Metabolic Brain Disorders
How do we turn the tide of T2D and Obesity?
If the members of the American medical establishment were to have a collective find-yourself-standing-naked-in-Times-Square-type nightmare, this might be it.
What is the cost of incorrect information?
The consequences:

- Obesity
- T2D
- Neurodegenerative Disorders
- Poor Quality of Life
American medical establishment dietary recommendations:
- Eat less fat, which means that one consumes more carbohydrates.
- Eat less, exercise more.
The Weight Watchers Diet

**Philosophy** Portion control. Nothing is off-limits, but everything must be in moderation.

**How It Works** Smaller portions mean fewer calories are taken in, so less fat gets stored. A point system assigns a value to portions of all sorts of foods to help tabulate—and limit—daily consumption. To lose half a kilogram a week, you generally need to consume 500 fewer calories a day.

**Downside** Hunger. Small portions can leave stomachs growling.

This is a "Calories in, Calories out" model.

Calories are mostly equivalent – so by limiting all food types and counting portions (proxy for calories) to less than what is expended then weight loss is inevitable.
The Ornish Diet

**Philosophy** Kiss meat goodbye. Cut down on fats and simple carbs like sugar and alcohol.

**How It Works** At nine calories per gram, fat is more than twice as dense as protein and carbs. Thus dieters can consume the same amount of food but still lose weight if they eat less fat. Focusing on complex carbs like whole grains helps stabilize blood sugar, and lots of fiber increases satiety.

**Downside** Strictness. Giving up meat is hard, but no fatty nuts or avocados? Sheesh.

This is a variant on the "Calories in, Calories out" model.

Fats are more calorie dense → therefore they should be avoided. Added sugars should be avoided as they don’t add nutritional value.
What if it was this recommendation that caused the T2D & obesity epidemic today??
The Atkins Diet

**Philosophy** Cut carbohydrates—they make you hungrier. Load up on fats and proteins.

**How It Works** When the body takes in very few carbs, it gets its energy by burning fat instead of carbs. This occurs when the liver turns stored fat into chemicals called ketones, which are used for fuel (and can give you less-than-fresh breath).

**Downside** Long-term adherance. It's hard to stick to a diet that restricts such a big chunk of the food pyramid.

This is model takes into account the metabolic and hormonal impact of foods. Foods are selected to minimize an insulin response. Ketogenic.

http://content.time.com/time/specials/2007/0,28757,1626795,00.html
But, what if Dr. Atkin’s right (about sugar and carbs), after all??
America is polarized...
The real divide is...

Not politics...😊
Dogma: Obesity is caused by excessive consumption of fat.

Low Fat; High Carb
LESS FAT = MORE CARBS

the staples: rice, pasta, bread
Obesity is caused by excessive consumption of fat. 

Implication: Less fat = More carbs

Obesity is caused by:

1. Too much fat
2. Not enough exercise
The: "ALTERNATIVE HYPOTHESIS"

Mozzarella
Fats & Proteins

Low Carb; No Added Sugar
Obesity is caused by:

- Sugar & refined carbs

Known as the "Alternative Hypothesis"

- Paleo
- Keto
- Atkins

Low carb; no added sugar
WE HAVE AN EPIDEMIC—
OBESITY, T2D, DEMENTIA!

IT IS BEYOND FOOD CHOICE:

LOW FAT vs. LOW CARB
WE HAVE AN EPIDEMIC—OBESITY, T2D, DEMENTIA!

IT IS BEYOND FOOD CHOICE:

LOW FAT vs. LOW CARB

"IF ONLY I ATE LESS & EXERCISED MORE"

{ We blame the patient!! }
IT IS NOT NECESSARILY THE PATIENT’S FAULT.
IT IS NOT NECESSARILY THE PATIENT'S FAULT.

FAILED POLICY & FAILED ASSUMPTIONS
Conventional calorie restricted diets failed.

