Less is more

The beneficial effects of short-term dietary restriction

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Disclosure: “I feel like a stange duck in the bite”
Health claims on food are ubiquitous

The Bad, the Bold and the Bogus: Food Industry Health Claims to Watch Out For

There are myriad ways packaged food companies mislead consumers through vague, false, meaningless health claims, and difficult to decipher nutritional panels.
Common sense
Why are we interested in (less) food?

- **Dietary Restriction (DR)** is defined as a reduction in food intake without malnutrition

- **Long-term DR:**
  - Increased lifespan
  - Less cardiovascular disease
  - Lower incidence of diabetes mellitus
  - Lower incidence of malignancies
  - Increased resistance to oxidative stress
Life-span extension by long-term DR:

- Saccharomyces cerevisiae (20-60%)
- Caenorhabditis elegans (10-35%)
- Drosophila melanogaster (20-30%)
- Nothobranchius furzeri (33-58%)
- Mus musculus (30-60%)
- Rattus norvegicus (30-60%)
Long-term DR improves resistance against oxidative stress in the liver

40% CR, 6 months

Resistance to paraquat toxicity

FIG. 10. Survival of mice fed a calorie-restricted diet and mice fed AL after challenge with the oxidizing agent paraquat. Six-month-old C57BL/6 mice fed a calorie-restricted diet and mice fed AL were injected intraperitoneally with paraquat at 70 mg/kg. Mice fed AL died significantly earlier than mice fed a calorie-restricted diet ($P = 0.0048$).

40% CR, 8 months

Resistance to paracetamol toxicity

Harper et al. 2006
Long-term restriction of dietary intake:

• delays the aging process
• increases resistance to oxidative stress

*Long-term food restriction in humans not feasible*
Does short-term dietary restriction increase resistance to oxidative stress?
Medically relevant oxidative damage

Ischemia-reperfusion injury (IRI)
Temporary lack of blood flow in an organ transplant (ischemia)
Followed by reperfusion with blood in recipient

Oxidative stress → injury → inflammation → organ dysfunction

Surgically induced IRI:
• Cardiothoracic bypass surgery
• Liver resection
• Organ transplantation

Drug side effects
Paracetamol
Chemotherapeutic drugs
A cold ischemia time (CIT) of >22 hours worsens kidney transplant survival
MOUSE KIDNEY AND LIVER ISCHEMIA-REPERFUSION MODELS
Dietary restricted and fasted animals are protected against ischemia-reperfusion injury of the kidney

Kidney damage

- Ad lib
- 30% DR
- 3d fast

Time after reperfusion (day)

- ATN

Time after reperfusion (hr)

- Serum LDH (U/L)
Protection from ischemia reperfusion injury by fasting is not specific to the kidney

**Figure 1:** Serum ALT (U/L) levels over time after reperfusion.

- **x-axis:** Time after reperfusion (hr)
- **y-axis:** ALT (U/L)
- **Legend:**
  - **ad lib**
  - **1d fast**
  - **2d fast**
  - **3d fast**

**Figure 2:** Hemorrhagic necrosis (%).

- **x-axis:** 24 hours after I/R
- **y-axis:** Hemorrhagic necrosis (%)

**Legend:**
- **ad lib fed**
- **1d fast**
- **2d fast**
- **3d fast**

**Notes:**
- Protection from ischemia reperfusion injury by fasting is not specific to the kidney.
- Hemorrhagic necrosis is significantly reduced in fasted groups compared to ad lib fed groups.

**Immunohistochemistry:**
- **ad libitum fed:**
- **72 hours fasted:**

**H&E 100x**
Increased resistance to oxidative damage by dietary restriction is induced rapidly and may be tapped for clinically relevant stressors such as ischemia-reperfusion injury.

