INSULIN RESISTANCE

Ted Naiman MD • Disclosures: NONE

Causes Of Death

Other: 30%

- Toxic
- Kinetic
- Microbial
- Genetic

Chronic disease: 70%

- Cardio-vascular
- Cancer
- Neuro-degenerative

Prevention: diet + exercise

Sedentation

- sarcopenia
- low mitochondrial density
- osteoporosis
- frailty

+

Malnutrition

- empty calories
- nutrient deficiency
- toxic hunger
- energy excess

↓

INSULIN RESISTANCE

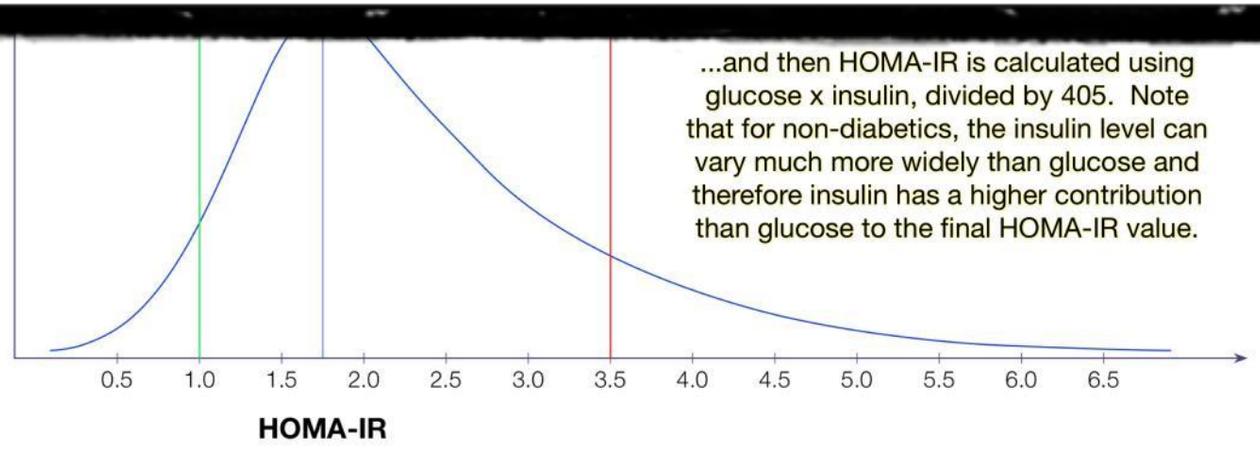
Homeostatic Model Assessment of Insulin Resistance: HOMA-IR

HOMA-IR is a simple way of measuring insulin resistance. It is calculated using the product of your fasting glucose times your fasting insulin. Essentially, this is asking (and answering) the following question: How much insulin does your body require to hold your fasting glucose at its current value?

$$\text{Glucose} \times \text{Insulin}$$

$$\text{Glucose} \times \text{Insulin}$$

HOMA-IR



...and then HOMA-IR is calculated using glucose x insulin, divided by 405. Note that for non-diabetics, the insulin level can vary much more widely than glucose and therefore insulin has a higher contribution than glucose to the final HOMA-IR value.

Interpretation:

Excellent:	≤ 1.00
Average:	~ 1.75
Resistant:	≥ 2.75

Homeostasis Model Assessment of Insulin Resistance in Relation to the Incidence of Cardiovascular Disease

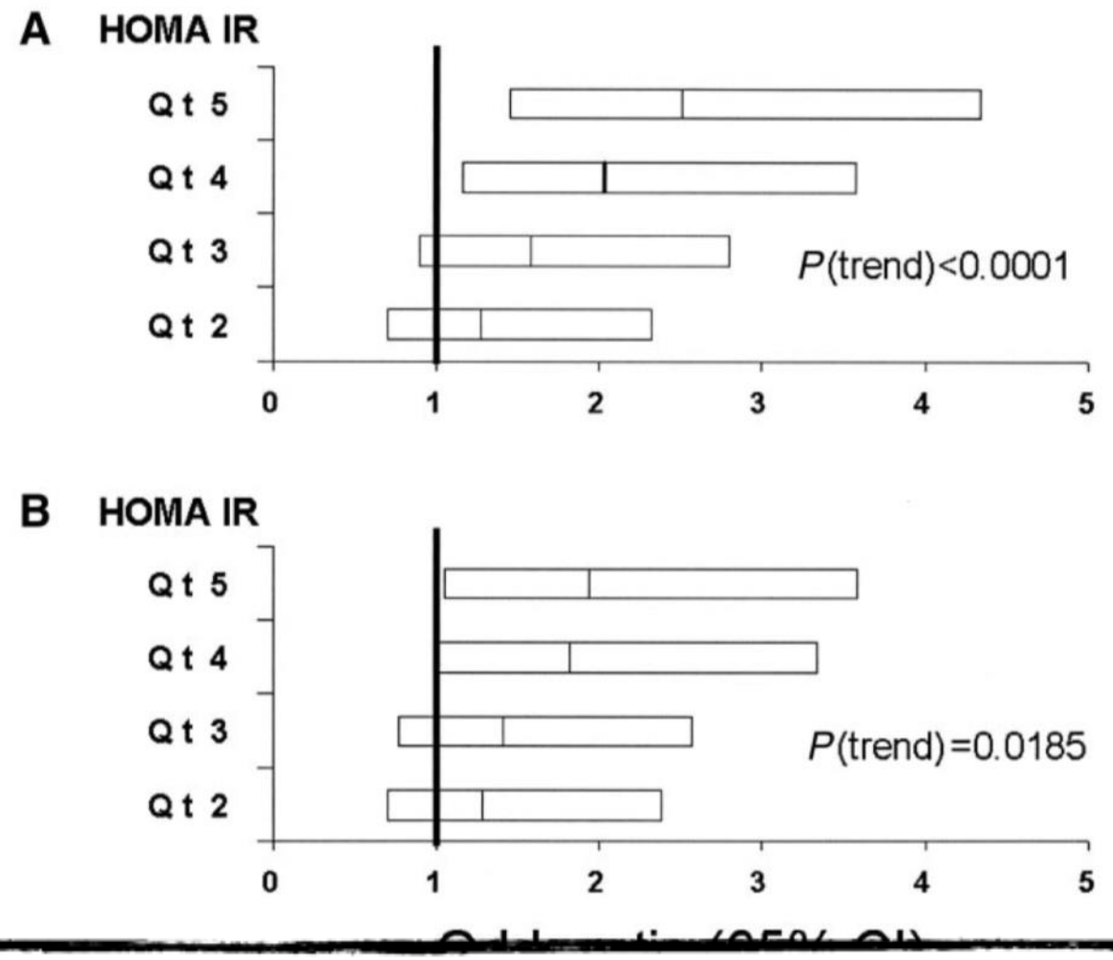
The San Antonio Heart Study

ANTHONY J.G. HANLEY, PHD[1,2]
KEN WILLIAMS, MSC[1]
MICHAEL P. STERN, MD[1]
STEVEN M. HAFFNER, MD[1]

OBJECTIVE — The prospective association between insulin levels and risk of car
disease (CVD) is controversial. The objective of the present study was to investigate t
ship of the homeostasis model assessment of insulin resistance (HOMA-IR), as we
levels, with risk of nonfatal and fatal CVD over the 8-year follow-up of the San An
Study.

RESEARCH DESIGN AND METHODS — Between 1984 and 1988, rando
Mexican-American and non-Hispanic white residents of San Antonio participated
examinations that included fasting blood samples for glucose, insulin, and lipids
tolerance test, anthropometric measurements, and a lifestyle questionnaire. Betwee
1996, 2,569 subjects who were free of diabetes at baseline were reexamined usi
protocol.

RESULTS — Over the follow-up period, 187 subjects experienced an incident ca
event (heart attack, stroke, heart surgery, angina, or CVD death). Logistic regress
indicated that risk of a CVD event increased across quintiles of HOMA-IR after adj
age, sex, and ethnicity (*P* for trend <0.0001; quintile 5 vs. quintile 1, odds ratio [OR
CI 1.46–4.36). Additional adjustment for LDL, triglyceride, HDL, systolic bloo
smoking, alcohol consumption, exercise, and waist circumference only modestly
magnitude of these associations (*P* for trend 0.02; quintile 5 vs. quintile 1, OR 1.
1.05–3.59). Furthermore, there were no significant interactions between HOMA-IR
ity, sex, hypertension, dyslipidemia, glucose tolerance (impaired glucose tolerance
mal glucose tolerance), or obesity. The magnitude and direction of the relationsh



CONCLUSIONS — We found a significant association between HOMA-IR and risk of CVD after adjustment for multiple covariates. The topic remains controversial, however, and additional studies are required, particularly among women and minority populations.

Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death

B. Hedblad*†, P. Nilsson*, G. Engström†, G. Berglund* and L. Janzon†

*Department of Medicine and
†Department of Community Medicine, Lund University, Malmö University Hospital, Malmö, Sweden

