Obesity- A Public Health Crisis

ACP Spring Chapter Meeting
March 3rd, 2018
David Scarborough, MD, FACP, FACE
Assoc. Prof. of Clinical Medicine
Chief, Endocrinology and Metabolism

LSU Health

SHREVEPORT
Disclosures – Nothing to Disclose
Topics For Today

- Obesity Basics – BMI, Morbidities
- Scope of the Problem
- Nature of the Problem – Character, Genetics, Biology
- Treatment Options – Diet & Exercise (Lifestyle), Drugs, Surgery
- What’s Old is New Again (Fasting and Time-Restricted Feeding)
# BMI Categories

<table>
<thead>
<tr>
<th>Label</th>
<th>Obesity Class</th>
<th>BMI kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td></td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>18.5 - 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td>25 - 29.9</td>
</tr>
<tr>
<td>Obese I</td>
<td>I</td>
<td>30 - 34.9</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>35 - 39.9</td>
</tr>
<tr>
<td>Extreme Obesity</td>
<td>III</td>
<td>40 +</td>
</tr>
</tbody>
</table>
BMI of 25, uptick in CVD


BMI = 30
Social Discrimination (esp from nurses & physicians) and Poor Self Esteem, Urinary Incontinence, Venous Stasis Disease, . . .more
Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 Years or older

Obesity (BMI $\geq$30 kg/m$^2$)

- 1994
- 2000
- 2010

Diabetes

- 1994
- 2000
- 2010

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2016

Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

Source: Behavioral Risk Factor Surveillance System

*Sample size < 50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%
Losing Weight

What is healthy weight loss?

It’s natural for anyone trying to lose weight to want to lose it very quickly. But evidence shows that people who lose weight gradually and steadily (about 1 to 2 pounds per week) are more successful at keeping weight off. Healthy weight loss isn’t just about a “diet” or “program”. It’s about an ongoing lifestyle that includes long-term changes in daily eating and exercise habits.

To lose weight, you must use up more calories than you take in. Since one pound equals 3,500 calories, you need to reduce your caloric intake by 500—1,000 calories per day to lose about 1 to 2 pounds per week.¹

Once you’ve achieved a healthy weight, by relying on healthful eating and physical activity most days of the week (about 60—90 minutes, moderate intensity), you are more likely to be successful at keeping the weight off over the long term.

In other words, “Eat Less and Move More”
Seven Deadly SINS

Lust

Move More

Pride

Move More

Sloth

Move More

Anger

Eat Less

Envy

Eat Less

Gluttony

Eat Less

Greed

Eat Less
They often think, “If these people would just eat less, and move more, all would be fine.”

**Physicians:**

Self-report studies show that physicians often view individuals affected by obesity as described below more often than they do individuals not affected by obesity:

- Non-compliant
- Dishonest
- Lazy
- Lacking in self-control
- Weak-willed
- Unintelligent
- Unsuccessful
Seriously ?

Net Worth
$3.4 billion
Craig and Kevin Stadler
Father & Son
Professional Golfers
Table 1. Body-Mass Index and Intrapair Correlations in Monozygotic and Dizygotic Pairs of Twins Reared Apart or Together.*

<table>
<thead>
<tr>
<th>Type</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO. OF PAIRS</td>
<td>BODY-MASS INDEX</td>
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<tr>
<td>Monozygotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reared apart</td>
<td>49</td>
<td>24.8±2.4</td>
</tr>
<tr>
<td>Reared together</td>
<td>66</td>
<td>24.2±2.9</td>
</tr>
<tr>
<td>Dizygotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reared apart</td>
<td>75</td>
<td>25.1±3.0</td>
</tr>
<tr>
<td>Reared together</td>
<td>89</td>
<td>24.6±2.7</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ±SD.
Environment
In Sweeping War on Obesity, Chile Slays Tony the Tiger

New regulations, which corporate interests delayed for almost a decade, require explicit labeling and limit the marketing of sugary foods to children.

By ANDREW JACOBS   FEB. 7, 2018
Figure 2  Changing intake of fructose and high-fructose corn syrup intake plotted against the increasing prevalence of obesity. Adapted from Bray et al.⁹
The rising tide of obesity is strongly associated with daily calorie intake and sedentary lifestyle-promoting transportation (refs. 84–86; [www.earth-policy.org/data_center/C23]). *US, approximate value. #Worldwide auto production.
Why Are We Gaining So Much Weight?

