IRNM

Insulin Resistance No More

Mary ET Boyle, Ph.D.
Department of Cognitive Science, UCSD
Though it might simplify messaging, a “one-size-fits-all” eating plan is not evident for the prevention or management of diabetes, and it is an unrealistic expectation given the broad spectrum of people affected by diabetes and prediabetes, their cultural backgrounds, personal preferences, co-occurring conditions (often referred to as comorbidities), and socioeconomic settings in which they live. Research provides clarity on many food choices and eating patterns that can help people achieve health goals and quality of life. The American Diabetes Association (ADA) emphasizes that medical nutrition therapy (MNT) is fundamental in the overall diabetes management plan, and the need for MNT should be reassessed frequently by health care providers in collaboration with people with diabetes across the life span, with special attention during times of changing health status and life stages (1–3).
Is MNT effective in improving outcomes?
Reported hemoglobin $A_{1c}$ (A1C) reductions from MNT can be similar to or greater than what would be expected with treatment using currently available medication for type 2 diabetes (9). Strong evidence supports the effectiveness of MNT interventions provided by RDNs for improving A1C, with absolute decreases up to 2.0% (in type 2 diabetes) and up to 1.9% (in type 1 diabetes) at 3–6 months. Ongoing MNT support is helpful in maintaining glycemic improvements (9).
Cost-effectiveness of lifestyle interventions and MNT for the prevention and management of diabetes has been documented in multiple studies (12,17, 24,25). The National Academy of Medicine recommends individualized MNT, provided by an RDN upon physician referral, as part of the multidisciplinary approach to diabetes care (7). Diabetes MNT is a covered Medicare benefit and should also be adequately reimbursed by insurance and other payers, or bundled in evolving value-based care and payment models, because it can result in improved outcomes such as reduced A1C and cost savings (12,17,25).
<table>
<thead>
<tr>
<th>Type of eating pattern</th>
<th>Description</th>
<th>Potential benefits reported*</th>
</tr>
</thead>
<tbody>
<tr>
<td>USDA Dietary Guidelines For Americans (DGA) (8)</td>
<td>Emphasizes a variety of vegetables from all of the subgroups; fruits, especially whole fruits; grains, at least half of which are whole intact grains; low-fat dairy; a variety of protein foods; and oils. This eating pattern limits saturated fats and trans fats, added sugars, and sodium.</td>
<td>DGA added to the table for reference; not reviewed as part of this Consensus Report</td>
</tr>
</tbody>
</table>
| Low-fat (26,45,80,83,100–106) | Emphasizes vegetables, fruits, starches (e.g., breads/crackers, pasta, whole intact grains, starchy vegetables), lean protein sources (including beans), and low-fat dairy products. In this review, defined as total fat intake ≤30% of total calories and saturated fat intake ≤10%. | • Reduced risk of diabetes  
• Weight loss |
| Very low-fat (107–109)      | Emphasizes fiber-rich vegetables, beans, fruits, whole intact grains, nonfat dairy, fish, and egg whites and comprises 70–77% carbohydrate (including 30–60 g fiber), 10% fat, 13–20% protein. | • Weight loss  
• Lowered blood pressure |

*Source: RCTs, meta-analyses, observational studies, nonrandomized single-arm studies, cohort studies. USDA, U.S. Department of Agriculture.
| Low-carbohydrate (110–112) | Emphasizes vegetables low in carbohydrate (such as salad greens, broccoli, cauliflower, cucumber, cabbage, and others); fat from animal foods, oils, butter, and avocado; and protein in the form of meat, poultry, fish, shellfish, eggs, cheese, nuts, and seeds. Some plans include fruit (e.g., berries) and a greater array of nonstarchy vegetables. Avoids starchy and sugary foods such as pasta, rice, potatoes, bread, and sweets. There is no consistent definition of “low” carbohydrate. In this review, a low-carbohydrate eating pattern is defined as reducing carbohydrates to 26–45% of total calories. | • A1C reduction  
• Weight loss  
• Lowered blood pressure  
• Increased HDL-C and lowered triglycerides |
| Very low-carbohydrate (VLC) (110–112) | Similar to low-carbohydrate pattern but further limits carbohydrate-containing foods, and meals typically derive more than half of calories from fat. Often has a goal of 20–50 g of nonfiber carbohydrate per day to induce nutritional ketosis. In this review a VLC eating pattern is defined as reducing carbohydrate to <26% of total calories. | • A1C reduction  
• Weight loss  
• Lowered blood pressure  
• Increased HDL-C and lowered triglycerides |