Accepted 26 November 2001

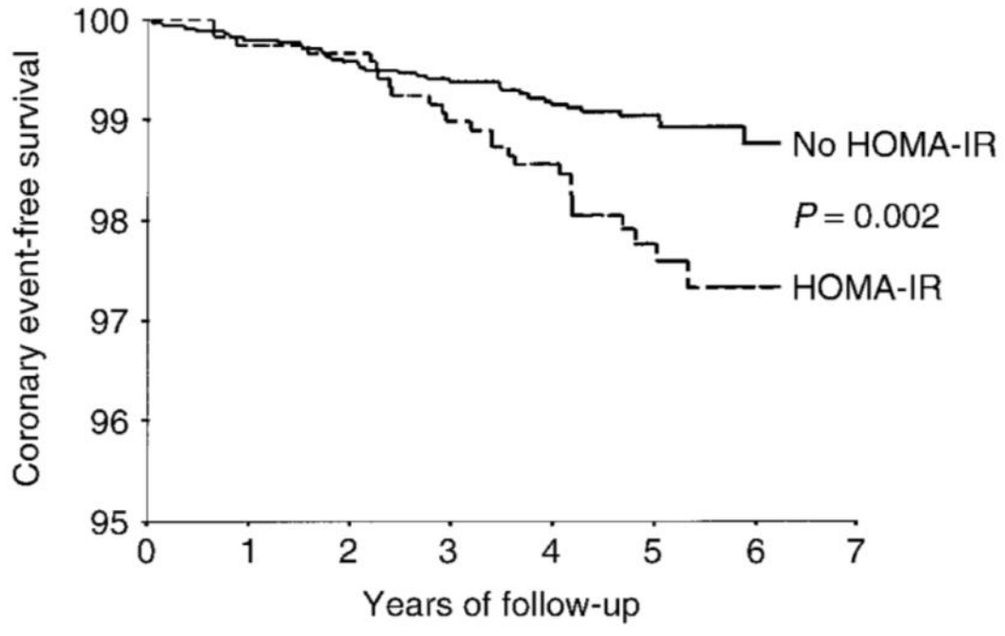
Abstract

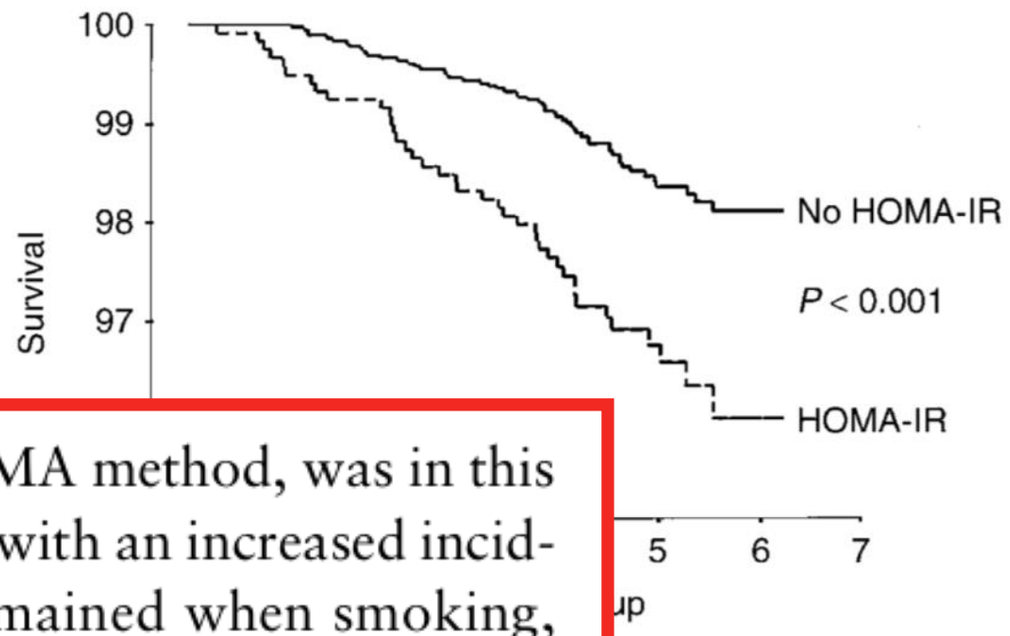
Aims To compare the incidence of myocardial infarction
diabetic subjects with and without insulin resistance.

Methods Population-based prospective cohort study, in M
4748 non-diabetic subjects (60% women), aged 46–68 years,
myocardial infarction or stroke. The prevalence of insulin re
lished by the homeostasis model assessment (HOMA) and
above the sex-specific 75th percentile (1.80 for women and 2.
ence of myocardial infarction and death is based on record
and national registers. Cox's proportional hazards model wa
influence of insulin resistance after adjustment for age, sex
raised arterial blood pressure, dyslipidaemia, central obes
leisure-time physical activity.

Results Sixty-two subjects suffered a coronary event, and
during the 6-year follow-up period. Insulin resistance was a
other factors included in the insulin resistance syndrome a
confounders, associated with an increased incidence of coron
risk (RR) 2.18; 95% confidence interval (CI) 1.22–3.87; P =
(RR 1.62; 1.03–2.55; P = 0.038).

Conclusions Insulin resistance, as assessed by the HOMA method, was in this cohort of middle-aged non-diabetic subjects associated with an increased incidence of myocardial infarction and death. This risk remained when smoking, low physical activity and factors included in the insulin resistance syndrome were taken into account in a stepwise regression model.





…n-fatal myocardial
…s, upper panel) and all-cause
…c subjects in relation to

Insulin resistance/hyperinsulinemia and cancer mortality: the Cremona study at the 15th year of follow-up

Gia[illegible]

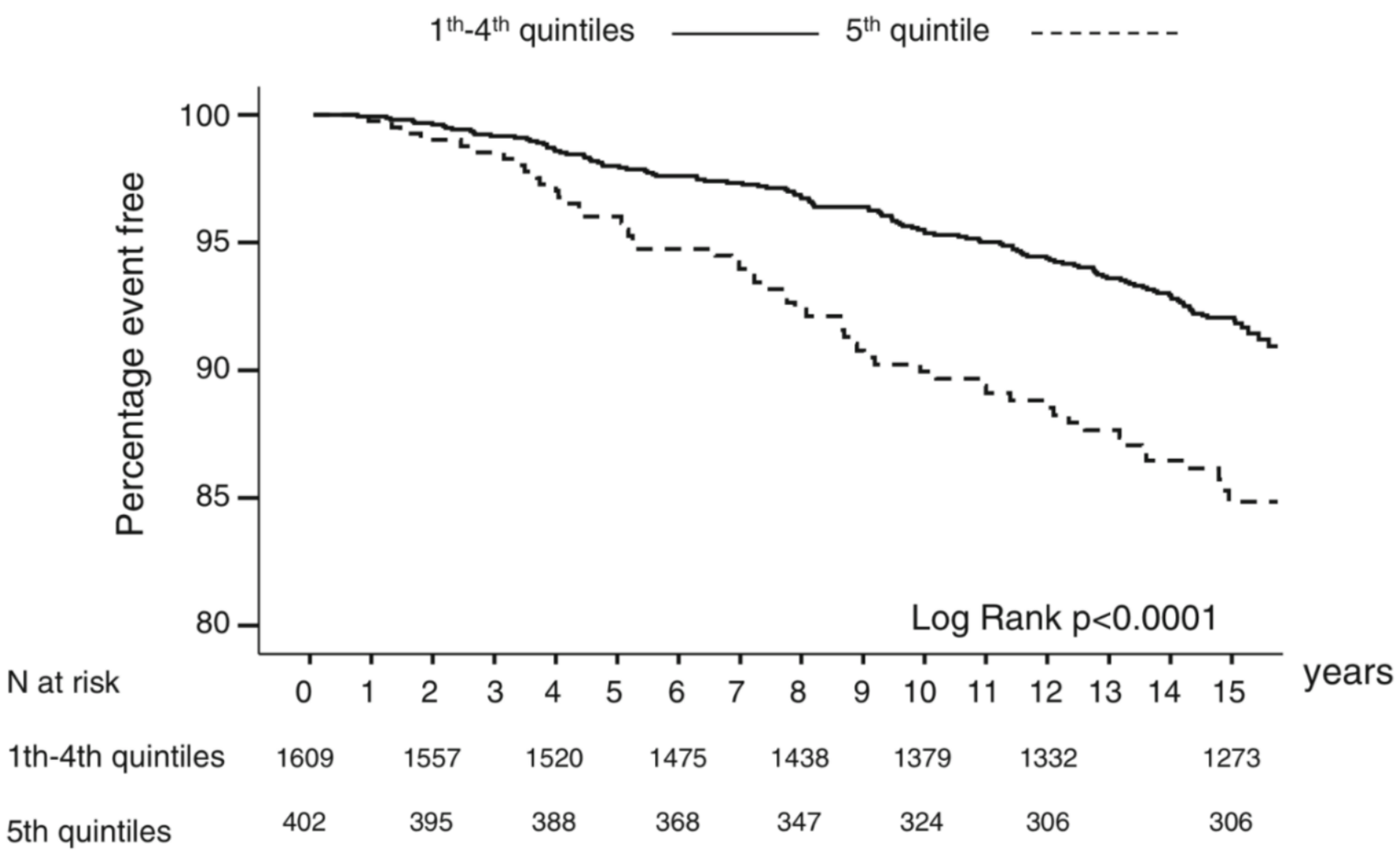


Fig. 1 Survival by Kaplan–Meier estimates of total cancer mortality. The association of insulinemia with total cancer mortality was estimated after a 15-year observational period. Subjects were divided according to fasting serum insulin level in two groups (subjects within the 1st to 4 th quintiles combined of fasting serum insulin versus subjects within the 5th quintile). Statistical analysis was performed by log-rank test

ASSOCIATION BETWEEN HOMA-IR AND CANCER

Article *in* International Journal of Publ

Odds Ratio:

12.25

☹

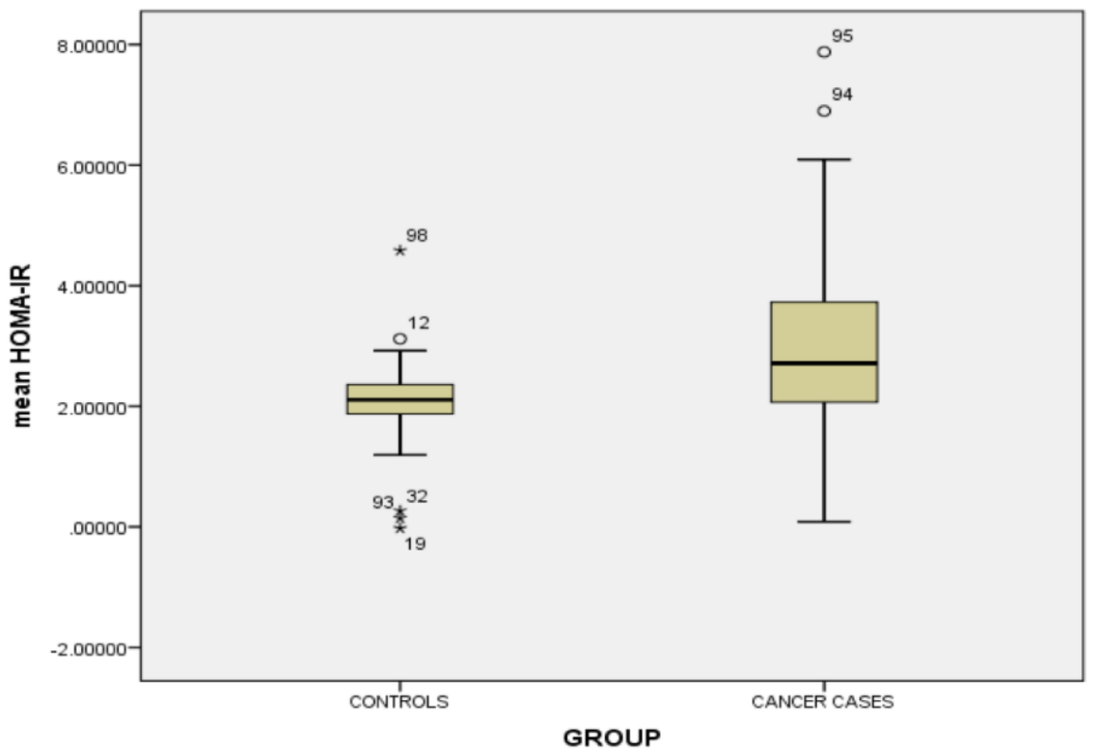


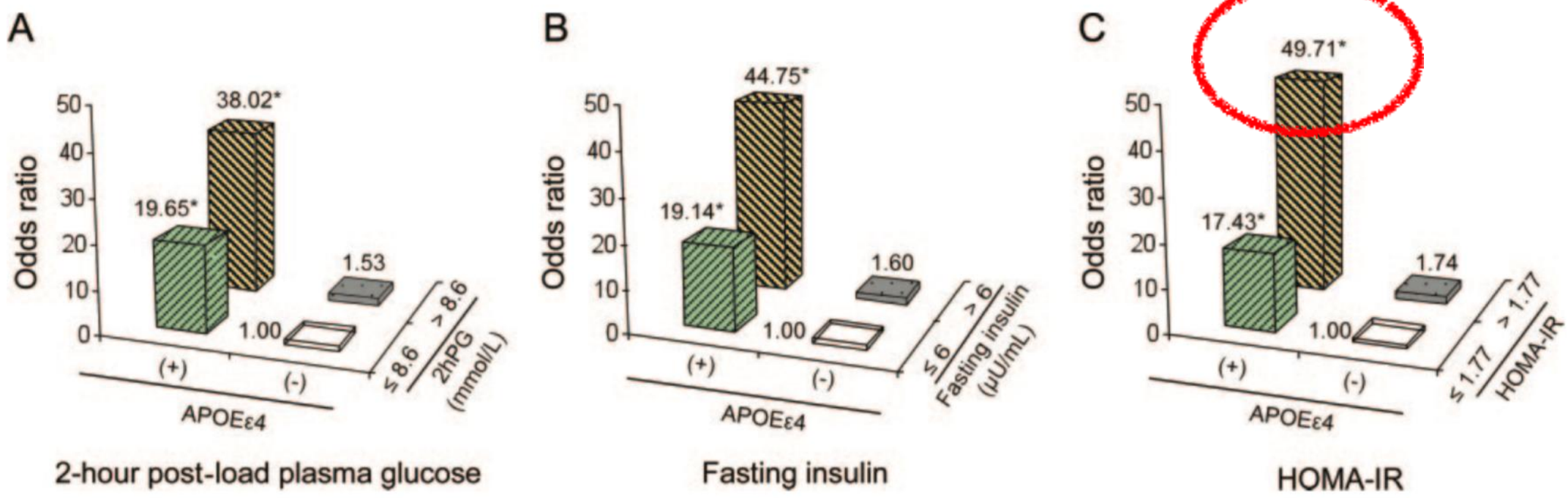
Figure 1: Mean HOMA-IR of cancer cases and controls

Multivariate Logistic Regression, Final Model Showing Adjusted Odds Ratio

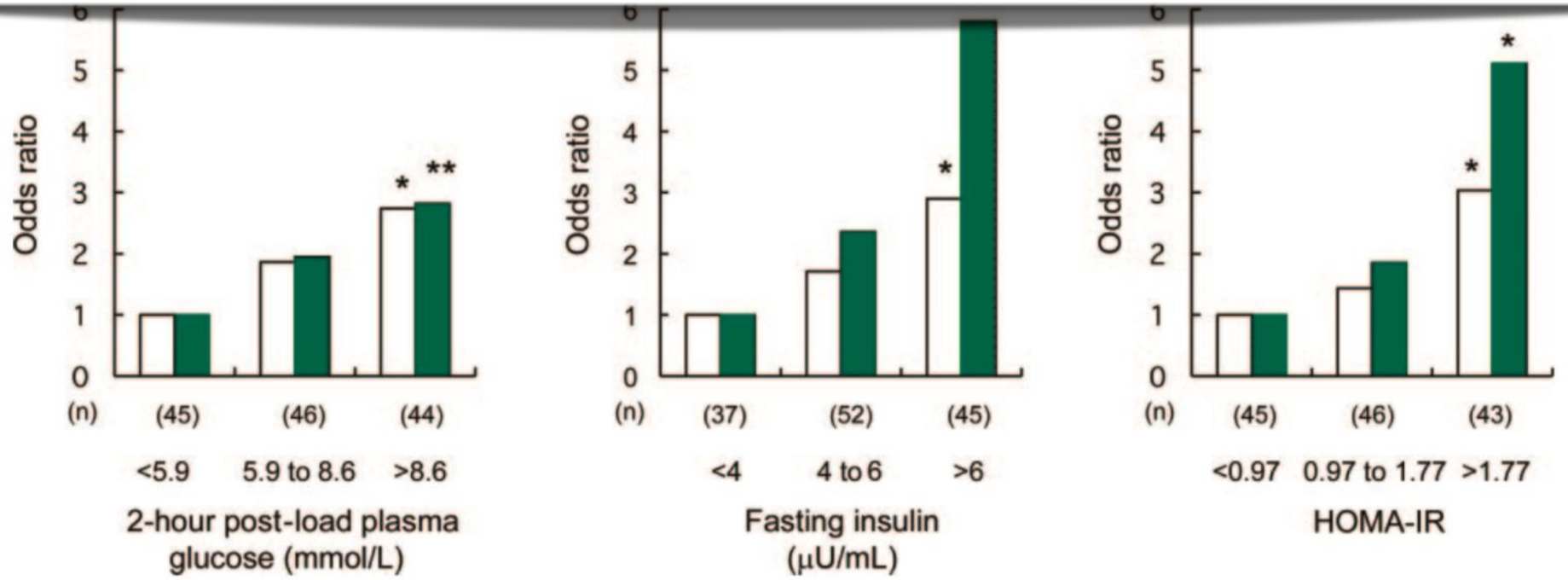
Table 3: Adjusted ORs for IR, Hypertension, Obesity and Triglycerides

	B	S.E	p value	Adjusted OR	95% C.I	
					Lower	Upper
HOMA-IR	2.505	0.684	<0.001	12.247	3.203	46.832
Hypertension	1.616	0.537	0.003	5.032	1.756	14.423
Obesity	1.203	0.576	0.037	3.331	1.076	10.307
Triglyceride levels	0.989	0.480	0.039	2.690	1.050	6.888

Figure 2 Odds ratios for the presence of neuritic plaques according to diabetes-related risk factors and *APOE* genotype



Adjusted for age, sex, and total cholesterol. The numbers in the figure are odds ratios vs the reference group (*APOE* ϵ4 noncarrier and lower level of glucose [A], insulin [B], or HOMA-IR [C]). *$p < 0.05$ vs reference group. 2hPG = 2-hour post-load plasma glucose; HOMA-IR = homeostasis model assessment of insulin resistance.



Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, systolic blood pressure, total cholesterol, body mass index, current smoking, regular exercise, and cerebrovascular disease. *$p < 0.05$, **$p < 0.10$ vs the lowest tertile. HOMA-IR = homeostasis model assessment of insulin resistance.

Insulin Resistance Predicts Mortality in Nondiabetic Individuals in the U.S.

KARLEE J. AUSK, MD[1]
EDWARD J. BOYKO, MD, MPH[2]
GEORGE N. IOANNOU, BMBCh, MS[1,3]

OBJECTIVE — Insulin resistance is a suspected causative factor in a wide variety of diseases. We aimed to determine whether insulin resistance, estimated by the homeostasis model assessment for insulin resistance (HOMA-IR), is associated with all-cause or disease-specific mortality among nondiabetic persons in the U.S.

RESEARCH DESIGN AND METHODS — We determined the association between HOMA-IR and death certificate–based mortality among 5,511 nondiabetic, adult participants of the third U.S. National Health and Nutrition Examination Survey (1988–1994) during up to 12 years of follow-up, after adjustment for potential confounders (age, sex, BMI, waist-to-hip ratio, alcohol consumption, race/ethnicity, educational attainment, smoking status, physical activity, C-reactive protein, systolic and diastolic blood pressure, plasma total and HDL cholesterol, and triglycerides).

RESULTS — HOMA-IR was significantly associated with all-cause mortality (adjusted hazard ratio 1.16 [95% CI 1.01–1.3], comparing successive quartiles of HOMA-IR in a linear model and 1.64 [1.1–2.5], comparing the top [HOMA-IR >2.8] to the bottom [HOMA-IR ≤1.4] quartile). HOMA-IR was significantly associated with all-cause mortality only in subjects with BMI <25.2 kg/m^2 (the median value) but not in subjects with BMI ≥25.2 kg/m^2. Subjects in the second, third, and fourth quartile of HOMA-IR appeared to have higher cardiovascular mortality than subjects in the lowest quartile of HOMA-IR. HOMA-IR was not associated with cancer-related mortality.