"Low Fat; ↑ Carb" since 1980's has led to an obesity & T2D epidemic. Fail.
Researchers studied 14 contestants who participated in the 30-week competition, which involves intensive diet and exercise training.
There used to be a mythology that if you just exercised enough you could keep your metabolism up, but that clearly wasn't the case, these folks were exercising an enormous amount and their metabolism was slowing by several hundred calories per day.

Their metabolisms didn't speed up again when they regained the weight.
Persistent Metabolic Adaptation 6 Years After “The Biggest Loser” Competition

Erin Fothergill\textsuperscript{1}, Juen Guo\textsuperscript{1}, Lilian Howard\textsuperscript{1}, Jennifer C. Kerns\textsuperscript{2}, Nicolas D. Knuth\textsuperscript{3}, Robert Brychta\textsuperscript{1}, Kong Y. Chen\textsuperscript{1}, Monica C. Skarulis\textsuperscript{1}, Mary Walter\textsuperscript{1}, Peter J. Walter\textsuperscript{1}, and Kevin D. Hall\textsuperscript{1}

Objective: To measure long-term changes in resting metabolic rate (RMR) and body composition in participants of “The Biggest Loser” competition.

Methods: Body composition was measured by dual energy X-ray absorptiometry, and RMR was determined by indirect calorimetry at baseline, at the end of the 30-week competition and 6 years later. Metabolic adaptation was defined as the residual RMR after adjusting for changes in body composition and age.

Results: Of the 16 “Biggest Loser” competitors originally investigated, 14 participated in this follow-up study. Weight loss at the end of the competition was (mean ± SD) 58.3 ± 24.9 kg ($P < 0.0001$), and RMR decreased by 610 ± 483 kcal/day ($P = 0.0004$). After 6 years, 41.0 ± 31.3 kg of the lost weight was regained ($P = 0.0002$), while RMR was 704 ± 427 kcal/day below baseline ($P < 0.0001$) and metabolic adaptation was $-499 ± 207$ kcal/day ($P < 0.0001$). Weight regain was not significantly correlated with metabolic adaptation at the competition’s end ($r = -0.1$, $P = 0.75$), but those subjects maintaining greater weight loss at 6 years also experienced greater concurrent metabolic slowing ($r = 0.59$, $P = 0.025$).

Conclusions: Metabolic adaptation persists over time and is likely a proportional, but incomplete, response to contemporaneous efforts to reduce body weight.
Figure 2: Individual (*) and mean (gray rectangles) changes in (A) body weight, (B) fat-free mass, and (C) fat mass at the end of “The Biggest Loser” 30-week weight loss competition and after 6 years. Horizontal bars and corresponding P values indicate comparisons between 30 weeks and 6 years. *P < 0.05 compared with baseline.

doi:10.1002/oby.21538
Weight loss is accompanied by a slowing of resting metabolic rate (RMR) that is often greater than would be expected based on the measured changes in body composition. This phenomenon is called “metabolic adaptation” or “adaptive thermogenesis,” and it acts to counter weight loss and is thought to contribute to weight regain (1,2). Several years ago, we investigated the body composition and RMR changes in 16 people with class III obesity undergoing an intensive diet and exercise intervention as part of “The Biggest Loser” televised weight loss competition (3). The participants rapidly lost massive amounts of weight, primarily from body fat mass (FM) with relative preservation of fat-free mass (FFM), likely due to the intensive exercise training. RMR was substantially reduced at the end of the competition, indicating a large degree of metabolic adaptation.
Here are the data - yes it's true TEE went down.