*Source: RCTs, meta-analyses, observational studies, nonrandomized single-arm studies, cohort studies. USDA, U.S. Department of Agriculture.*
The top 10 causes of death

24 May 2018

Of the 56.9 million deaths worldwide in 2016, more than half (54%) were due to the top 10 causes. Ischaemic heart disease and stroke are the world’s biggest killers, accounting for a combined 15.2 million deaths in 2016. These diseases have remained the leading causes of death globally in the last 15 years.

https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
Top 10 global causes of deaths, 2016

1. Ischaemic heart disease
2. Stroke
3. Chronic obstructive pulmonary disease
4. Lower respiratory infections
5. Alzheimer disease and other dementias
6. Trachea, bronchus, lung cancers
7. Diabetes mellitus
8. Road injury
9. Diarrhoeal diseases
10. Tuberculosis

56.9 million deaths worldwide in 2016

### Top 10 global causes of deaths, 2016

<table>
<thead>
<tr>
<th>Cause Group</th>
<th>Deaths (mils)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>9.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.8</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>3.9</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>3.8</td>
</tr>
<tr>
<td>Alzheimer disease and other dementias</td>
<td>2.3</td>
</tr>
<tr>
<td>Trachea, bronchus, lung cancers</td>
<td>1.6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.9</td>
</tr>
<tr>
<td>Road injury</td>
<td>1.7</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>1.4</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.3</td>
</tr>
</tbody>
</table>

### Diabetes vs Not Diabetes (2016)

<table>
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<tr>
<th>Disease</th>
<th>Millions</th>
</tr>
</thead>
<tbody>
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<td>Ischemic heart disease</td>
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</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.9</td>
</tr>
<tr>
<td>Not Diabetes Related</td>
<td>37.5</td>
</tr>
</tbody>
</table>
World Diabetes Day 2018: Family and diabetes

14 November 2018. On World Diabetes Day 2018, WHO joins partners around the world to highlight the impact diabetes has on families and the role of family members in supporting prevention, early diagnosis and good management of diabetes. More than 400 million people live with diabetes worldwide, and the prevalence is predicted to continue rising if current trends prevail. Diabetes is a major cause of premature dying, blindness, kidney failure, heart attack, stroke and lower limb amputation. It was the seventh leading cause of death in 2016.

— Read more
— Social media materials

422 Million adults have diabetes.

1.6 million deaths are directly attributed to diabetes each year.

1 in 3 adults aged over 18 years is overweight and 1 in 10 is obese.

Global report on diabetes
Fact sheet: diabetes
10 facts about diabetes

https://www.who.int/diabetes/en/
What is diabetes?
Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. The most common is type 2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin. In the past three decades the prevalence of type 2 diabetes has risen dramatically in countries of all income levels. Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin by itself. For people living with diabetes, access to affordable treatment, including insulin, is critical to their survival. There is a globally agreed target to halt the rise in diabetes and obesity by 2025.

About the diabetes programme
The mission of the WHO Diabetes Programme is to prevent type 2 diabetes and to minimize complications and maximize quality of life for all people with diabetes. Our core functions are to set norms and standards, promote surveillance, encourage prevention, raise awareness and strengthen prevention and control.