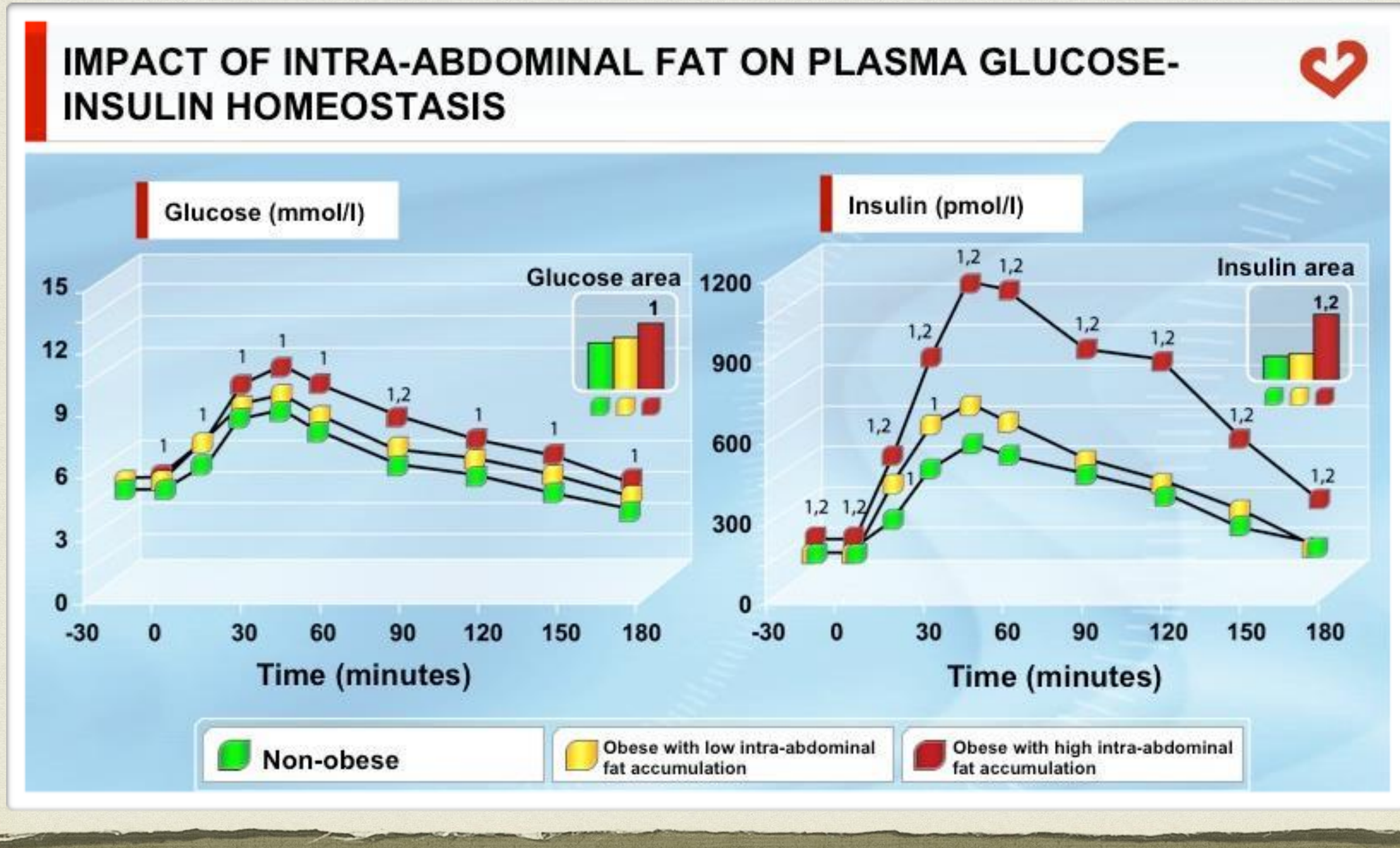
CONCLUSIONS — HOMA-IR is associated with all-cause mortality in the nondiabetic U.S. population but only among persons with normal BMI. HOMA-IR is a readily available measure that can be used in the future to predict mortality in clinical or epidemiological settings.

insulin resistance, such as race, sex, physical activity, and genetic factors, while as-yet-unknown causes of insulin resistance also likely exist.

The homeostasis model assessment for insulin resistance (HOMA-IR) estimates insulin resistance from fasting plasma glucose and serum insulin levels (11). There is good correlation between values of insulin resistance obtained using HOMA-IR and the euglycemic hyperinsulinemic clamp method (12), the gold-standard test that is too costly and technically demanding to be used in epidemiologic studies or clinical practice. Given the combination of accuracy and ease of testing, HOMA-IR is considered an appropriate method for measurement of insulin resistance in epidemiologic studies (12).

Our aim was to determine the association between HOMA-IR and [illegible] nondiabetic people in the U.S. independently of other important predictors of mortality. This finding would be impor-

Insulin resistance: obesity?



Ectopic fat accumulation: an important cause of insulin resistance in humans

Hannele Yki-Järvinen

J R Soc Med 2002;**95**(Suppl. 42)

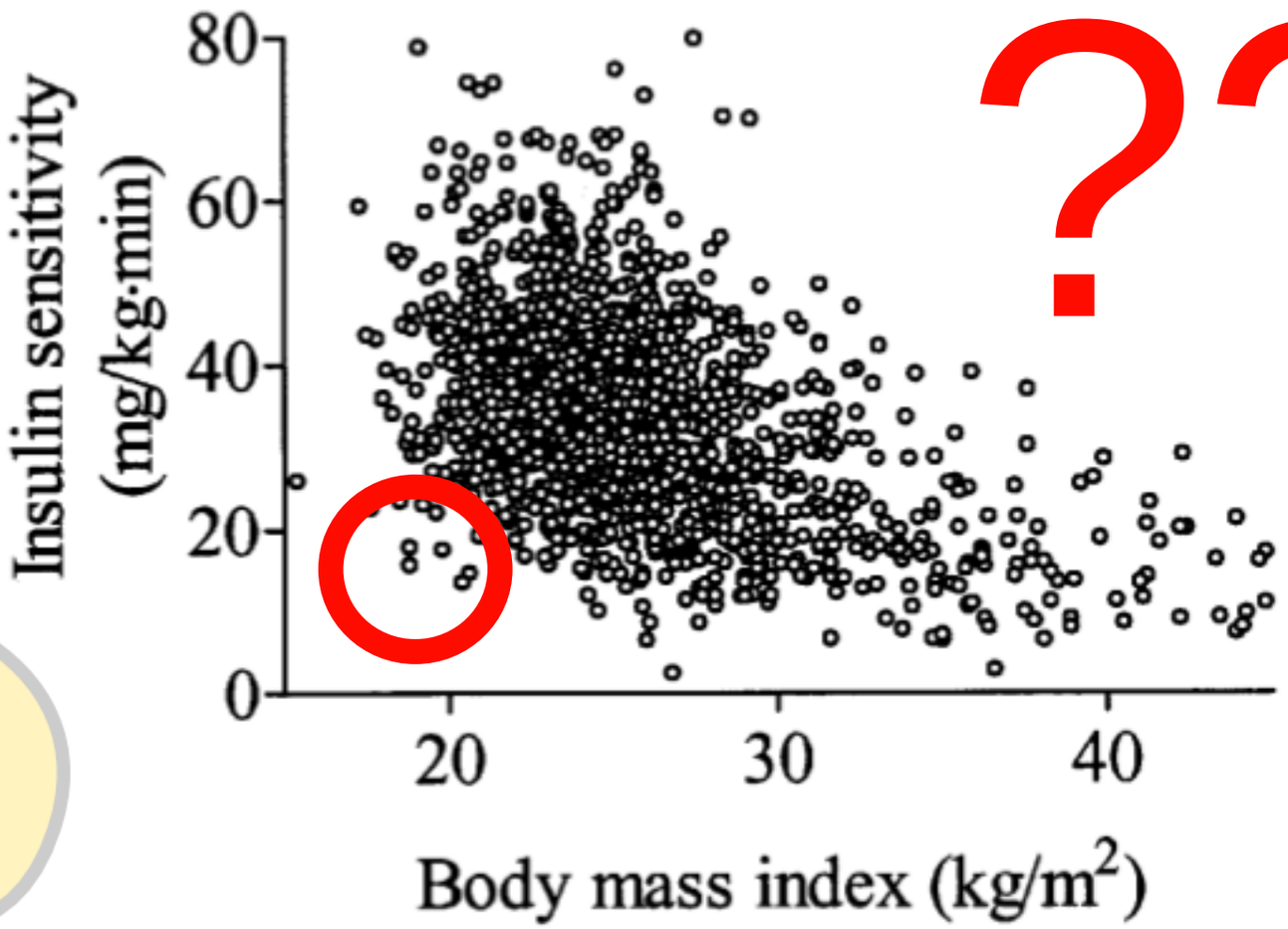


Figure 1 **Relationship between body mass index and insulin sensitivity, measured using the euglycaemic clamp technique, in 1394 healthy non-diabetic European men and women whose data have been included in the European Group for Insulin Resistance (EGIR) database** [data used by permission from the EGIR]

The Role of Adipose Cell Size and Adipose Tissue Insulin Sensitivity in the Carbohydrate Intolerance of Human Obesity

LESTER B. SALANS, JEROME L. KNITTLE, and JULES HIRSCH

From The Rockefeller University, New York

ABSTRACT Glucose metabolism and insulin sensitivity of isolated human adipose tissue was studied as a function of adipose cell size and number. Glucose metabolism by these tissues was closely related to the number of cells in the fragment, irrespective of cell size. Adipose cells of obese individuals metabolized glucose to carbon dioxide and triglyceride at rates similar to adipose cells of nonobese subjects. In contrast, insulin reduction in adipose cell size restored plasma insulin concentration to normal, concomitant with the return of normal tissue insulin sensitivity.

INTRODUCTION

Glucose intolerance is often observed in obese individuals without clinically manifest diabetes mellitus. Furthermore, excessive increase in plasma insulin after glucose ingestion has been well documented in obese patients in the presence or absence of decreased glucose tolerance (1–3). It has been postulated that "insulin resistance" of the peripheral tissues of the obese subject is responsible for these abnormalities of glucose and insulin metabolism (4–6). Such studies, however, afford little or no information as to which tissues may be "responsible" for the insulin resistance of obesity. Techniques are now available for sampling adipose tissue from various depots in man by needle aspiration (8), for in vitro measurement of the metabolic activity of these tissue samples and their sensitivity to insulin, and for determination of adipose cell number and size (9). Development of these methods has made possible a detailed study of human adipose tissue in relation to the metabolic abnormalities described above.

In the present study these techniques have been used to examine glucose metabolism and insulin responsiveness of adipose tissue of obese and nonobese subjects. These studies indicate that the cellularity of the tissue sample is of prime

A preliminary report of these studies was presented at the May 1967 meeting of the American Society for Clinical Investigation.