| TABLE 1 Anthropometric and energy expenditure variables in 14 of the original 16 study subjects who participated in “The Biggest Loser” 30-week weight loss competition |
|---|---|---|---|---|---|---|
| | Baseline | End of competition at 30 weeks | Follow-up at 6 years | Baseline vs. 30 weeks | Baseline vs. 6 years | 30 weeks vs. 6 years |
| Age (years) | 34.9 ± 10.3 | 35.4 ± 10.3 | 41.3 ± 10.3 | <0.0001 | <0.0001 | <0.0001 |
| Weight (kg) | 148.9 ± 40.5 | 90.6 ± 24.5 | 131.6 ± 45.3 | <0.0001 | 0.0294 | 0.0002 |
| BMI (kg/m²) | 49.5 ± 10.1 | 30.2 ± 6.7 | 43.8 ± 13.4 | <0.0001 | 0.0243 | 0.0004 |
| % Body fat | 49.3 ± 5.2 | 28.1 ± 8.9 | 44.7 ± 10 | <0.0001 | 0.0894 | 0.0003 |
| FM (kg) | 73.4 ± 22.6 | 26.2 ± 13.6 | 61.4 ± 30 | <0.0001 | 0.0448 | 0.0011 |
| FFM (kg) | 75.5 ± 21.1 | 64.4 ± 15.5 | 70.2 ± 18.3 | <0.0001 | 0.0354 | 0.0101 |
| R0 | 0.77 ± 0.05 | 0.75 ± 0.03 | 0.81 ± 0.02 | 0.272 | 0.0312 | <0.0001 |
| RMR measured (kcal/d) | 2,607 ± 649 | 1,996 ± 358 | 1,903 ± 466 | 0.0004 | <0.0001 | 0.3481 |
| RMR predicted (kcal/d) | 2,577 ± 574 | 2,272 ± 435 | 2,403 ± 507 | <0.0001 | 0.0058 | 0.0168 |
| Metabolic adaptation (kcal/d) | 29 ± 206 | -275 ± 207 | -499 ± 207 | <0.0001 | <0.0001 | 0.0075 |
| TEE (kcal/d) | 3,804 ± 926 | 3,002 ± 573 | 3,429 ± 581 | 0.0014 | 0.0189 | 0.0034 |
| Physical activity (kcal/kg/d) | 5.6 ± 1.8 | 10.0 ± 4.6 | 10.1 ± 4.0 | 0.0027 | 0.0001 | 0.8219 |

Note: 120 kg = 242.5 lbs

329 lbs < 198 lbs

lean muscle

The predicted RMR was obtained using a linear regression equation developed using baseline data on body composition, age, and sex in the full 16-subject cohort. The P values were not adjusted for multiple comparisons.

BMI, body mass index; FM, fat mass; FFM, fat-free mass; RMR, resting metabolic rate; R0, respiratory quotient; TEE, total energy expenditure.
Working out and exercising like crazy is only part of the puzzle.

Why did they gain back the weight?

Let’s look at their homonal profiles.
### TABLE 2 Plasma hormone and metabolite concentrations in the overnight fasted state