- No generally agreed upon main answer
- Food abundance & affluence
- Eating out, increased portion sizes
- Higher fat diet
- Higher refined carbohydrates in diet
- Less fiber
- Less sleep
- Less exercise

Table 1. Causes of Obesity

<table>
<thead>
<tr>
<th>Primary Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic causes</td>
</tr>
<tr>
<td>Monogenic disorders</td>
</tr>
<tr>
<td>Melanocortin-4 receptor mutation</td>
</tr>
<tr>
<td>Leptin deficiency</td>
</tr>
<tr>
<td>POMC deficiency</td>
</tr>
<tr>
<td>Syndromes</td>
</tr>
<tr>
<td>Prader-Willi</td>
</tr>
<tr>
<td>Bardet-Biedl</td>
</tr>
<tr>
<td>Cohen</td>
</tr>
<tr>
<td>Alström</td>
</tr>
<tr>
<td>Froehlich</td>
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<tr>
<td>Secondary Causes</td>
</tr>
<tr>
<td>Neurological</td>
</tr>
<tr>
<td>Brain injury</td>
</tr>
<tr>
<td>Brain tumor</td>
</tr>
<tr>
<td>Consequences of cranial irradiation</td>
</tr>
<tr>
<td>Hypothalamic obesity</td>
</tr>
<tr>
<td>Endocrine</td>
</tr>
<tr>
<td>Hypothyroidism*</td>
</tr>
<tr>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>GH deficiency</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
</tr>
<tr>
<td>Psychological</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Eating disorders</td>
</tr>
</tbody>
</table>

Drug-Induced
- Tricyclic antidepressants
- Oral contraceptives
- Antipsychotics
- Anticonvulsants
- Glucocorticoids
- Sulfonlureas
- Glitazones
- β blockers

*Controversial whether hypothyroidism causes obesity or exacerbates obesity.

b Depression associated with overeating or binging.
Treatment Options
So, Treatments

❖ Diet and Exercise / Lifestyle (Nutrition, Physical Activity)
❖ Drugs (Medications)
❖ Surgery and Other Invasive
❖ Somethings Old - Now New Again
2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society

Box 11a. Offer or Refer for High Intensity Comprehensive Lifestyle Intervention

The most effective behavioral weight loss treatment is in-person, high-intensity (i.e., ≥14 sessions in 6 months) comprehensive weight loss interventions provided in individual or group sessions by a trained interventionist† (CQ4). The principal components of an effective high-intensity, on-site comprehensive lifestyle intervention include: 1) prescription of a moderately-reduced calorie diet; 2) a program of increased physical activity; and 3) the use of behavioral strategies to facilitate adherence to diet and activity recommendations. As shown in CQ4, comprehensive lifestyle intervention consisting of diet, physical activity, and behavior therapy produces average weight losses of approximately 8 kg in a 6 month period of frequent, in-person treatment. This approximates losses of 5% to 10% of initial weight. The observed average weight loss of approximately 8 kg includes people who have variable weight loss (i.e., some more and some less than average), so accurate prediction of individual weight loss is not possible. After 6 months, most patients will equilibrate (caloric intake balancing energy expenditure) and will require adjustment of energy balance if they are to lose additional weight. As demonstrated in CQ4, continued intervention contact following initial weight loss treatment is associated with better maintenance of lost weight (Box 15).

*Nutrition professional: In the studies that form the evidence base for this recommendation, a registered dietitian usually delivered the dietary guidance; in most cases, the intervention was delivered in university nutrition departments or in hospital medical care settings where access to nutrition professionals was available.
†Trained Interventionist: In the studies reviewed, trained interventionists included mostly health professionals (e.g., registered dietitians, psychologists, exercise specialists, health counselors, or professionals in training) who adhered to formal protocols in weight management. In a few cases, lay persons were used as trained interventionists; they received instruction in weight management protocols (designed by health professionals) in programs that have been validated in high quality trials published in peer-reviewed journals.