How about other stressors?
Short-term dietary restriction, cancer and chemotherapy

Potential benefits:

• Reduction of tumor growth
• Augmentation of irradiation effect
• Improved resistance to irradiation
• Protection against adverse side effects of chemotherapy
• Improved postoperative recovery
Protection against adverse side effects of chemotherapy

Side effects of the chemotherapeutic drug Irinotecan are dose limiting:

- Fatigue
- Hair loss
- Nausea
- Vomiting
- Diarrhea
- Low blood counts

Protection against adverse side effects of chemotherapy
3 days fasting protects mice against a lethal dose of Irinotecan

- Fed group: weight loss, diarrhea, reduced mobility, ruffled coat, hunched back posture, leukopenia
- Fasted group: weight gain, no adverse side effects
But how about the anti cancer effect of Irinotecan in fasted mice?

Tumor weight in mice with coloncarcinoma treated with Irinotecan

Huisman et al., unpublished
Towards clinical application

- Composition
- Time
- Adherence
Calorie restriction trial
• Feasibility and safety of a preoperative diet
• Effects on postoperative recovery

Pre-operative dietary restriction is feasible in live-kidney donors

Dietary Restriction Modifies Certain Aspects of the Postoperative Acute Phase Response

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The Protein and Calorie restriction Trial

PROTECT Study

Effects of a preoperative protein and caloric restricted diet on postoperative recovery and genomic changes in healthy (kidney donation) and unhealthy (bariatric surgery) individuals undergoing surgery
Self reported compliance

• **Erasmus MC:**
  - Scandishake: 8/10 (80%)
  - Nutridrink: 4/10 (40%)

• **Maasstad:**
  - Scandishake*: 12/18 (67%)
  - Nutridrink: 9/10 (90%)

**Self reported adverse effects**

**Scandishake:**
- 50%:
  - Hunger
  - General discomfort
  - Bad taste

**Nutridrink:**
- 70%:
  - Hunger
  - Bad taste
  - Diarrhea
  - Nausea
Why broccoli sprouts?

Practical limitations to dietary restriction fuel the search for “dietary restriction mimetics”

Broccoli, like dietary restriction, is able to extend lifespan!

Longevity in the red flour beetle *Tribolium castaneum* is enhanced by broccoli and depends on *nrf-2, jnk-1* and *foxo-1* homologous genes

Stefanie Grünwald · Julia Stellzig · Iris V. Adam · Kristine Weber · Sarai Binger · Michael Boll · Eileen Knorr · Richard M. Twyman · Andreas Völckers · Uwe Wenzel

Can broccoli consumption mimic the effects of dietary restriction and fasting?
Theoretical considerations

Dietary restriction

- Activation of nutrient sensing pathways
- Activation of adaptive stress response

Broccoli - Sulforaphane

Nrf2 pathway

- Drug metabolism / detoxification
- Anti-oxidants
- Anti-inflammation
The effects of pre-operative broccoli cress consumption on the response to surgery and on postoperative recovery

AIM:
• To investigate whether a broccoli cress enriched diet induces a protective response in patients undergoing surgery.
The effects of pre-operative broccoli cress consumption on the acute phase response after surgery and on postoperative recovery

- **Study population:**
  40 healthy people (>18 years) who are listed to undergo kidney donation at the Erasmus Medical Center.

- **Intervention:**
  Two patient groups. Broccoli enriched diet (8 gram of broccoli cress) or control (8 gram of lettuce, no *Brassicaceae* in diet) during 5 days before surgery.

**Main study parameter:**
Acute phase response by measurement of leukocytes, C-reactive protein and IL-6, TNF-α, IFN-γ, IL-10 in blood.

- **Secondary parameters:**
  The Nrf2 mediated stress response will be measured in kidney tissue.
  Well-being and postoperative recovery with the help of standardized questionnaires (VAS, MFI-20, SF-36, EuroQol and work related scores).
Take home

• Short-term dietary restriction and fasting protect against medically relevant stressors

• Activation of the Nrf2 pathway is important in inducing this protection

• Sulforaphane-precursor containing vegetables may induce similar protective effects

• Do these rapidly induced effects predict long-term health benefits?