Address requests for reprints to Dr. Lester B. Salans, The Rockefeller University, New York 10021.

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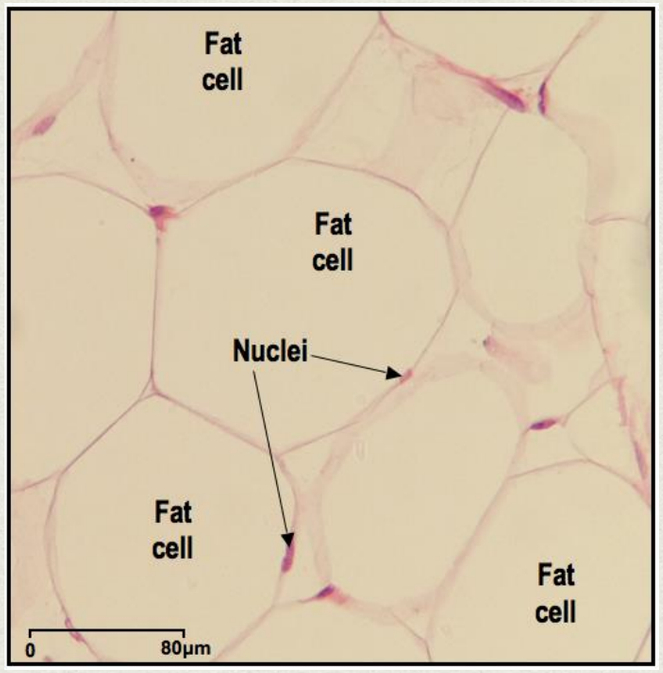
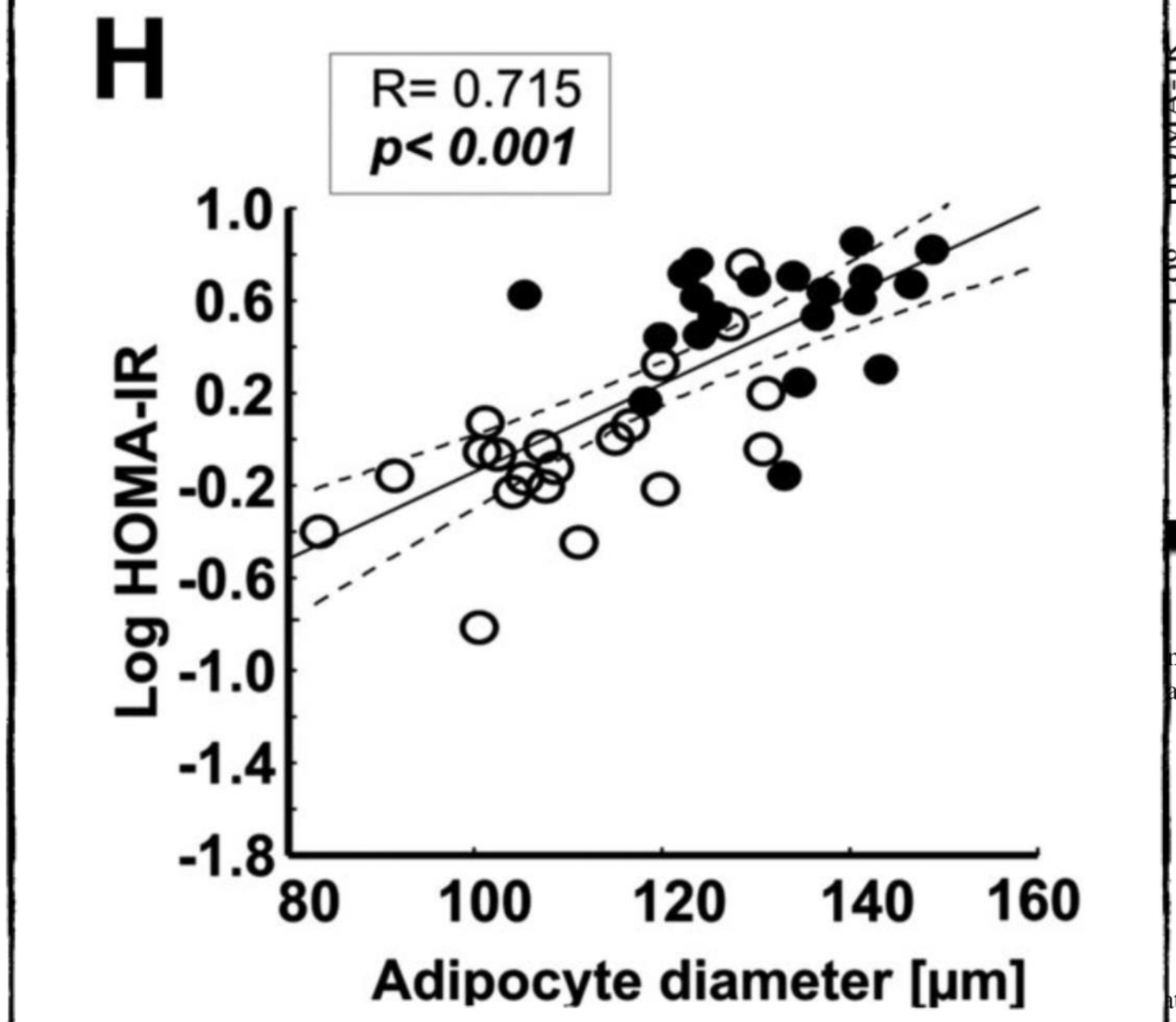


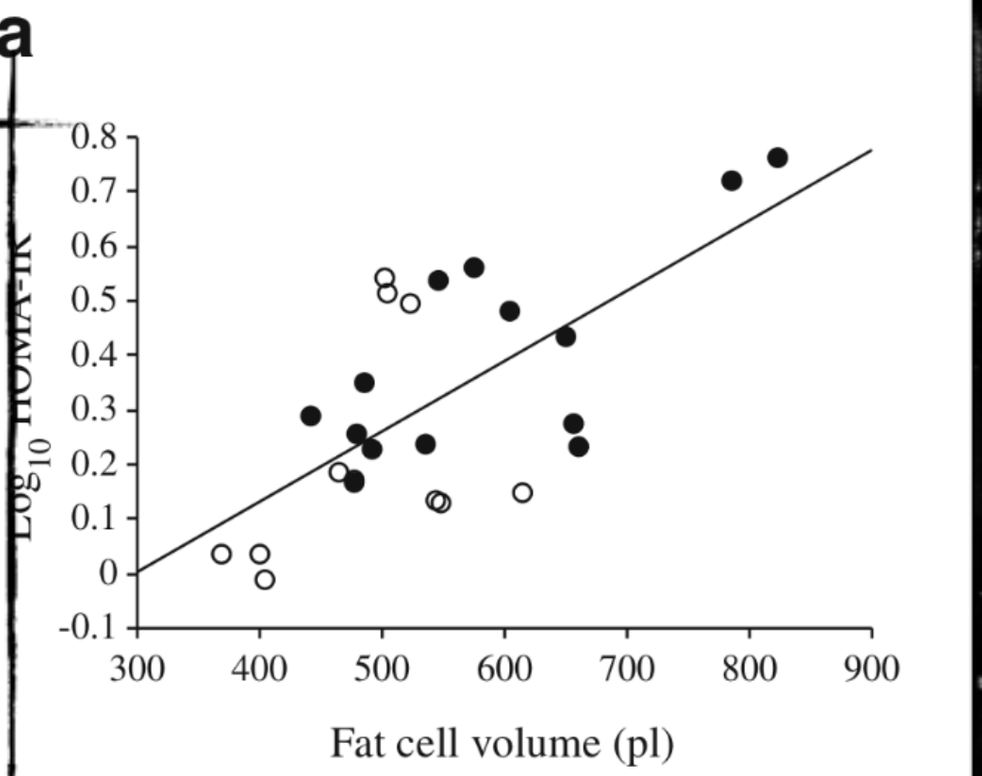
The Journal of Clinical Investigation Volume 47 1968

Increased fat cell size: a major phenotype of subcutaneous white adipose tissue in non-obese individuals with type 2 diabetes

Juan R. Acos
Mikael Rydé

Fig. 1 An inter-relationship between fat cell volume, insulin





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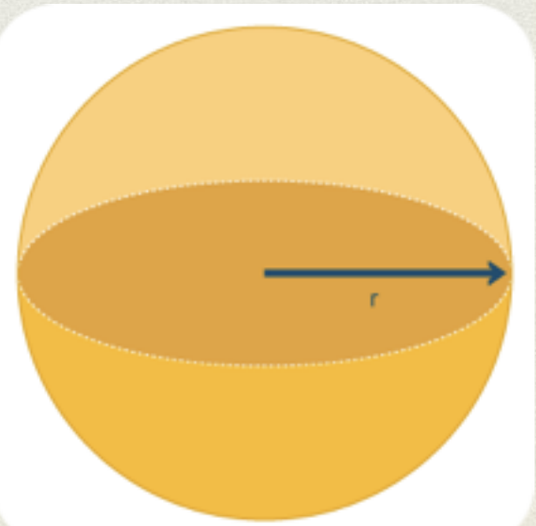


Adipocyte size predicts incidence of type 2 diabetes in women

ders have been hypothesized, the detailed mechanisms are not completely understood (38). Large adipocytes are resistant to the antilipolytic effect of insulin leading to elevated plasma free fatty acid levels, in turn, affecting metabolism in a negative way. Moreover, large adipocytes, filled to capacity, may also reflect failure of the adipose tissue to further store excess energy. Instead, surplus energy is stored ectopically, in the liver, muscle, possibly the pancreas and other nonadipose

AAS and FAS (WHtR-HR 2.6 and 2.7, respectively; $P<0.001$). To conclude, in addition to the amount and distribution of body fat in women, subcutaneous adipocyte size, particularly in the abdominal region, predicts incidence of T2D in later life.—Lönn, M., Mehlig,

Adipocyte Hypertrophy, Inflammation and Fibrosis Characterize Subcutaneous Adipose Tissue of Healthy, Non-Obese Subjects Predisposed to Type 2 Diabetes

A. M. Josefin Henninger, Björn Eliasson, Lachmi E. Jenndahl, Ann Hammarstedt*

[illegible]