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<thead>
<tr>
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<th>Baseline vs. 6 years</th>
<th>30 weeks vs. 6 years</th>
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<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>95.7 ± 16.3</td>
<td>70.2 ± 21.9</td>
<td>104.9 ± 48.7</td>
<td>0.0042</td>
<td>0.4759</td>
<td>0.0264</td>
</tr>
<tr>
<td>Insulin (μU/mL)</td>
<td>10.4 ± 8.5</td>
<td>3.9 ± 1.9</td>
<td>12.1 ± 7.5</td>
<td>0.0126</td>
<td>0.3204</td>
<td>0.0013</td>
</tr>
<tr>
<td>C-peptide (ng/mL)</td>
<td>3 ± 1.4</td>
<td>1.3 ± 0.9</td>
<td>2.7 ± 1.1</td>
<td>0.0019</td>
<td>0.4241</td>
<td>0.0016</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.5 ± 2.2</td>
<td>0.7 ± 0.4</td>
<td>3.6 ± 4.6</td>
<td>0.0134</td>
<td>0.1892</td>
<td>0.0431</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>128.5 ± 76.3</td>
<td>57.4 ± 22.3</td>
<td>92.9 ± 43.9</td>
<td>0.0019</td>
<td>0.053</td>
<td>0.0082</td>
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<tr>
<td>Cholesterol (mg/dL)</td>
<td>174 ± 41.2</td>
<td>192.4 ± 52.8</td>
<td>180.9 ± 45.9</td>
<td>0.2115</td>
<td>0.5945</td>
<td>0.3549</td>
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<tr>
<td>LDL (mg/dL)</td>
<td>105 ± 30</td>
<td>126 ± 46</td>
<td>108 ± 35</td>
<td>0.132</td>
<td>0.8343</td>
<td>0.1083</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>42.5 ± 17.6</td>
<td>54.6 ± 14.9</td>
<td>54.5 ± 21.2</td>
<td>0.0036</td>
<td>0.001</td>
<td>0.9751</td>
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<tr>
<td>Adiponectin (mg/mL)</td>
<td>2.46 ± 1.28</td>
<td>4.69 ± 2.05</td>
<td>7.29 ± 4.71</td>
<td>0.003</td>
<td>0.0025</td>
<td>0.0164</td>
</tr>
<tr>
<td>T3 (ng/dL)</td>
<td>9.42 ± 2.78</td>
<td>5.31 ± 1.45</td>
<td>11.15 ± 1.81</td>
<td>0.006</td>
<td>0.0623</td>
<td>&lt;0.0001</td>
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<td>T4 (μg/dL)</td>
<td>7.3 ± 1.58</td>
<td>6.95 ± 1.43</td>
<td>6.18 ± 1.12</td>
<td>0.3814</td>
<td>0.0486</td>
<td>0.0828</td>
</tr>
<tr>
<td>TSH (mIU/mL)</td>
<td>1.52 ± 1.26</td>
<td>1.42 ± 0.73</td>
<td>1.93 ± 0.9</td>
<td>0.7175</td>
<td>0.1933</td>
<td>0.0641</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>41.14 ± 16.91</td>
<td>2.56 ± 2.19</td>
<td>27.68 ± 17.48</td>
<td>&lt;0.0001</td>
<td>0.013</td>
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The *P* values were not adjusted for multiple comparisons.

HOMA-IR, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; T3, triiodothyronine; T4, thyroxin; TG, triglyceride; TSH, thyroid stimulating hormone.
Q: Did the metabolism slow down due to low TSH?

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Hypothyroidism: when the thyroid produces too few hormones, it causes the metabolism to slow down.

TSH range: 0.35 – 3.5μIU/mL
T4 (bound and free) range: 4.5 – 11.5 μg/dL

https://www.thyroid.org/thyroid-function-tests/
Leptin levels correlate positively with level of adiposity.

Leptin - Obese: range 28.2-77.4 ng/mL;
Leptin - Non-obese range: range 6.6-18.8 ng/mL

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<th>Weight (kg)</th>
<th>329 lbs.</th>
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% Body fat: 49.3 ± 5.2 | 28.1 ± 8.9 | 44.7 ± 10
FM (kg): 73.4 ± 22.6 | 26.2 ± 13.6 | 61.4 ± 30
FFM (kg): 75.5 ± 21.1 | 64.4 ± 15.5 | 70.2 ± 18.3

J Pak Med Assoc. 2013 Feb;63(2):245-8

https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/91378
Adiponectin levels drop with increased adiposity. Adiponectin - Obese: range 2 - 22mg/mL;

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*J Pak Med Assoc*. 2013 Feb;63(2):245-8
Pathophysiology of T2D

1. IR (insulin resistance)

2. β-cell dysfunction
Pathophysiology of T2D

1. IR (insulin resistance)
2. β-cell dysfunction

How to screen for IR & β function
Pathophysiology of T2D

1. IR (insulin resistance)
2. β-cell dysfunction

How to ??