“equilibrate” – such a bland word for something so important
“adjustment of energy balance” = eat even less and exercise even more
Weight Loss Maintenance

Typically, obesity is a chronic condition that develops over an individual’s lifetime. The prevalence of obesity has greatly increased over the past 30 years, most likely because of environmental changes that promote increased consumption of high-calorie palatable foods, decreased physical activity, and more sedentary behavior. In this environment, it is difficult to maintain a healthy weight and prevent weight gain. Long-term research has shown that continuing weight loss maintenance interventions produce better long-term results than limited-term intervention programs. Clinicians must acknowledge the lifelong challenge that patients experience with obesity, provide support and encouragement, be prepared to assist patients with addressing small weight gains before they become larger ones, and reinstitute weight management efforts as early as possible in the course of regain.

The usual pattern of weight loss in patients undergoing a lifestyle intervention is that maximum weight loss is achieved at 6 months, followed by plateau and gradual regain over time. This is also true for medication-assisted weight loss, although weight regain may be slower with continued medication use. For bariatric surgery patients, it may take much longer for weight to plateau (CQ3, CQ4, and CQ5).

The strategies for weight maintenance after successful loss differ from the strategies for achieving weight loss. Flexibility and willingness to try different approaches are recommended. Patients should be advised that participation in a long-term (>1 y) comprehensive weight loss maintenance program with monthly or more frequent contact, in person or by telephone, can improve successful weight maintenance. Strategies such as frequent self-weighing (at least weekly), consumption of a reduced-calorie diet, and high levels of physical activity (>200 min/wk) are associated with better weight maintenance over time.
Sustainability

VLCD = < 800 kcal/d
BMOD = 1200 kcal/d
Rx Period = 6 months
One Decade of My Chronic Relapsing Condition

- 21 yo: U of C
- Running & cal counting
- Stress frax’s
- Graduate U of C
- Got Married & Started Med School

21 yo 30 yo
Long-Term F/U DPP* Trial: Wt & DM

3-4 yr intervention
5-7 yr follow-up

*DPP: Diabetes Prevention Program
Weight-Loss Outcomes: A Systematic Review and Meta-Analysis of Weight-Loss Clinical Trials with a Minimum 1-Year Follow-Up

MARION J. FRANZ, MS, RD; JEFFREY J._VM, WORMER, MS; A. LAUREN CRAIN, PhD; JACKIE L. BOUCHER, MS, RD; TRINA HISTON, PhD; WILLIAM CAPLAN, MD; JILL D. BOWMAN; NICOLAS P. PRONK, PhD

Figure 1. Average weight loss of subjects completing a minimum 1-year weight-management intervention; based on review of 80 studies (N=26,455; 18,199 completers [69%]).
Slowing Weight Loss and Weight Regain

- Body weight goes down so that calories used to move it decline.
- Less tissue requiring support of basal metabolic activities.
- Lower thermic effect of food because less food intake.
- Decreased physical activity.
- Decreased RMR owing to decreased adaptive thermogenesis.
- Boredom and fatigue and disillusionment.
- Anything else . . . ????

NIH Working Group Report: Innovative Research to Improve Maintenance of Weight Loss

Paul S. MacLean¹, Rena R. Wing², Terry Davidson³, Leonard Epstein⁴, Bret Goodpaster⁵, Kevin D. Hall⁶, Barry E. Levin⁷, Michael G. Perrit⁸, Barbara J. Rolls⁹, Michael Rosenbaum¹⁰, Alexander J. Rothman¹¹, and Donna Ryan¹²


Why obesity is called chronic and relapsing.
Drugs for Weight Loss

Redux: dexfenfluramine

18 million prescriptions in 1996

Withdrawn from the market by the FDA in 1997

Time Cover Sept 1996
Surgery & Other Invasive
Vertical Sleeve Gastrectomy
Figure 3. Gastric bypass partitioned. In this version of gastric bypass, the stomach is partitioned rather than divided. A Roux-en-Y gastrojejunostomy is done with variable lengths. The alimentary limb refers to the jejunal Roux-en-Y limb anastomosed to the stomach. The biliopancreatic limb transmits bile and pancreatic secretions to the jejunoojejunostomy where the ingested nutrients and digestive juices first mix. The common channel refers to the distance from the enteroenterostomy to the ileocecal valve.
Sjostrom CD, et al., NEJM, 357, August 23, 2007, pp 746

HR mortality, 0.71
Table 1. Comorbidity Reduction According to Type of Bariatric Procedure

