Insulin resistance

It starts here...

► How it develops
► Who is at risk
► Solutions
eat carbohydrates (glucose)

store it

muscles & body use it
Eating carbohydrates (glucose) leads to storage. Short-term storage occurs in muscles and liver. Long-term storage happens in fat.
Muscles

**STEP 1**

Insulin binds to the insulin receptor in a muscle cell.
**STEP 4**

Glucose enters the muscle cell via GLUT4.

**STEP 5**

The cell uses ATP to function.
This is equivalent to spending money immediately!
Store it for later

muscles

STEP 6

muscle cell

glycogen
This is equivalent to putting money in your wallet → short term storage.
Insulin is your FAT storage hormone!

INSULIN DOES THIS, too

store it for later

FAT

long term storage
This is equivalent to putting money in the bank → long term storage.
However, when INSULIN is present → you CANNOT get your money out of the bank!
Q: When is insulin present?

A: When you eat...
Q. ② when do you burn fat??

A: when you don't have insulin & ↓↓ glycogen stores
Ben Schwartz could hardly be described as overweight. The slimly-built 28-year-old does not like junk food and keeps busy all day, working as a runner for a television production company.

Thanks to MRI, doctors can look at the body's composition in a new light. The remarkable images, revealed here for the first time, show how much 'internal fat' even slim people carry - and raise fresh questions about how healthy people are. Doctors are increasingly concerned that people can look slim on the outside but still have a problem with fat.

https://www.theguardian.com/science/2006/dec/10/medicineandhealth.health
Figure 1: Relationship between body mass index and insulin sensitivity, measured using the euglycaemic clamp technique, in 1394 healthy non-diabetic European men and women whose data have been included in the European Group for Insulin Resistance (EGIR) database [data used by permission from the EGIR].
Plasma glucose and insulin levels during a 75-g oral glucose tolerance test in lean control men (•) and in obese men with either low (T) or high (•) levels of visceral adipose tissue.
It is the intra-abdominal component of excess fat, and not total fat, that is strongly associated with impaired insulin action.

- The obese men in this study had identical amounts of total body fat.
- The obese groups only differed in the amount of intra-abdominal fat levels.
- The low intra-abdominal fat group’s responses were essentially the same as the lean group’s response.
- It was only the men with high intra-abdominal fat that had greater glucose and insulin responses.
Adipose Tissue Remodeling: Its Role in Energy Metabolism and Metabolic Disorders

Sung Sik Choe, Jin Young Huh, In Jae Hwang, Jong In Kim and Jae Bum Kim*

Department of Biological Sciences, National Creative Research Initiatives Center for Adipose Tissue Remodeling, Institute of Molecular Biology and Genetics, Seoul National University, Seoul, South Korea
Choe et al. (2016), Frontiers in Endocrinology, Volume 7
Two Modes of Adipose Tissue Expansion

**Hyperplasia**
- cell number ↑
- FFA release ↓
- adiponectin ↑
- pro-inflammatory cytokines ↓
- immune cell recruitment ↓
- hypoxia and fibrosis ↓
- insulin sensitivity ↑

**Hypertrophy**
- cell size ↑
- FFA release ↑
- adiponectin ↓
- pro-inflammatory cytokines ↑
- immune cell recruitment ↑
- hypoxia and fibrosis ↑
- insulin sensitivity ↓

increased numbers of adipocytes

enlarged adipocytes

Choe et al. (2016), Frontiers in Endocrinology, Volume 7
When the adipocyte becomes hypertrophied, the cytoskeleton is unable to hold in place the glucose transporters, thus impairing insulin responsivity.

Choe et al. (2016), Frontiers in Endocrinology, Volume 7
Review

Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome — An allostatic perspective

Sam Virtue *, Antonio Vidal-Puig *

Institute of Metabolic Science, Metabolic Research Laboratories, University of Cambridge, Box 289, Level 4, Addenbrooke’s Hospital, Cambridge CB2 0QQ, UK
The adipose tissue expandability hypothesis

While it is clear that obesity is associated with diabetes based on population studies, there is some controversy as to the mechanisms by which this occurs on an individual level. One hypothesis, which perhaps links many others, is that of limited adipose tissue expandability. The adipose tissue expandability hypothesis can be stated as follows; adipose tissue has a defined limit of expansion for any given individual. As an individual gains weight a point will eventually be reached when their adipose tissue can no longer store more lipid. Once adipose tissue storage capacity is exceeded then net lipid flux to non-adipose organs will increase and lipids will begin to be deposited ectopically. Ectopic lipid accumulation in cells such as myocytes hepatocytes and beta cells then causes toxic effects such as insulin resistance and apoptosis.
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once you hit the limit

insulin resistant!!
Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts Type II diabetes independent of insulin resistance