4 methods

1. Clamp - hyperinsulinemic euglycemic
2. Frequent glucose testing (i.v.)
3. C-Peptide to glucose ratio
4. HOMA - model (homeostasis model assessment)
Use and Abuse of HOMA Modeling

TARA M. WALLACE, MD
JONATHAN C. LEVY, MD
DAVID R. MATTHEWS, MD

Homeostatic model assessment (HOMA) is a method for assessing β-cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C-peptide concentrations. It has been reported in >500 publications, 20 times more frequently for the estimation of IR than β-cell function.
HOMA looks at the relationship between Glucagon and Insulin response.

- **Hepatic Glucose Output**
- **Glycogen Genolysis**
- **Glycogen → Glucose**
- **β Cell Insulin O/P**
- **Fasted State**

**GLUCAGON**
**HEPATIC GLUCOSE O/P**
**β CELL INSULIN RESPONSE**
HOMA-2 MODEL

provides information on:

1. β cell function (% B)
2. insulin sensitivity (% S)
The use of HOMA in the normal population

Although it has been argued that HOMA is no better than fasting insulin concentrations for the estimation of insulin sensitivity in normal individuals, there are several reasons why the use of HOMA in normal subjects is worthwhile. The use of HOMA to quantify insulin sensitivity and β-cell function can be helpful in normal populations as it allows 1) comparisons of β-cell function and insulin sensitivity to be made with subjects with abnormal glucose tolerance and 2) the collection of longitudinal data in subjects who go on to develop abnormal glucose tolerance.

HOMA-%S in individuals

HOMA can be used to track changes in insulin sensitivity and β-cell function longitudinally in individuals. The model can also be used in individuals to indicate whether reduced insulin sensitivity or β-cell failure predominates. When used in individuals, triplicate insulin samples should be used to improve the CV.

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<td>C-peptide (ng/mL)</td>
<td>3 ± 1.4</td>
<td>1.3 ± 0.9</td>
<td>2.7 ± 1.1</td>
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HOMA2 Calculator

Baseline values

Plasma glucose: 95.7 mmol/l 146.4
C-Peptide: 3 nmol/l 44.7
IR: 2.24
Preproinsulin $\rightarrow$ Proinsulin $\rightarrow$ Insulin + C-peptide
Using HOMA2 with C-Peptide vs Insulin

C-Peptide: Plasma glucose: 95.7 mmol/l, C-Peptide: 3 nmol/l
%B: 146.4, %S: 44.7, IR: 2.24

Insulin: Plasma glucose: 95.7 mmol/l, Insulin: 10.4 pmol/l
%B: 103.5, %S: 73.3, IR: 1.36
What do these values tell us?

%β 146.4 %S 44.7 IR 2.24

100% is normal

β cell function

Insulin sensitivity
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<td>44.7</td>
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<td>2.24</td>
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**What happened?**

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β cell function is improved

Insulin resistance

*most sensitive to insulin*
**What happened?**

- **β cell function is improved**

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- They gained back their weight b/c of **insulin resistance**
  - Most sensitive to insulin!!
Why is insulin key to obesity and T2D?

Illustration for TIME by David Plunkert
Your body’s metabolism is similar to a hybrid car. 😊
The gas part

The electric part
Plug in and change your car @ home & @ school

Commute back & forth

Home

UCSD
Electric Part

Plug in and charge your car at home & school

Commute back & forth

UCSD

Like eating

Insulin response
But—One day you forget to charge your car....

Commute back forth

This is like glucose

The gas part

The electric part

This is like ketone bodies
GAS PART OF CAR:

THIS IS THE FASTING STATE

KETONE BODIES
If you always charge the car, you will never use the gas.
EAT FOOD

- Insulin Response:
  a. Fill glycogen stores
  b. Store left over energy in fat
As long as insulin is involved:

- You will store fat (not use it!!)
Jason Fung analogy: 2 compartment model:

- Fat is stored in freezer
- Glycogen is stored in fridge
FAT — UNLIMITED STORAGE

GLYCOGEN/GLUCOSE - LIMITED

2 COMPARTMENTS USED FOR DIFFERENT PURPOSES
INCONVENIENT TO USE

FAT – UNLIMITED STORAGE

GLYCOGEN/GLUCOSE – LIMITED

EASY & EFFORTLESS
Will not use fat unless glycogen stores are depleted.