<table>
<thead>
<tr>
<th></th>
<th>GASTRIC BANDING</th>
<th>GASTROPLASTY</th>
<th>GASTRIC BYPASS</th>
<th>BPD OR DS</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>% EWL</td>
<td>47%</td>
<td>68%</td>
<td>62%</td>
<td>70%</td>
<td>61%</td>
</tr>
<tr>
<td>Resolution of T2DM</td>
<td>48%</td>
<td>72%</td>
<td>84%</td>
<td>99%</td>
<td>77%</td>
</tr>
<tr>
<td>Resolution of hyperlipidemia</td>
<td>59%</td>
<td>74%</td>
<td>97%</td>
<td>99%</td>
<td>79%</td>
</tr>
<tr>
<td>Resolution of hypertension</td>
<td>43%</td>
<td>69%</td>
<td>68%</td>
<td>83%</td>
<td>62%</td>
</tr>
<tr>
<td>Resolution of sleep apnea</td>
<td>95%</td>
<td>78%</td>
<td>80%</td>
<td>92%</td>
<td>86%</td>
</tr>
</tbody>
</table>


BPD, biliopancreatic diversion; DS, duodenal switch; EWL, excess weight loss; T2DM, type 2 diabetes.
Late Complications of Bariatric Surgery

• Abdominal pain
  - Rapid food consumption
  - LES dilation and spasm
  - Strictures
  - Ulcers
  - Leaks
  - Gallstones
  - Band malfunction or malposition

• Dumping syndrome
• Diarrhea
  - Dumping syndrome
  - Malabsorption
  - Bile salt diarrhea

• Gastrointestinal bleeding
• Nutritional deficiencies
• Postprandial hyperinsulinemic hypoglycemia

Lee et al. Curr Opin Gastroenterol 2007; 23:636-643
ILEAL TRANSPOSITION

Other Invasive Techniques Include

1- Intestinal Sleeve
2- Electronic Vagal Stimulation
3- Endoscopically placed gastric balloons
4- post-meal stomach drainage
50 years on previous diets, beginning age 14; now 68. Previous lowest weight as an adult 141 lbs. Sep 1974 BMI 21.1
Highest weight 231 lbs, Feb 2009, BMI 34.6
Main program: 1200-1400 kcal/day, CHO < 75 gm, normal protein, low glycemic vegetables with each meal. My Fitness Pal diary last 4.5 years.
Lost 100 lbs, 43% of body weight from highest weight to spring 2017.
The last 20 lbs employed modest TRF and IF approach.
Sjostrom CD, et al., NEJM, 357, August 23, 2007, pp 746

HR mortality, 0.71

- 43%, or 100% EWL
Fifty Years of Behavioral/Lifestyle Interventions for Overweight and Obesity: Where Have We Been and Where Are We Going?

Donald A. Williamson

Intensive Lifestyle Interventions (ILIs) as exemplified by the DPP, Look AHEAD, Pounds Lost, and CALERIE have shown that significant weight loss can be achieved with favorable effects on metabolic risk factors and diabetes development. This has led to some funding and program guidelines for ILIs (CDC, CMMS, USPSTF), which are welcome and very recent. To date these emphasize daily calorie restriction (eating less), much individual and group counseling, and exercise programs (moving more). Long term costs versus benefits and sustainability remain uncertain.

More research to refine and improve these models is needed.

What other approaches might there be?
What’s Old Is New Again
Phases of Starvation

In the transition from the fed to the fasted state in man, a sequence of metabolic alterations occurs to provide calories for survival and are listed as follows with their approximate duration:

1) Gastrointestinal absorption of substrate 1–8 hours
2) Glycogenolysis (liver and muscle) 1–2 days
3) Gluconeogenesis (liver) first week
4) Ketosis 3–4 days onward
5) Diminishing gluconeogenesis and increasing cerebral ketone consumption second week onward
A metabolic shift to ketogenesis that occurs with fasting bolsters neuronal bioenergetics. Liver glycogen stores are typically depleted within 10–12 h of fasting, which is followed by liberation of fatty acids from adipose tissue cells into the blood. The fatty acids are then transported into liver cells where they are oxidized to generate Acetyl-CoA. Acetyl-CoA is then converted to 3-hydroxy-3-methylglutaryl-CoA, which is in turn used to generate the ketones acetoacetate and β-hydroxybutyrate (β-OHB). The ketones are released into the blood and are transported into various tissues, including the brain, where they are taken up by neurons and used to produce acetyl-CoA. Acetyl-CoA enters the tricarboxylic acid (TCA) cycle to generate ATP.
Reduced food intake, avoiding malnutrition, can ameliorate aging and aging-associated diseases in invertebrate model organisms, rodents, primates, and humans. Recent findings indicate that meal timing is crucial, with both intermittent fasting and adjusted diurnal rhythm of feeding improving health and function, in the absence of changes in overall intake. Lowered intake of particular nutrients rather than of overall calories is also key, with protein and specific amino acids playing prominent roles. Nutritional modulation of the microbiome can also be important, and there are long-term, including inter-generational, effects of diet.