On World Heart Day WHO calls for accelerated action to prevent the world’s leading global killer

Cardiovascular diseases (CVDs) take the lives of 17.9 million people every year, 31% of all global deaths. Triggering these diseases are tobacco smoking, unhealthy diet, physical inactivity and the harmful use of alcohol. These in turn show up in people as raised blood pressure, elevated blood glucose and overweight and obesity. Through the Global Hearts Initiative, WHO is supporting governments to scale-up efforts on CVD prevention and control through three technical packages: MPower for tobacco control, SHAKE for salt reduction and HEARTS for strengthening CVD management in primary health care. Launched in September 2016, the initiative has been rolled out in several countries, where health workers are being trained to better deliver tested and affordable measures to protect people from CVDs and help them recover following a heart attack or stroke. A new global initiative - Resolve to Save Lives - will give renewed impetus to these efforts.

— More information

17.9 million people die each year from CVDs, an estimated 31% of all deaths worldwide. >75% of CVD deaths occur in low-income and middle-income countries. 85% of all CVD deaths are due to heart attacks and strokes.
422 Million
adults have diabetes.

1.6 million
deaths are directly attributed to
diabetes each year.

1 in 3 adults
aged over 18 years is overweight and 1 in 10 is obese.

*Related*

CVD

Dementia

17.9 million
people die each year from CVDs, an estimated 31% of all deaths worldwide.

>75% of CVD deaths occur in low-income and middle-income countries.

85% of all CVD deaths are due to heart attacks and strokes.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cost</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>$818 billion</td>
<td>5th</td>
</tr>
<tr>
<td>Dementia cost</td>
<td>The majority of care is provided by family carers.</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fact sheet: dementia
Fact sheet: The top 10 causes of death
Insulin Resistance as an Independent Predictor of Cardiovascular Mortality in Patients with End-Stage Renal Disease

KAYO SHINOHARA,* TETSUO SHOJI,* MASANORI EMOTO,* HIDEKI TAHARA,* HIDENORI KOYAMA,* EIJI ISHIMURA,† TAKAMI MIKI,‡ TSUTOMU TABATA,§ and YOSHIKI NISHIZAWA*

*Department of Metabolism, Endocrinology and Molecular Medicine, †Department of Nephrology, and ‡Department of Geriatrics and Neurology, Osaka City University Medical School, Osaka, Japan; and §Division of Internal Medicine, Inoue Hospital, Suita, Japan.
Abstract. Insulin resistance is closely associated with atherosclerosis and cardiovascular mortality in the general population. Patients with end-stage renal disease (ESRD) are known to have insulin resistance, advanced atherosclerosis, and a high cardiovascular mortality rate. We evaluated whether insulin resistance is a predictor of cardiovascular death in a cohort of ESRD. A prospective observational cohort study was performed in 183 nondiabetic patients with ESRD treated with maintenance hemodialysis. Insulin resistance was evaluated by the homeostasis model assessment method (HOMA-IR) using fasting glucose and insulin levels at baseline, and the cohort was followed for a mean period of 67 mo. Forty-nine deaths were recorded, including 22 cardiovascular deaths. Cumulative incidence of cardiovascular death by Kaplan-Meier estimation was significantly different between subjects in the top tertile of HOMA-IR (1.40 to 4.59) and those in the lower tertiles of HOMA-IR (0.28 to 1.39), and the hazard ratio (HR) was 2.60 (95% confidence interval [CI], 1.12 to 6.01; \( P = 0.026 \)) in the univariate Cox proportional hazards model. In multivariate Cox models, the positive association between HOMA-IR and cardiovascular mortality remained significant (HR, 4.60; 95% CI, 1.83 to 11.55; \( P = 0.001 \)) and independent of age, C-reactive protein, and presence of preexisting vascular complications. Further analyses showed that the effect of HOMA-IR on cardiovascular mortality was independent of body mass index, hypertension, and dyslipidemia. In contrast, HOMA-IR did not show such a significant association with noncardiovascular mortality. These results indicate that insulin resistance is an independent predictor of cardiovascular mortality in ESRD.