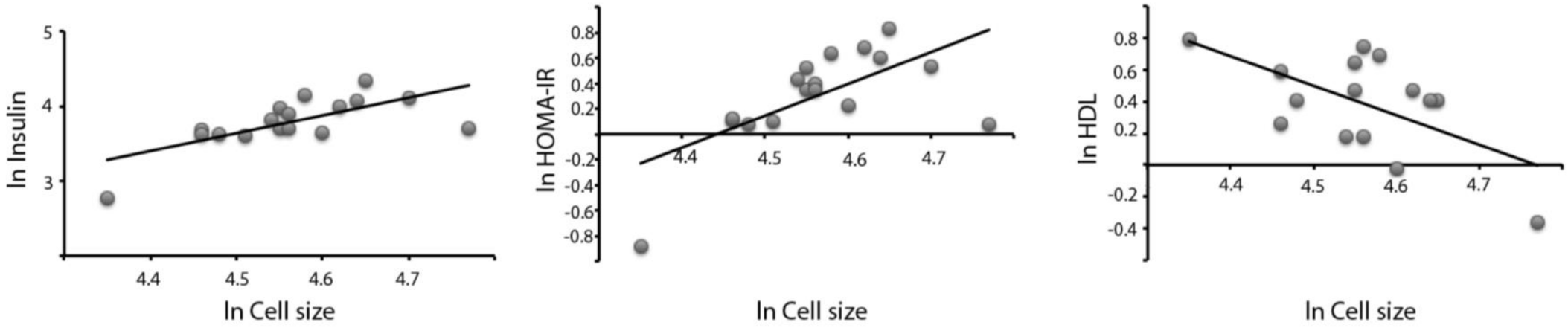


Figure 1. Adipocyte cell size and metabolic parameters in FDRs. Adipocyte cell size in relation to (A) fasting insulin (R = 0.69, p = 0.003), (B) HOMA-IR (R = 0.64, p = 0.006) and (C) serum HDL (R = −0.50, p = 0.019).
doi:10.1371/journal.pone.0105262.g001

group, but not among [illegible] was accompanied by increased inflammation and Wnt-signal activation. In addition, signs of tissue remodeling and fibrosis were observed indicating presence of early alterations associated with adipose tissue dysfunction in the FDRs.

Conclusion: Genetic predisposition for type 2 diabetes is associated with impaired insulin sensitivity, adipocyte hypertrophy and other markers of adipose tissue dysfunction. A dysregulated subcutaneous adipose tissue may be a major susceptibility factor for later development of type 2 diabetes.

The Relationship of Omental and Subcutaneous Adipocyte Size to Metabolic Disease in Severe Obesity

Anna Kwasnik[1], N
hea[1,7]
sity Hospital, Dublin, Ireland
spital and St Columcille's Hos
nt Unit, St Vincent's Universi
Vincent's University Hospital

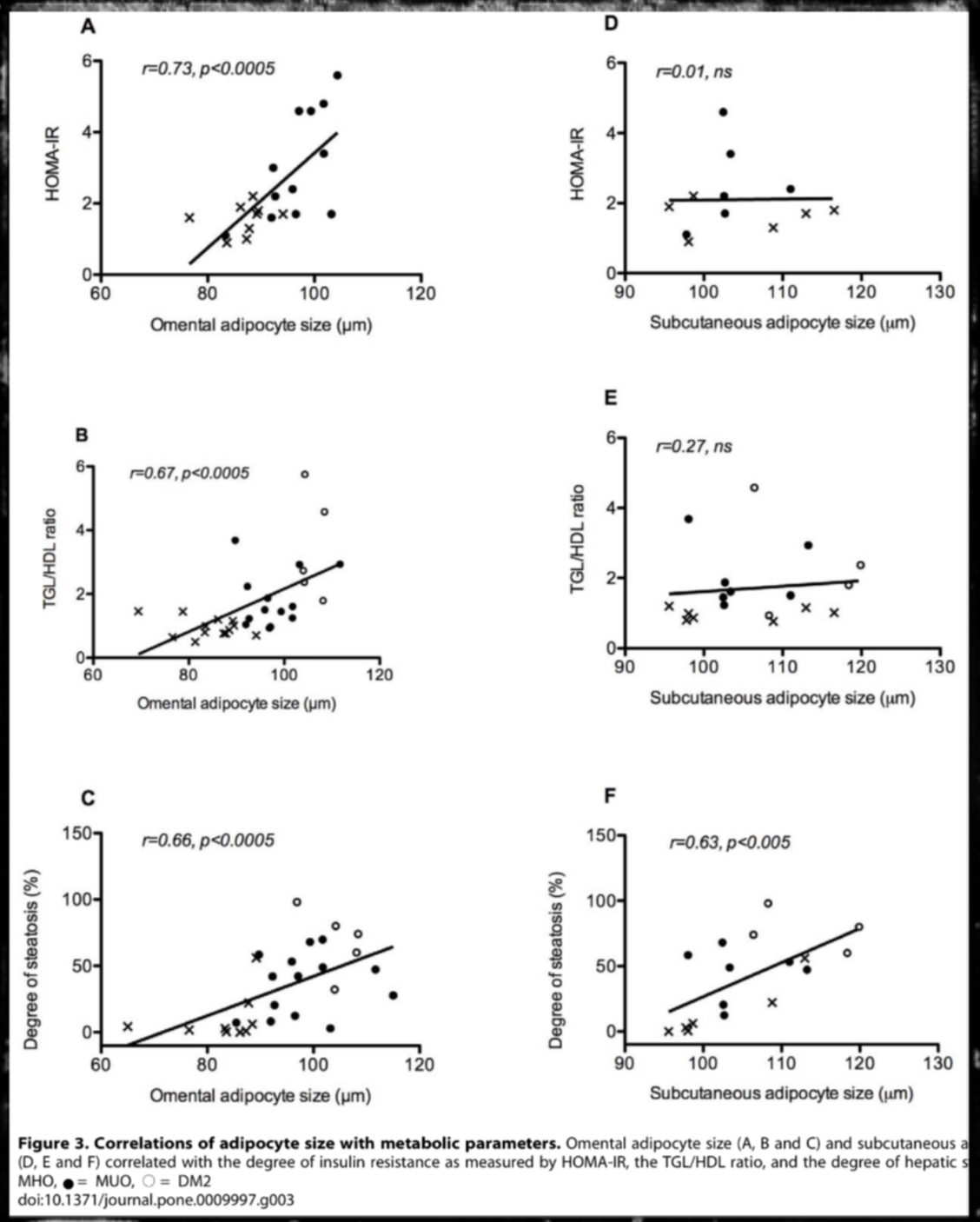
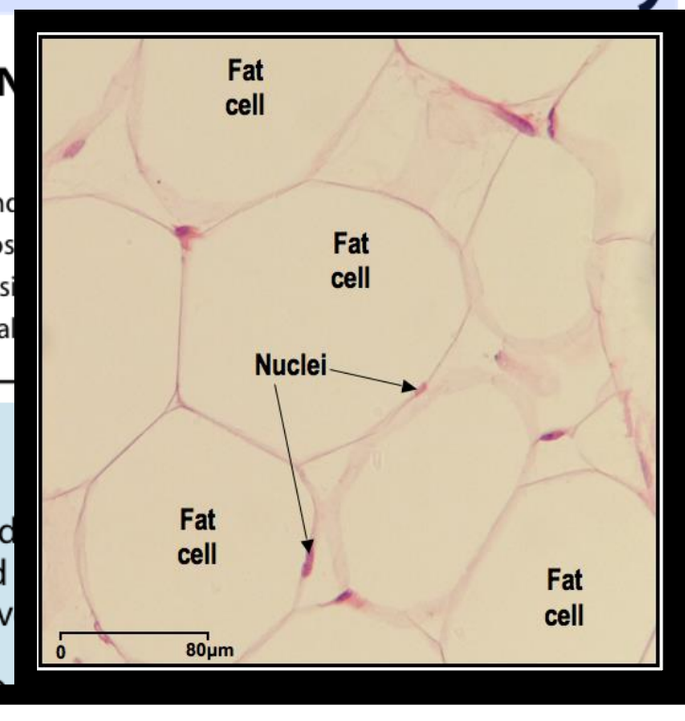
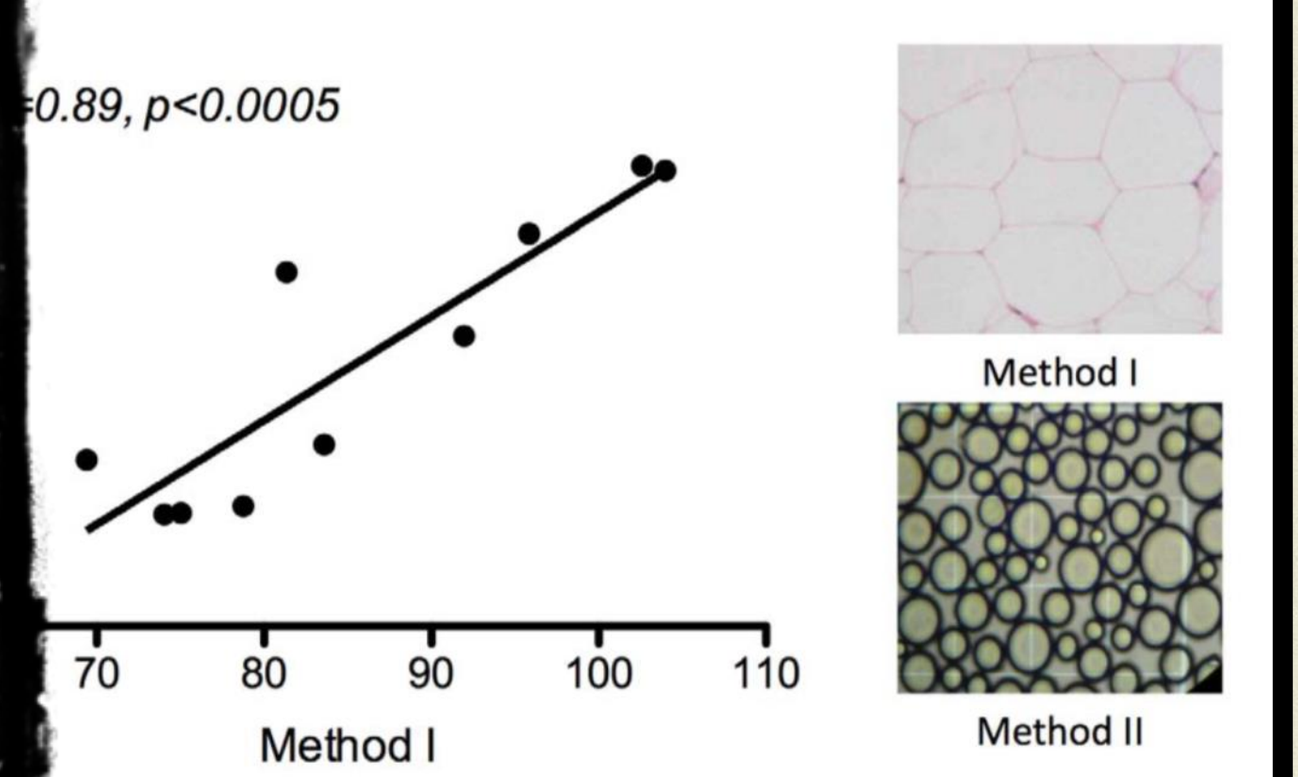