Cell: 2015, 161(1) 106-118.
Figure 1. Dietary Restriction Increases Healthy Lifespan in Diverse Single-Celled, Invertebrate, and Vertebrate Animals
<table>
<thead>
<tr>
<th>Table 1. Interventions Extending Mean and/or Maximal Lifespan in Wild-Type Mice Fed Normal Chow</th>
</tr>
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<tbody>
<tr>
<td><strong>Dietary Interventions</strong></td>
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<tr>
<td>Calorie restriction</td>
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<tr>
<td>Intermittent fasting</td>
</tr>
<tr>
<td>Protein restriction</td>
</tr>
<tr>
<td>Methionine restriction</td>
</tr>
<tr>
<td>Tyrosine restriction</td>
</tr>
<tr>
<td><strong>Physical Exercise Interventions</strong></td>
</tr>
<tr>
<td>Endurance exercise</td>
</tr>
<tr>
<td><strong>Genetic Interventions</strong></td>
</tr>
<tr>
<td>Ames and Snell dwarf</td>
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<tr>
<td>GH receptor KO</td>
</tr>
<tr>
<td>IGF-1 R KO</td>
</tr>
<tr>
<td>Klotho TG</td>
</tr>
<tr>
<td>Fat Insulin Receptor KO</td>
</tr>
<tr>
<td>Insulin Receptor Substrate 1 KO</td>
</tr>
<tr>
<td>Brain IRS-2 KO</td>
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<tr>
<td>PAPP-A KO</td>
</tr>
<tr>
<td>Ribosomal S6 protein kinase-1 KO</td>
</tr>
<tr>
<td>FGF-21 TG</td>
</tr>
<tr>
<td>mIR-17TG</td>
</tr>
<tr>
<td>DGAT1KO</td>
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<td>p53shc KO</td>
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<td>ATG5 TG</td>
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<tr>
<td>Type 5 Adenylyl Cyclicase KO</td>
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<tr>
<td>Angiotensin II type 1 receptor KO</td>
</tr>
<tr>
<td>Catalase targeted to mitochondria TG</td>
</tr>
<tr>
<td>Ink4/Arf-TG/TG</td>
</tr>
<tr>
<td>C/EBP β/δ</td>
</tr>
<tr>
<td>Mcl1KO</td>
</tr>
<tr>
<td>Hct-UCP2 TG</td>
</tr>
<tr>
<td>Macrophage migration inhibitory factor KO</td>
</tr>
<tr>
<td>E-DNIκB TG</td>
</tr>
<tr>
<td>PEA RIIβ KO</td>
</tr>
<tr>
<td>RasRFF1 KO</td>
</tr>
<tr>
<td>Sirt6 TG</td>
</tr>
<tr>
<td>Brain-specific Sirt1 TG</td>
</tr>
<tr>
<td>TRPV1 pain receptor KO</td>
</tr>
</tbody>
</table>
Figure 2. TOR pathway, a conserved mediator of lifespan extension in multiple species

The diagram represents the genetic interactions in the TOR signaling network that execute lifespan extension in yeast, worms, flies and mice. The diagram summarizes the lifespan data for genes in the TOR signaling pathway or those that demonstrate a genetic interaction with mutants in the TOR pathway. The shaded area refers to components of the TOR pathway that show conserved effects on lifespan extension in different species. See main text for details.
Yoshinori Ohsumi - Nobel Lecture

Autophagy - an Intracellular Recycling System

Yoshinori Ohsumi delivered his Nobel Lecture on 7 December 2016 at Aula Medica, Karolinska Institutet in Stockholm. He was introduced by Professor Maria Masucci of the Nobel Assembly.
Fasting: Molecular Mechanisms and Clinical Applications