"IR is an independent predictor of cardiovascular mortality in ESRD [end-stage renal disease]."
Conclusions

The relative risk of cardiovascular disease was higher for an increase of one standard deviation in HOMA-IR compared to an increase of one standard deviation in fasting glucose or fasting insulin concentration. It may be useful to add HOMA-IR to a cardiovascular risk prediction model.

“it may be useful to add HOMA-IR to cardiovascular risk prediction model.”
Insulin Resistance is Associated with Cognitive Decline Among Older Koreans with Normal Baseline Cognitive Function: A Prospective Community-Based Cohort Study

Sung Hye Kong1, Young Joo Park1, Jun-Young Lee2, Nam H. Cho3 & Min Kyong Moon1,4
We evaluated whether metabolic factors were associated with cognitive decline, compared to baseline cognitive function, among geriatric population. The present study evaluated data from an ongoing prospective community-based Korean cohort study. Among 1,387 participants who were >65 years old, 422 participants were evaluated using the Korean mini-mental status examination (K-MMSE) at the baseline and follow-up examinations. The mean age at the baseline was 69.3 ± 2.9 years, and 222 participants (52.6%) were men. The mean duration of education was 7.1 ± 3.6 years. During a mean follow-up of 5.9 ± 0.1 years, the K-MMSE score significantly decreased (−1.1 ± 2.7 scores), although no significant change was observed in the homeostasis model assessment of insulin resistance (HOMA-IR) value. Participants with more decreased percent changes in K-MMSE scores had a shorter duration of education (p = 0.001), older age (p = 0.022), higher baseline K-MMSE score (p < 0.001), and increased insulin resistance (ΔHOMA-IR, p = 0.002). The correlation between the percent changes in K-MMSE and ΔHOMA-IR values remained significant after multivariable adjustment (B = −0.201, p = 0.002). During a 6-year follow-up of older Koreans with normal baseline cognitive function, increased insulin resistance was significantly correlated with decreased cognitive function.

“Increased IR was significantly correlated with decreased cognitive function.”
In conclusion, increased insulin resistance was associated with decreased cognitive function during a 6-year follow-up of older individuals with normal baseline cognitive function. However, baseline HbA1c, baseline BMI, ΔHbA1c, and ΔBMI values were not associated with changes in cognitive function. These relationships were independent of apolipoprotein E ε4 genotype status. Based on our results, further interventional studies are needed to evaluate the effect of controlling insulin resistance on cognitive dysfunction among older individuals.

Increased IR was associated with decreased cognitive function ... however changes in HbA1c and BMI were not associated with cognitive function.
Original Investigation

September 2015

Association of Insulin Resistance With Cerebral Glucose Uptake in Late Middle-Aged Adults at Risk for Alzheimer Disease

Auriel A. Willette, PhD\textsuperscript{1,2}; Barbara B. Bendlin, PhD\textsuperscript{3,4}; Erika J. Starks, BS\textsuperscript{3}; et al

Abstract

Importance Converging evidence suggests that Alzheimer disease (AD) involves insulin signaling impairment. Patients with AD and individuals at risk for AD show reduced glucose metabolism, as indexed by fludeoxyglucose F 18-labeled positron emission tomography (FDG-PET).

Does insulin resistance lead to impaired glucose metabolism in Alzheimer’s disease patients?

Objectives  To determine whether insulin resistance predicts AD-like global and regional glucose metabolism deficits in late middle-aged participants at risk for AD and to examine whether insulin resistance-predicted variation in regional glucose metabolism is associated with worse cognitive performance.

Question:  Does insulin resistance predict dementia in middle-aged individuals?

