLC rats. (A) Insulin secretion at 2.8 mmol/L glucose was determined during 60-minute static incubations in KRB medium containing either 2.8 mmol/L glucose only (basal) or with various inhibitors. (B) Percent inhibition resulting from the various treatments. MH, mannoheptulose 15 mmol/L; IOA, iodoacetate 1 mmol/L; CPI, CPI975 10 μ mol/L; R/O, rotenone 1 μ mol/L plus oligomycin 2 μ g/mL; Dia, diazoxide 250 μ mol/L; Nitr, nitrendipine 0.5 μ mol/L; 23C, incubation at 23°C. Data represent the mean \pm SE of 4-5 separate experiments. * $P < .05$ and ** $P < .01$ v incubation with 2.8 mmol/L glucose alone (basal secretion).

Zhou Y et al. *Metabolism*. 1999;48(7):857-64.

The Glucokinase Pathway



Glucose metabolism in liver.

Studying Anti-Aging Compounds in Humans

- Insulin sensitivity is a potential marker for longevity in humans.
- For example: testing insulin sensitivity in humans treated with avacadoes or mannoheptulose
- Treating elderly people randomized to a food intervention vs. a placebo measuring death, since anti-aging interventions in lower animals work at any age.

Conclusions

- The common theme of anti-aging agents seems to be insulin sensitivity, not food intake or metabolic rate.
- Avacadoes contain mannoheptulose which decreases insulin secretion suggesting a reduction in insulin resistance.
- Avacadoes await a clinical trial measuring insulin sensitivity or longevity.