Figure 3. Correlations of adipocyte size with metabolic parameters. Omental adipocyte size (A, B and C) and subcutaneous a
(D, E and F) correlated with the degree of insulin resistance as measured by HOMA-IR, the TGL/HDL ratio, and the degree of hepatic s
MHO, ● = MUO, ○ = DM2
doi:10.1371/journal.pone.0009997.g003





Adipose Tissue and Metabolic Alterations: Regional Differences in Fat Cell Size and Number Matter, But Differently: A Cross-Sectional Study

Mikael Rydén, Daniel P. Andersson, Ingrid B. Bergström,

Department of Medicine, Karolinska Institutet, Karolinska University Hosp
Stockholm, Sweden

Objective: White adipose tissue can expand by increasing the size
Although increased sc and visceral fat cell size associates with an a
relationship with fat cell number in either depot is unknown. We
number and size displayed different relationships with clinically rel

Methods: This was a cross-sectional study of 204 patients scheduled
cell size and number were determined in visceral and abdominal sc
insulin sensitivity (by hyperinsulinemic euglycemic clamp), fasting p
erides and high-density lipoprotein (HDL) cholesterol.

Results: Visceral and sc fat cell volumes were positively correlated
levels and negatively with insulin sensitivity and HDL-cholesterol (P
although visceral fat cell number did not associate with any meta
number displayed a positive association with insulin sensitivity and H
relationship with insulin and triglyceride levels ($P = .0014$ or better)
of body fat mass.

Conclusions: Variations in fat cell size and number correlate differen
in obesity. Increased fat cell size in visceral and sc depots associate
profile, whereas increased sc, but not visceral, fat cell number corr
phenotype. Whether determination of sc fat cell number, in additio
a predictive value for the risk of type 2 diabetes needs to be de
mechanistic studies. **(*J Clin Endocrinol Metab* 99: E1870–E1876, 20**

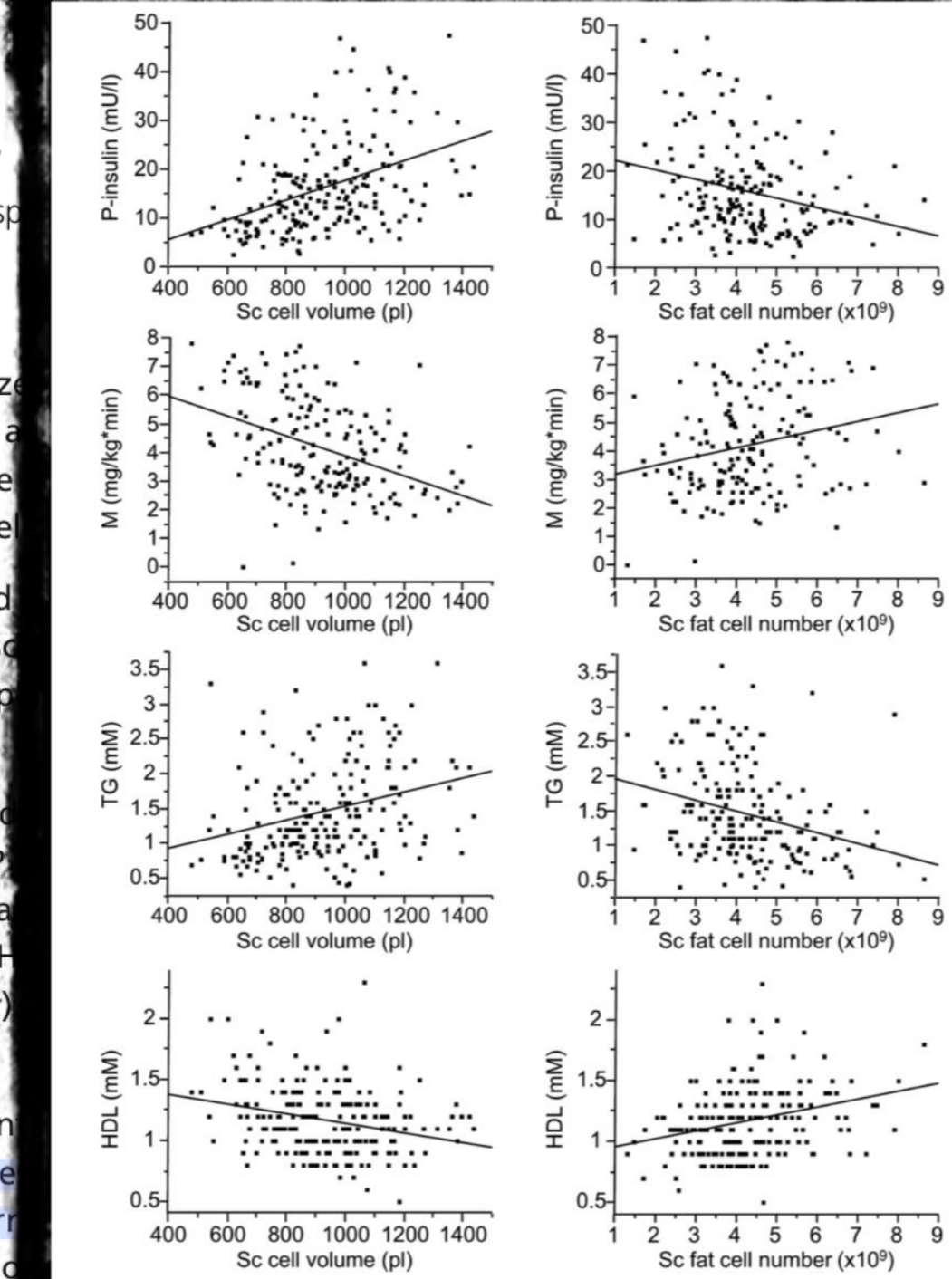


Figure 2. The relationship between sc fat cell volume or number and plasma insulin (P-insulin), insulin sensitivity (M-value), plasma triglycerides (TG), or plasma HDL-cholesterol.

Adipocyte Size Threshold Matters: Link with Risk of Type 2 Diabetes and Improved Insulin Resistance After Gastric Bypass

Aurelie Cotillard, Christine Poitou, Adriana Torcivia, Jean-Luc Bo
Arne Dietrich, Nora Klöting, Cécile Grégoire, Karine Lolmede, M
and Karine Clément

Sorbonne Universities (A.C., C.P., K.C.), University Pierre et Marie Curie-Paris 6, U
Nutriomics, F-75013 Paris, France; Institute of Cardiometabolism and Nutrition, IC
C.G., K.C.), Pitié-Salpêtrière hospital, F-75013 Paris, France; INSERM, UMR_S U11
Nutriomics, F-75013 Paris, France; Assistance Publique-Hôpitaux de Paris (A.T.), P
Surgery Department, F-75013 Paris, France; Assistance Publique-Hôpitaux de Pari
Paré Hospital, Surgery Department, F-92012 Boulogne-Billancourt, France; Depar
(A.D.), University of Leipzig, 04003-04357 Leipzig, Germany; Department of Med
University of Leipzig, 04003-04357 Leipzig, Germany; and Junior Research Group
IFB Obesity Diseases, University of Leipzig, 04003-04357 Leipzig, Germany; Adipo
F-75013 Paris, France

Context: Adipocyte volume has been associated with insulin resistance an

Objective: Our purpose was to identify an adipocyte volume threshold linked wit
tance risk, and to examine its association with insulin resistance improvement aft

Setting and Design: We investigated two cohorts of Caucasian women, c
surgery, from two institutional centers in France (age 42.0 ± 11.5 years; bo
6.9 kg/m^2) and Germany (age 41.3 ± 11.2 years; body mass index, 49.5 ± 8
subjects had gastric bypass surgery and were followed for 6 months after
defined a group of subjects with type 2 diabetes or at risk of type 2 diabetes (
the relations between adipocyte volume and this status before and after s

Results: In both cohorts, subjects with DRD presented enlarged adipocytes
Germany, $P = 3\times10^{-10}$) and we were able to determine thresholds in eac
diabetes risk was potentially increased (France: 1003±42 pL, Germany: 798±
those adipocyte thresholds were less prone to disappearance of the DRD stat
(France, risk ratio = 2.1, $P = .024$; Germany, risk ratio = 1.3, $P = .05$).