Inconvenient to use

Fat - unlimited storage

Glycogen/glucose - limited

Easy & effortless
This is why calories-in/calories-out method won’t work for weight loss.
INSIGHT: 2 compartments are used sequentially!

WILL NOT USE FAT UNLESS GLYCOGEN STORES ARE DEPLETED.

INCONVENIENT TO USE

EASY & EFFORTLESS
INSULIN PREVENTS YOU FROM GETTING THE FAT USED

INCONVENIENT TO USE

FAT — UNLIMITED STORAGE

GLYCOGEN/GLUCOSE—LIMITED

EASY & EFFORTLESS

* INSULIN INHIBITS LIPOLYSIS
Recall — BIGGEST LOSERS?

Researchers studied 14 contestants who participated in the 30-week competition, which involves intensive diet and exercise training.

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They gained back their weight b/c of INSULIN RESISTANCE!!

INSULIN LEVELS ARE CHRONICALLY HIGH → °° NO FAT BURNING
so, when you cannot burn fat & you reduce calories
Recall - Biggest Losers

Insulin levels are chemically high
No fat burning

so, when you cannot burn fat & you reduce calories...

Your body reduces its metabolism...

6 Years after The Biggest Loser; Metabolism Is Slower and Weight Is Back Up

The work provides new insights into why it is difficult to keep off the pounds

Researchers studied 14 contestants who participated in the 30-week competition, which involves intensive diet and exercise training.
IT IS TIME TO CONSIDER

THE ALTERNATIVE

HYPOTHESIS

"CARBOHYDRATE-INSULIN MODEL OF

OBESITY"
Your body reduces its metabolism... so, when you cannot burn fat & you reduce calories...

You cannot simply cut calories when you are IR.

INTERMITTENT FASTING (IF)
The Carbohydrate-Insulin Model of Obesity Beyond "Calories In, Calories Out"

David S. Ludwig, MD, PhD; Cara B. Ebbeling, PhD
Yet - there is sooooo much debate!

CIM: carbohydrate insulin model

CM: conventional model
But, “IF” is now catching on.
Google Searches (US): Intermittent Fasting vs. Low Fat

- Intermittent fasting: (United States)
- Low fat: (United States)
Intermittent Fasting

LOW FAT

1. Hawaii
   - Blue: 57
   - Red: 43

2. Wyoming
   - Blue: 53
   - Red: 47

3. California
   - Blue: 52
   - Red: 48

4. Utah
   - Blue: 51
   - Red: 49

5. Nevada
   - Blue: 50
   - Red: 50

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How did Joe Thomas drop all that playing weight?

By Nick Toney
Published: March 18, 2019 at 01:13 p.m.  0 Likes  |  0 Comments

Pick any passer off Joe Thomas' infamous 21-quarterback list. They'd probably be hard-pressed to identify their old blind side protector now.

That's because Thomas looks less like an All-Pro left tackle and more like a CrossFit instructor these days. Check out Thomas' incredible transformation after a year in retirement:

Use the Retweet button as a round of applause for @joethomas73 incredible transformation.
It started in high school with a very aggressive PB&J diet.

Joe Thomas
@joethomas73

Tip for guys trying to gain weight for football. When I was in HS, I would take an entire loaf of bread, make it all into PBJ sandwiches. Then I’d eat 1/2 a sandwich every hour and wash it down with a glass of whole milk. Guaranteed weight gain.

8,529 8:00 PM - Mar 22, 2018

2,268 people are talking about this

In the NFL, that program ballooned -- and so did Thomas.

Joe Thomas
@joethomas73

Back when I used to practice (llloooonnnngg time ago😂) I used to drink 2 big glasses of whole milk and a sleeve of thin mint Girl Scout cookies before bed just to get enough calories in the day to maintain weight.

