INSULIN RESISTANCE & WEIGHT MANAGEMENT

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OBESITY MEDICINE ASSOCIATION: DEFINITION OF OBESITY

"Obesity is defined as a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences."

Thus, the dangers of obesity must be addressed in any weight loss effort.

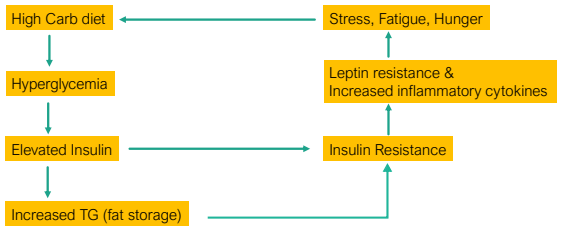
I will focus on adipose tissue dysfunction.

ADIPOSE TISSUE DYSFUNCTION

- In addition to storing calories as triglycerides, adipocytes also secrete a large variety of adipokines: proteins, including cytokines, chemokines and hormone-like factors, such as leptin, adiponectin and resistin. (1)
  - These molecules impact vascular function, immunity, bone metabolism, and neurological function.
- "The release of adipokines by either adipocytes or adipose tissue-infiltrated macrophages leads to a chronic sub-inflammatory state that could play a central role in the development of insulin resistance and type 2 diabetes, and the increased risk of cardiovascular disease associated with obesity." (2)
  - Insulin resistance leads to the release of free fatty acids from adipose tissue, increased hepatic production of very-low-density lipoproteins and decreased high-density lipoproteins.
  - Increased free fatty acids, inflammatory cytokines, adipokines and mitochondrial dysfunction contribute to impaired insulin signaling, decreased skeletal muscle glucose uptake, increased hepatic gluconeogenesis, and β cell dysfunction, leading to hyperglycemia.

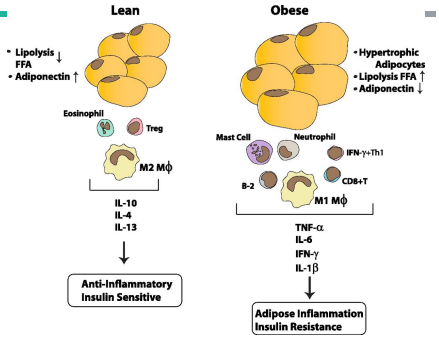
Calabro P, Yeh E, Subcell Biochem. 2007;42:63
Antuna-Puente B, et al. Diabetes Metab. 2008;34(1):2
Gallagher E, et al. Mt Sinai J Med. 2010;77(5):511

VICIOUS CYCLE: INSULIN RESISTANCE & OBESITY



OBESITY & INSULIN RESISTANCE

Macrophages respond to the cytokine environment in which they reside.



http://d3md5dngttnvbj.cloudfront.net/content/bloodjournal/122/20/3415/F3.large.jpg

DIAGNOSIS OF INSULIN RESISTANCE & METABOLIC SYNDROME

- Insulin Resistance HOMA-IR [Homeostasis Model Assessment of Insulin Resistance]:
  - [Fasting plasma insulin (mU/L) x Fasting plasma glucose (mmol/L)]/22.5
  - Many online calculators available
- IR likely present when:
  - **HOMA-IR > 2.0;** The adult optimal HOMA-IR cut-off points for the presence of insulin resistance reported in the literature range from 2.0 – 3.8
    - [Tang Q, Drug Discov Ther. 2015 Dec;9(6):380-5]
  - Fasting Insulin > 3.16 uIU/mL -or-
  - fasting G:I ratio of < 4.5 (<7 in teenagers and young adults)
- If patient has fasting glucose >100mg/dL or HgA1c >5.6, metabolic syndrome likely if:
  - visceral adiposity
  - elevated TG >150mg/dL
  - ***waist circumference >40 in.(101cm) in men and >35 in. (80cm) in women***

TARGETED METABOLIC SUPPORT FOR INSULIN RESISTANCE AND OBESITY

- Caloric restriction
- Berberine (Berberis spp, Mahonia aquifolium, Hydrastis canadensis)
- Magnesium
- Cinnamomum zeylanicum and C. cassia (True, or Ceylon, Cinnamon, Chinese cinnamon)
- Vaccinium spp. (Blueberries)
- Camellia sinensis [Green tea]
- Trigonella foenum-graecum (Fenugreek)
- Gymnema sylvestre (Gymnema)
- Prunus cerasus (Tart Cherry)
- Exercise

METABOLIC EFFECTS OF DIET

Table 1. Metabolic effect of various dietary restriction regimes in C57BL/6 mice and insulin-resistant humans