**Results** Higher HOMA-IR was associated with lower global glucose metabolism ($\beta = -0.29$; $P < .01$) and lower regional glucose metabolism across large portions of the frontal, lateral parietal, lateral temporal, and medial temporal lobes ($P < .001$). The association was especially robust in the left medial temporal lobe ($R^2 = 0.178$). Lower glucose metabolism in the left medial temporal lobe predicted by HOMA-IR was significantly related to worse performance on the immediate memory ($\beta = 0.317$; $t_{148} = 4.08$; $P < .001$) and delayed memory ($\beta = 0.305$; $t_{148} = 3.895$; $P < .001$) factor scores.

Higher HOMA-IR is associated with lower glucose metabolism in significant regions associated with memory processing and formation.
Conclusions and Relevance Our results show that insulin resistance, a prevalent and increasingly common condition in developed countries, is associated with significantly lower regional cerebral glucose metabolism, which in turn may predict worse memory performance. Midlife may be a critical period for initiating treatments to lower peripheral insulin resistance to maintain neural metabolism and cognitive function.

“Midlife may be a critical period for initiating treatments to lower peripheral insulin resistance to maintain neural metabolism and cognitive function.”
Biomarkers of Alzheimer Disease, Insulin Resistance, and Obesity in Childhood

Rosa Luciano, MSc\textsuperscript{a}, Gloria Maria Barraco, MSc\textsuperscript{b}, Maurizio Muraca, MD, PhD\textsuperscript{b}, Simonetta Ottino, MD\textsuperscript{a}, Maria Rita Spreghini, MSc\textsuperscript{c}, Rita Wietrzykowska Sforza, MD\textsuperscript{b}, Carmela Rustico, MD\textsuperscript{c}, Giuseppe Stefano Morino, MD, PhD\textsuperscript{a}, Melania Manco, MD, PhD, FACN\textsuperscript{b}

PEDIATRICS Volume 135, number 6, June 2015
OBJECTIVE: To answer the question of whether onset of insulin resistance (IR) early in life enhances the risk of developing dementia and Alzheimer disease (AD), serum levels of 2 molecules that are likely associated with development of AD, the amyloid β-protein 42 (Aβ42) and presenilin 1 (PSEN1), were estimated in 101 preschoolers and 309 adolescents of various BMI.

Does early onset of IR increase the risk of dementia later in life?
METHODS: Participants (215 boys; 48.8%) were normal weight ($n = 176$; 40%), overweight ($n = 135$; 30.7%), and obese ($n = 129$; 29.3%). The HOMeostasis Model of IR (HOMA-IR), HOMA percent β-cell function (HOMA-β) and QUantitative Insulin-sensitivity Check Index (QUICKI) were calculated.

HOMA-IR correlates with increased AD markers in adolescents.

RESULTS: Obese adolescents had values of Aβ42 higher than overweight and normal-weight peers ($190.2 \pm 9.16$ vs $125.9 \pm 7.38$ vs $129.5 \pm 7.65$ pg/mL; $P < .0001$) as well as higher levels of PSEN1 ($2.34 \pm 0.20$ vs $1.95 \pm 0.20$ vs $1.65 \pm 0.26$ ng/mL; $P < .0001$). Concentrations of Aβ42 were significantly correlated with BMI ($\rho = 0.262$; $P < .0001$), HOMA-IR ($\rho = 0.261$; $P < .0001$) and QUICKI ($\rho = -0.220$; $P < .0001$). PSEN1 levels were correlated with BMI ($\rho = 0.248$; $P < .0001$), HOMA-IR ($\rho = 0.242$; $P < .0001$), and QUICKI ($\rho = -0.256$; $P < .0001$). Western blot analysis confirmed that PSEN1 assays measured the full-length protein.
CONCLUSION: Obese adolescents with IR present higher levels of circulating molecules that might be associated with increased risk of developing later in elderly cognitive impairment, dementia, and AD.

“Obese adolescents with IR ... increased risk of developing cognitive impairment.”