Will Brinson
@WillBrinson
Replying to @joethomas73

What was your go-to calorie bomb?
Thomas told NFL.com he was more eager to shed those pounds than "almost anything in retirement."

He stopped eating to excess and developed an entirely different regimen.

The secret to Thomas' weight-loss plan? Lots and lots of pool time.

Facts: I think the first 25 fell off in a month, than I had to kick my butt to keep going. Swimming is the best from a cardio standpoint, and #keto w/ intermittent fasting is gold. I can eat 1500-2000 cals/day and feel full.
Joe Thomas @joethomas73

Easy, 2 steps:

Any questions?

Mike Culleton @mikeculleton
Replying to @joethomas73

I need to learn more about the #Keto w/intermittent fasting. Congrats by they way.

❤ 1,428 7:14 PM - Mar 17, 2019

A low carb, high fat diet that has helped many shed a lot of unwanted weight. It shifts the body's metabolism to using fat for fuel instead of relying on carbs.

Joe says he only eats between noon and six pm.
IF / TRF

* will normalize & resensitize insulin

and help your brain!
Intermittent Metabolic Switching

By Got My Ion You (Andy, Lexi, Ryan, Sofia, Vicky & Yuval)

Intermittent metabolic switching, neuroplasticity and brain health

Mark P. Mattson¹,², Keelin Moehl¹, Nathaniel Ghena¹, Maggie Schmaedick¹ and Aiwu Cheng¹

Abstract | During evolution, individuals whose brains and bodies functioned well in a fasted state were successful in acquiring food, enabling their survival and reproduction. With fasting and extended exercise, liver glycogen stores are depleted and ketones are produced from adipose-cell-derived fatty acids. This metabolic switch in cellular fuel source is accompanied by cellular and molecular adaptations of neural networks in the brain that enhance their functionality and bolster their resistance to stress, injury and disease. Here, we consider how intermittent metabolic switching, repeating cycles of a metabolic challenge that induces ketosis (fasting and/or exercise) followed by a recovery period (eating, resting and sleeping), may optimize brain function and resilience throughout the lifespan, with a focus on the neuronal circuits involved in cognition and mood. Such metabolic switching impacts multiple signalling pathways that promote neuroplasticity and resistance of the brain to injury and disease.

**Fasting and exercise**

- Glucose-to-ketone switch
  - Bioenergetic challenge
  - ↑ Ketones
  - ↑ Ghrelin
  - ↑ Myokines
  - ↓ Glucose
  - ↓ Leptin
  - ↓ Insulin
  - ↓ Cytokines
- Cellular stress resistance
  - Molecular recycling and repair pathways
- Ketone-to-glucose switch
  - Recovery period
  - ↓ Ketones
  - ↓ Ghrelin
  - ↓ Myokines
  - ↑ Leptin
  - ↑ Insulin
  - ↑ Cytokines

**Eating, resting and sleeping**

- IMS
- Ketone-to-glucose switch
  - Recovery period
  - ↑ Ketones
  - ↑ BDNF, FGF2
  - ↑ CREB, PGC1α
  - ↑ SIRT1, SIRT3
  - ↑ Autophagy, DNA repair
  - ↓ Ketones
  - ↓ BDNF
  - ↓ CREB
  - ↓ SIRT1, SIRT3
  - ↓ Autophagy
- Cell growth and plasticity pathways
  - Mitochondrial biogenesis
- Enhanced synaptic plasticity and neurogenesis
- Enhanced performance (cognition, mood, motor and ANS function)
- Resistance to neuronal degeneration and enhanced recovery from injury
If you decide to do TRF:

1. Ease into it → Start slow
2. Prioritize your sleep
3. Think about how your body will respond to what you eat.
4. It is a lifestyle, not a diet.
ZOE & SAMANTHA are THE BEST!

thank you for an amazing quarter!