Parameter	*FGF21*		*IGF-1*		*Insulin*		*Glucose*		*BHB*		*Body weight*	
Species	*Mouse*	*Human*	*Mouse*	*Human*	*Mouse*	*Human*	*Mouse*	*Human*	*Mouse*	*Human*	*Mouse*	*Human*
Starvation [C]	↑	↑	↓	↓	↓	[C] ↓	↓	↓	↑	↑	↓	↓
Calorie restriction	↗a	↗a	↘a	↘a	↘ab	↘b	↘b	↘ab	↗b	↗b	↓	↓
Protein-deficient diet, isocaloric	↑	↑	↓	↓	↓	↑, —	↘b	↗b	—	—	↓	↑
Protein-deficient diet, hypocaloric	↑	↑	↓	↓	↓	↘b	↘b	↘b	—	—	↓	↓
KD, isocaloric	—	—	—	—	—	—, ↓	↑	—, ↓	↑	↑	↑	↓, —
KD, hypocaloric	↗a	↗ a	↘a	↘a	↓	↓	↓	↓	↑	↑	↓	↓

Abbreviations: BHB, β-hydroxybutyrate; FGF21, fibroblast growth factor 21; KD, ketogenic diet. a, mainly dependent on the degree of protein restriction; b, mainly dependent on the degree of CHO restriction. The protein-deficient diet is defined as a diet containing < 10E% protein. The KD is assumed to contain > 10E% protein.

Common denominator across the most successful diets = **low calorie** diets!

Klement RJ and Fink MK. Oncogenesis. 2016;5:e193.

CALORIC RESTRICTION

- Animal studies have shown protective effects of daily continuous energy restriction (CER) and weight loss on reducing tumor formation
- Over 100 years of research.
- However, CER is difficult to maintain, thus intermittent energy restriction (IER) or intermittent fasting (IF) have been studied as strategies with greater potential for compliance.
- Mirrors Paleolithic periods of food abundance and scarcity
- Traditional Mediterranean diet includes periodic fasting
- Continuum of energy restricted diets:

Overnight Fast ≥ 13 hr — 2 days/week ≤ 500 kcal/d — 10%-15% continuous caloric restriction

Harvie M and A Howell. Proc Nutr Soc. 2012;71:263-75.

COMPARISON BETWEEN IER/IF AND CER DIETS

- Intermittent Energy Restriction (IER) commonly restricts caloric intake by 50%-70%, typically for 2-3 days per week
- Continuous Energy Restriction (CER) is commonly a 20% reduction in caloric intake that results in 5% to ≥ 30% weight reduction
- All diets reduce fat stores and thus lower levels of mitogens such as insulin, IGF-1, estradiol, androgens, TNFa, IL-6, leptin, decreased kinase signaling, and increased adiponectin.

Harvie M and A Howell. Proc Nutr Soc. 2012;71:263-75.

IER VS. CER AND WEIGHT

- In 107 overweight pre-menopausal women, 2d of a 70% IER (2.71MJ/d) and 5d Mediterranean-type diet per week was compared to an isocaloric 25% continuous energy restricted diet for 6 months.
- Both diets resulted in reduced body fat: by 6.4kg in IER compared to 5.6kg in CER diet (P = 0.34)
  - Reduction in fasting insulin and insulin resistance in both groups but greater in IER
  - Reductions in leptin, hsCRP, total and LDL cholesterol, TG
  - Increases in SHBG and IGF-BP1 and IGF-BP2
- In another study of 51 men with DB2, IER (4.18 MJ for 4 d with 3 d regular diet/week) v. CER (6.0–7.0 MJ/d) showed no difference in terms of weight or fasting insulin.

Harvie MN, et al. Int J Obes (Lond). 2011;35(5):714-27.
Ash S, et al. J Obes Relat Metab Disord.2003;27:797-802.

IER AND OXIDATIVE STRESS

- CER reduces oxidative stress.
- The effect of IER on oxidative stress is not clear.
- However, IER has been shown to increase cellular stress resistance, and increase resistance to oxidative stress by 'hormesis', whereby repeated spells of moderate stress with IER increases the production of restorative proteins and antioxidant enzymes.
- This is also known as "adaptive homeostasis", a process by which a damaging or stressful influence activates signal transduction pathways to increase the expression of protective genes → prevention
  - Conversely, this same damaging influence at high concentration and/or duration will lead to damage

Davies J. GeroScience. 2017; 39:499.
Mattson MP. Ageing Res Rev. 2008;7:1-7.

LESS AGGRESSIVE FORM OF INTERMITTENT FASTING: OVERNIGHT FASTING

- 13 -16 hours of fasting overnight to synch with circadian rhythms appears to reset the body's peripheral clocks leading to optimal clock gene expression and enhanced energy metabolism.
- This study used data from the National Health and Nutrition Examination Survey. 1,066 women were included.
- Associations between nighttime fasting, HbA1c and 2-hour glucose concentrations were examined.
- Each 3-hour increase in nighttime fasting was associated with:
  - 4% lower 2-hr glucose measurement
  - 20% reduced odds of elevated HbA1c
- These improved biomarkers of glucose control may, in turn, reduce breast cancer risk given the established association between HbA1c as well as fasting glucose and breast cancer incidence.

Marinac C. Cancer Epidemiol Biomarkers Prev. 2015;24(5):783-9

CONCLUSIONS

- Weight loss is more likely when insulin sensitivity is increased via:
  - Changes in food timing
  - Caloric restriction
  - Selected foods
  - Botanicals and nutrients
  - Increased physical activity