Valter D. Longo¹ and Mark P. Mattson²,³

¹Longevity Institute, Davis School of Gerontology and Department of Biological Sciences, University of Southern California, Los Angeles, CA 90089-2520, USA
²National Institute on Aging Intramural Research Program, National Institutes of Health, Baltimore, Maryland 21224, USA
³Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA

Abstract

Fasting has been practiced for millennia, but only recently studies have shed light on its role in adaptive cellular responses that reduce oxidative damage and inflammation, optimize energy metabolism and bolster cellular protection. In lower eukaryotes, chronic fasting extends longevity in part by reprogramming metabolic and stress resistance pathways. In rodents intermittent or periodic fasting protects against diabetes, cancers, heart disease and neurodegeneration, while in humans it helps reduce obesity, hypertension, asthma and rheumatoid arthritis. Thus, fasting has the potential to delay aging and help prevent and treat diseases while minimizing the side effects caused by chronic dietary interventions.

Time-restricted feeding for prevention and treatment of cardiometabolic disorders

Girish C. Melkani¹ and Satchidananda Panda²

¹Department of Biology, Molecular Biology and Heart Institutes, San Diego State University San Diego, CA 92182, USA
²Regulatory Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037, USA


Resting energy expenditure in short-term starvation is increased as a result of an increase in serum norepinephrine\textsuperscript{1,2}

Christian Zauner, Bruno Schneeweiss, Alexander Kranz, Christian Madl, Klaus Ratheiser, Ludwig Kramer, Erich Roth, Barbara Schneider, and Kurt Lenz

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>ENERGY METABOLISM IN EARLY STARVATION</th>
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<tbody>
<tr>
<td>Biochemical values\textsuperscript{1}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td>Norepinephrine (pmol/L)</td>
<td>1716 ± 574</td>
</tr>
<tr>
<td>Epinephrine (pmol/L)</td>
<td>425 ± 180</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>71 ± 21</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.9 ± 0.5</td>
</tr>
<tr>
<td>Fatty acids (μmol/L)</td>
<td>240 ± 191</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>0.87 ± 0.3</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.88 ± 0.6</td>
</tr>
<tr>
<td>β-Hydroxybutyrate (μmol/L)</td>
<td>182.7 ± 262.9</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>4.58 ± 1</td>
</tr>
</tbody>
</table>

\textsuperscript{1}\textsuperscript{Y} ± SD of data for each day. BUN, blood urea nitrogen.

\textsuperscript{2}Significantly different from day 1, \textit{P} < 0.05.

\textsuperscript{3}Significantly different from day 2, \textit{P} < 0.05.

\textsuperscript{4}Significantly different from day 3, \textit{P} < 0.05.

Glucose 88 to 63 day 1 to day 4
### TABLE 2
Results of metabolic studies

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNP (g/d)</td>
<td>7.47 ± 3.6</td>
<td>7.07 ± 2.1</td>
<td>10.94 ± 3.4&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>7.56 ± 2.3&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>VO₂ (mL/min)</td>
<td>199 ± 45</td>
<td>224 ± 44&lt;sup&gt;2&lt;/sup&gt;</td>
<td>234 ± 45&lt;sup&gt;2&lt;/sup&gt;</td>
<td>229 ± 46&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>VCO₂ (mL/min)</td>
<td>165 ± 35</td>
<td>165 ± 34</td>
<td>167 ± 31</td>
<td>162 ± 32</td>
</tr>
<tr>
<td>RQ</td>
<td>0.83 ± 0.05</td>
<td>0.74 ± 0.04&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.72 ± 0.03&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.71 ± 0.04&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>REE (kJ/min)</td>
<td>3.97 ± 0.9</td>
<td>4.37 ± 0.9&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4.53 ± 0.9&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4.43 ± 0.9&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nonprotein RQ</td>
<td>0.83 ± 0.06</td>
<td>0.73 ± 0.04&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.70 ± 0.04&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.70 ± 0.04&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.2 ± 13.5</td>
<td>63.5 ± 13.3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>62.6 ± 13.2&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>61.5 ± 13.2&lt;sup&gt;2,3,4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>x ± SD of data for each day. UNP, urea-nitrogen appearance rate; VO₂, oxygen consumption; VCO₂, carbon dioxide production; RQ, respiratory quotient; REE, resting energy expenditure.

<sup>2</sup>Significantly different from day 1, *P* < 0.05.

<sup>3</sup>Significantly different from day 2, *P* < 0.05.