C. Weyer, J. E. Foley, C. Bogardus, P. A. Tataranni, R. E. Pratley
Clinical Diabetes and Nutrition Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona, USA

There was a positive correlation between adipocyte size and percent body fat. The rate of insulin stimulated glucose disposal was inversely related to the size of the adipocyte. The relationship between insulin stimulated glucose disposal and the average size of adipocyte.

Cross-sectional studies indicate that enlarged subcutaneous abdominal adipocyte size is associated with hyperinsulinaemia, insulin resistance and glucose intolerance.

Asians prone to TOFI – thin on the outside, fat on the inside

MATT STEWART  •  20:18, Oct 13 2015

"Surprisingly perhaps, when matched against their European, Maori or Pacific counterparts, Asian consumers are at greater risk of poor metabolic health and that highlights the need for food and beverage products that provide better nutrition."

Scientists suspect the answer to why some people are more prone to diseases such as diabetes lies in how body fat is stored.

Even small amounts of weight could lead to fat spilling over from connective tissue into vital organs such as muscle, liver and pancreas, causing "metabolic mayhem", Cameron-Smith said.
Q: 2
When do you burn fat??
A: When you don't have insulin & ↓↓ glycogen stores

⇒ Recall this – insulin is the reason that the adipocytes are overfilled
A possible solution —

Stop triggering insulin release.

recall this —
insulin is the reason that the adipocytes are overfilled.

Q: when do you burn fat??
A: when you don't have insulin & fat glycogen stores.
A possible solution—

stop triggering insulin release.

**FAST**

**How??**

← DON'T EAT!
A possible solution:

* How??

Stop triggering insulin release.

* Why?

FAST

DON'T EAT!

T2D & I12 can be reversed.
YOUR BRAIN needs you to fast, too.
Intermittent metabolic switching, neuroplasticity and brain health

Mark P. Mattson1,2, Keelin Moehl1, Nathaniel Chena1, 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.
INTERMITTENT FASTING

Fasting Time

Eating Window

eg: 16:8

Eating Time

Fasting Time
You want to let insulin levels drop for a while. Use fat for energy.
amazing results from his clinic
Amazing results from his clinic

When the adipocytes shrink

Insulin resistance ↓↓ 😊
**Fasting and exercise**

Glucose-to-ketone switch (bioenergetic challenge)
- ↑ Ketones
- ↑ Ghrelin
- ↑ Myokines
- ↓ Glucose
- ↓ Leptin
- ↓ Insulin
- ↓ Cytokines
- ↓ Ketones
- ↑ BDNF, FGF2
- ↑ CREB, PGC1α
- ↑ SIRT1, SIRT3
- ↑ Autophagy, DNA repair

**Eating, resting and sleeping**

Ketone-to-glucose switch (recovery period)
- ↓ Ketones
- ↓ Ghrelin
- ↓ Myokines
- ↓ Glucose
- ↓ Leptin
- ↓ Insulin
- ↓ Cytokines
- ↑ Ketones
- ↓ BDNF
- ↓ CREB
- ↓ SIRT1, SIRT3
- ↓ Autophagy
- ↑ Glucose
- ↑ Leptin
- ↑ Insulin
- ↑ Cytokines
- ↑ mTOR
- ↓ Protein synthesis
- ↓ Cytokines
- ↑ Protein synthesis
- ↑ Mitochondrial biogenesis

**Cellular stress resistance (molecular recycling and repair pathways)**

**Cell growth and plasticity pathways (mitochondrial biogenesis, synaptogenesis and neurogenesis)**

- Enhanced synaptic plasticity and neurogenesis
- Enhanced performance (cognition, mood, motor and ANS function)
- Resistance to neuronal degeneration and enhanced recovery from injury
Carbs and sugar in our diet is a huge part of the problem.
Snacking is a problem

Snacking promotes continuous insulin release and keeps stuffing the adipocytes.
Insulin signaling is only part of the problem.
Our Brain

Thrives when it switches between ketones and glucose.
Fixing IR will heal your heart
Intermittent Fasting

Current Solution
“Your body is resilient

IR+T2D do not have to be life sentences