PEDIATRICS Volume 135, number 6, June 2015
Insulin resistance

It starts here...

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

store it

muscles & body use it
Muscles

**Step 1**

Insulin binds to the insulin receptor on the muscle cell.
**STEP 2**

intracellular stuff

**STEP 3**

glucose transporter

muscle cell

muscle cell
**Step 4**

Glucose enters cell via GLUT4

**Step 5**

ATP
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!
However, when INSULIN is present → you CANNOT get your money out of the bank!

Q: When is insulin present?

A: When you eat...
A: When you don’t have insulin & ↓↓ glycogen stores

Q. 2
when do you burn fat??

However, when INSULIN is present → you CANNOT get your money out of the bank!
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.
Ectopic fat accumulation: an important cause of insulin resistance in humans

Hannele Yki-Järvinen

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.

https://doi.org/10.2337/diab.41.7.826
It is the intra-abdominal component of excess fat, and not total fat, that is strongly associated with impaired insulin action.
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 Molecular Biology and Genetics, Seoul National University, Seoul, South Korea
Choe et al. (2016), Frontiers in Endocrinology, Volume 7

**BAT**
- Supraclavicular
- Paravertebral
  - Core body thermal regulation
  - Energy burning
  - Abundant mitochondria
  - High expression of UCP-1

**Visceral WAT**
- Perirenal
- Retroperitoneal
- Omental
- Mesenteric
  - Energy storage
  - Various adipokine secretion
  - Correlation with high incidence of metabolic disorders

**Subcutaneous WAT**
- Abdominal
- Gluteal
- Femoral
  - Insulating layer
  - Energy storage
  - Various adipokine secretion
  - Correlation with low incidence of metabolic disorders
Two Modes of Adipose Tissue Expansion

**Hyperplasia**
- cell number $\uparrow$
- FFA release $\downarrow$
- adiponectin $\uparrow$
- pro-inflammatory cytokines $\downarrow$
- immune cell recruitment $\downarrow$
- hypoxia and fibrosis $\downarrow$
- insulin sensitivity $\uparrow$

**Hypertrophy**
- cell size $\uparrow$
- FFA release $\uparrow$
- adiponectin $\downarrow$
- pro-inflammatory cytokines $\uparrow$
- immune cell recruitment $\uparrow$
- hypoxia and fibrosis $\uparrow$
- insulin sensitivity $\downarrow$

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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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

"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. 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.
A possible solution—

Stop triggering insulin release.

How??

FAST

← Don’t eat!
FAST \rightarrow \text{DON'T EAT!}

T2D & IIZ can be reversed

\textbf{How??}

\textbf{Why?}

stop triggering insulin release.
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 time

Eating window

16:8

Fasting time
You want to let insulin levels drop for a while. Use fat for energy.
Fasting
Heal Your Body Through
Intermittent, Alternate-Day, and Extended Fasting
Dr. Jason Fung
Fasting

https://idmprogram.com/

Amazing results from his clinic
When the adipocytes shrink, insulin resistance decreases.
Fasting and exercise

Glucose-to-ketone switch (bioenergetic challenge)
- ↑ Ketones
- ↑ Ghrelin
- ↑ Myokines
- ↓ Glucose
- ↓ Leptin
- ↓ Insulin
- ↓ Cytokines

Cellular stress resistance (molecular recycling and repair pathways)
- mTOR
- Protein synthesis
- Cytokines

IMS

Eating, resting and sleeping

Ketone-to-glucose switch (recovery period)
- ↓ Ketones
- ↓ Ghrelin
- ↓ Myokines
- ↑ Glucose
- ↑ Leptin
- ↑ Insulin
- ↑ Cytokines

Cell growth and plasticity pathways (mitochondrial biogenesis, synaptogenesis and neurogenesis)
- mTOR
- Protein synthesis
- Mitochondrial biogenesis

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"
Thank You

Mary