<sup>4</sup>Significantly different from day 3, *P* < 0.05.

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**Metabolic Changes over 4 days of fasting**

![Graph showing changes in Weight (kg), REE, and VO₂ over 4 days of fasting](image.png)

High Caloric Intake at Breakfast vs. Dinner Differentially Influences Weight Loss of Overweight and Obese Women

Daniela Jakubowicz,¹ Maayan Barnea,² Julio Wainstein¹ and Oren Froy²

Objective: Few studies examined the association between time-of-day of nutrient intake and the metabolic syndrome. Our goal was to compare a weight loss diet with high caloric intake during breakfast to an isocaloric diet with high caloric intake at dinner.

Design and Methods: Overweight and obese women (BMI 32.4 ± 1.8 kg/m²) with metabolic syndrome were randomized into two isocaloric (~1400 kcal) weight loss groups, a breakfast (BF) (700 kcal breakfast, 500 kcal lunch, 200 kcal dinner) or a dinner (D) group (200 kcal breakfast, 500 kcal lunch, 700 kcal dinner) for 12 weeks.

Results: The BF group showed greater weight loss and waist circumference reduction. Although fasting glucose, insulin, and ghrelin were reduced in both groups, fasting glucose, insulin, and HOMA-IR decreased significantly to a greater extent in the BF group. Mean triglyceride levels decreased by 33.6% in the BF group, but increased by 14.6% in the D group. Oral glucose tolerance test led to a greater decrease of glucose and insulin in the BF group. In response to meal challenges, the overall daily glucose, insulin, ghrelin, and mean hunger scores were significantly lower, whereas mean satiety scores were significantly higher in the BF group.

Conclusions: High-calorie breakfast with reduced intake at dinner is beneficial and might be a useful alternative for the management of obesity and metabolic syndrome.

Body weight decreased significantly (P < 0.0001) in both the BF and D groups over 12 weeks. However, compared with the D group, the BF group showed a 2.5-fold greater weight loss (-8.7 kg vs. -3.6 kg, respectively) (One-way ANOVA P < 0.0001). As a result, the BMI was significantly different between the groups (P < 0.0001), with 10% reduction in the BF group and only 5% reduction in the D group (Table 2).
Comparison of a carbohydrate-free diet vs. fasting on plasma glucose, insulin and glucagon in type 2 diabetes (7 male subjects off all meds)
Nuttall FQ et al. Metabolism 64 (2015) 253-262

Standard Diet consisted of 55% carbohydrate, 15% protein and 30% fat. Cross-over design with washout between arms.
Time-Restricted Feeding without Reducing Caloric Intake Prevents Metabolic Diseases in Mice Fed a High-Fat Diet

Megumi Hatori,¹,⁴ Christopher Vollmers,¹,⁴ Amir Zarrinpar,¹,²,⁴ Luciano DiTacchio,¹,⁴ Eric A. Bushong,³ Shubhroz Gill,¹ Mathias Leblanc,¹ Amandine Chaix,¹ Matthew Joens,¹ James A.J. Fitzpatrick,¹ Mark H. Ellisman,³ and Satchidananda Panda¹,∥

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The ability to adapt to lack of food is a very basic need of organisms. Organisms can adapt via dormancy (spores, hibernation), through consumption of stored energy (lipolysis), and targeted consumption of damaged functional elements (apoptosis, autophagy, mitophagy). When rest and food return, anabolism and growth replace the cells and components previously catabolized with new healthier ones.

Across species seasonal and circadian rhythms in biology are correlated with food availability. We grow and reproduce in plenty and hunker down and survive in scarcity.

Stressors such as exercise and fasting stimulate the protective metabolic adaptations.

Molecular clocks such as the hypothalamic light sensitive master clock have recently been found to coordinate with molecular clocks in peripheral tissues such as liver and kidney.

Molecular clocks, fasting, exercise, aging all seem to depend on conserved control pathways involving nutrient sensors such as insulin, mTOR, and AMPK.

Invoking our ancestral patterns of activity and energy intake may be an effective path to better metabolic health and healthier aging.
Intermittent Fasting and TRF

These are old patterns and yet got lost over the last century.

It’s hard to make money encouraging people to eat less sometimes, but not all the time.

People “fear the fast”, yet it has the potential do more than trying to eat less and move more every day.

There is precedent for changing public attitudes and habits: smoking, dietary fat, all day eating.