Conclusions: We show in two cohorts of morbidly obese subjects that a spe
threshold may predict an increased risk for obesity-associated type 2 di
threshold might be established for each specific investigation site. Having a
associated with a lower improvement of insulin resistance after bypass su
(*J Clin Endocrinol Metab* 99: E1466–E1470, 2014)

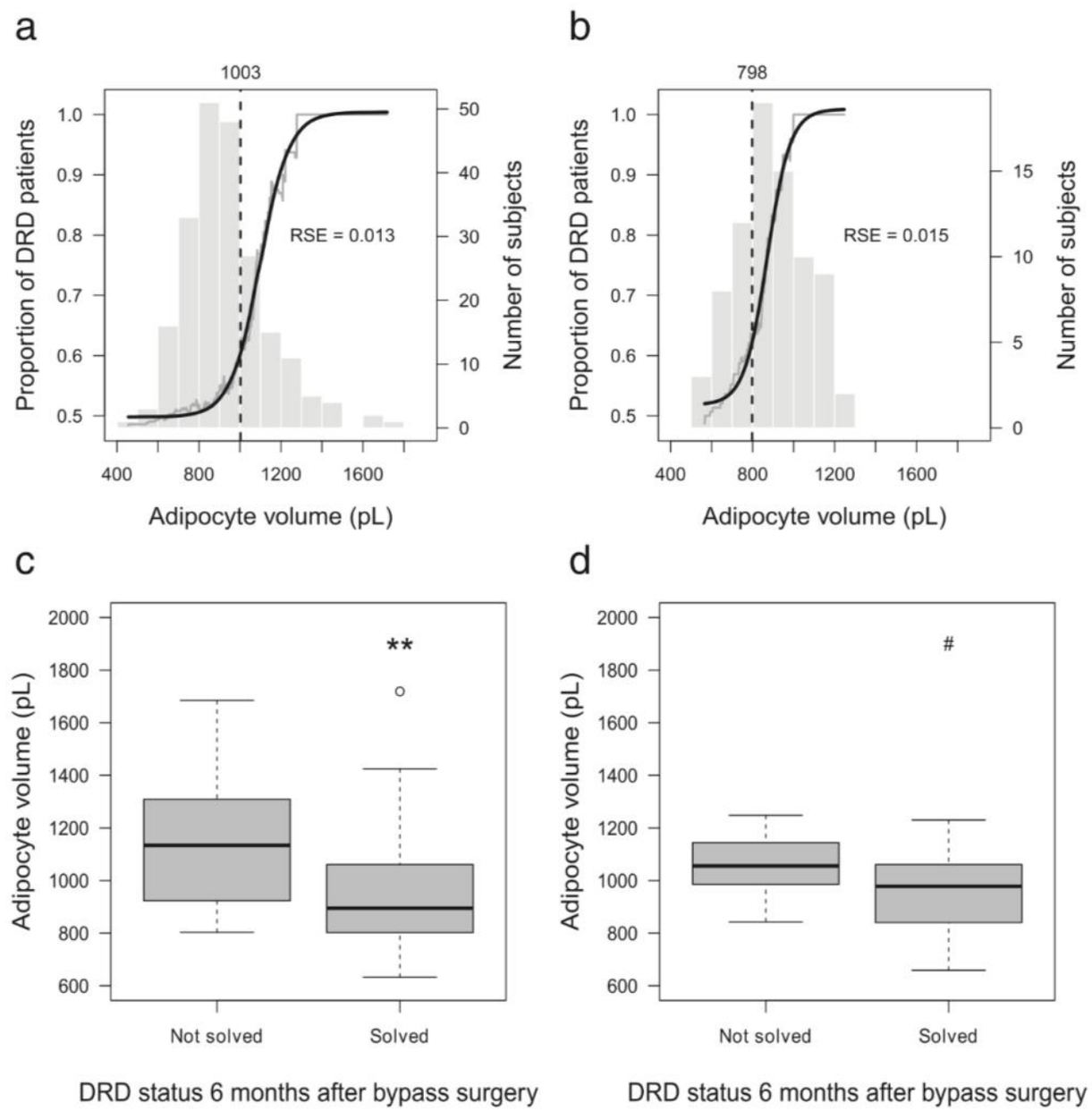


Figure 1. DRD status before and after surgery in association with adipocyte volume. A) and B): prevalence of DRD subjects above each threshold of adipocyte volume in the French cohort A) and in the German cohort B). A logistic function (black line) was fitted on the gray curve. The dashed line stands for the maximum acceleration in the increase of diabetes risk. The gray histogram illustrates the distribution of adipocyte volume in the population. RSE: residual SE for the sigmoid fit. C) and D): Adipocyte volume in subjects solving or not their DRD status in the French cohort C) and in the German cohort D). **, $P < .01$; #, $P < .1$.

Changes in Subcutaneous Fat Cell Volume and Insulin Sensitivity After Weight Loss

Diabetes Care 2014;37:1831–1836 | DOI: 10.2337/dc13-2395

OBJECTIVE

Large subcutaneous fat cells associate with insulin resistance and high risk of developing type 2 diabetes. We investigated if changes in fat cell volume and fat mass correlate with improvements in the metabolic risk profile after bariatric surgery in obese patients.

RESEARCH DESIGN AND METHODS

Fat cell volume and number were measured in abdominal subcutaneous adipose tissue in 62 obese women before and 2 years after Roux-en-Y gastric bypass (RYGB). Regional body fat mass by dual-energy X-ray absorptiometry; insulin sensitivity by hyperinsulinemic-euglycemic clamp; and plasma glucose, insulin, and lipid profile were assessed.

RESULTS

RYGB decreased body weight by 33%, which was accompanied by decreased adipocyte volume but not number. Fat mass in the measured regions decreased and all metabolic parameters were improved after RYGB ($P < 0.0001$). Whereas reduced subcutaneous fat cell size correlated strongly with improved insulin sensitivity ($P = 0.0057$), regional changes in fat mass did not, except for a weak correlation between changes in visceral fat mass and insulin sensitivity and triglycerides. The curve-linear relationship between fat cell size and fat mass was altered after weight loss ($P = 0.03$).

CONCLUSIONS

After bariatric surgery in obese women, a reduction in subcutaneous fat cell volume associates more strongly with improvement of insulin sensitivity than fat mass reduction per se. An altered relationship between adipocyte size and fat mass may be important for improving insulin sensitivity after weight loss. Fat cell size reduction could constitute a target to improve insulin sensitivity.

when the present prospective cohort was investigated at baseline, subcutaneous fat cell volume correlated more strongly than visceral fat cell volume with insulin sensitivity (15). This suggests that for subcutaneous adipose tissue, fat cell size may be of greater importance than fat mass. It is possible that the lack of effect of liposuction on the metabolic profile (3,4) is dependent on the fact that such an intervention does not alter the size of fat cells in the remaining subcutaneous adipose tissue. A decrease in subcutaneous fat cell size rather than a decrease in subcutaneous adipose mass per se may therefore be of greater importance for improvement of insulin sensitivity after weight loss. At present we cannot identify which functional aspects related to fat cell size play a causal role in the reversal of insulin resistance after weight

Adipocyte size as a determinant of metabolic disease and adipose tissue dysfunction

Sofia Laforest[1,2,3], Jennifer Labrecque[1,2,3], Andréanne Michaud[1,2,3], Katherine Cianflone[3], and André Tchernof[1,2,3]

DOI: 10.3109/10408363.2015.1041582

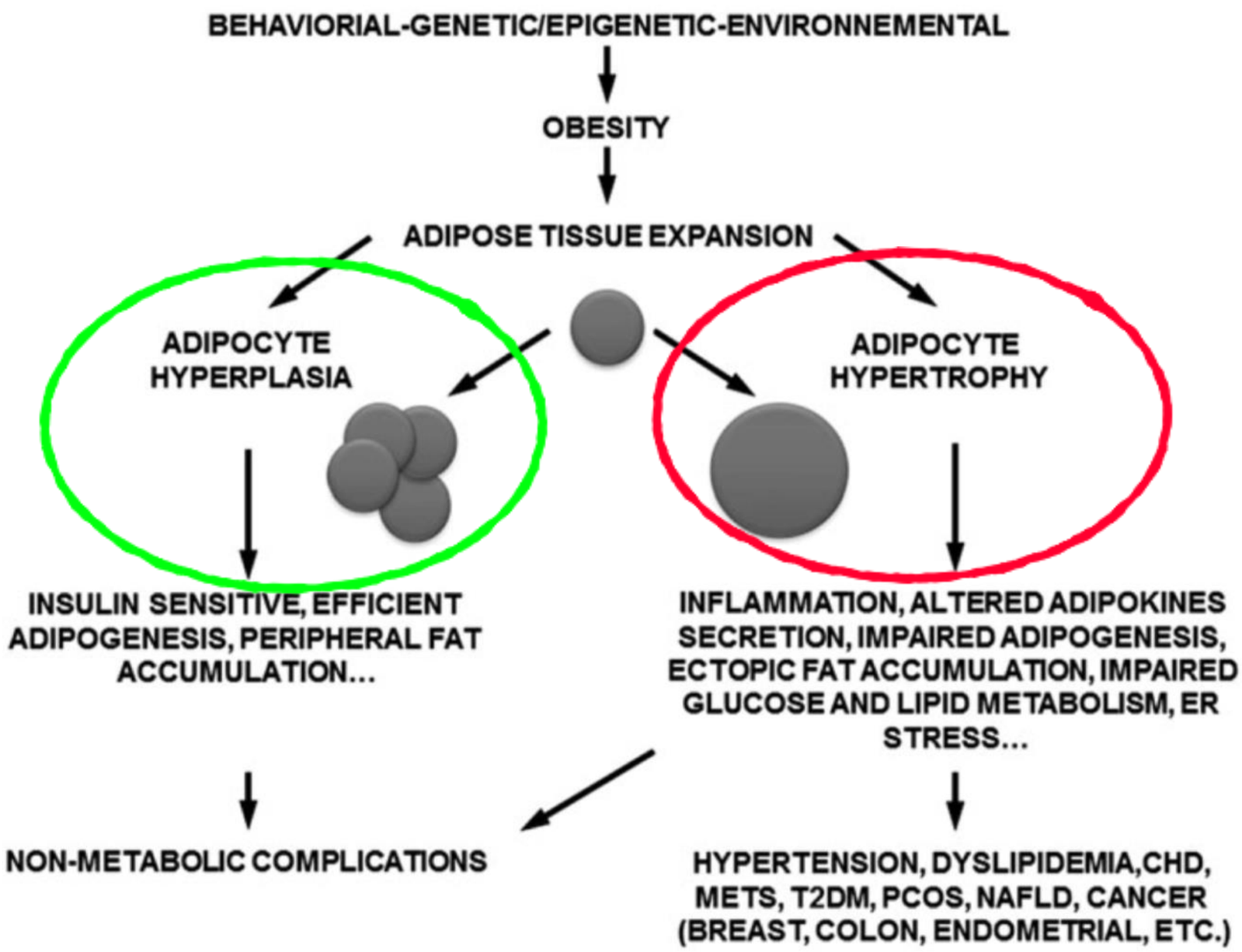
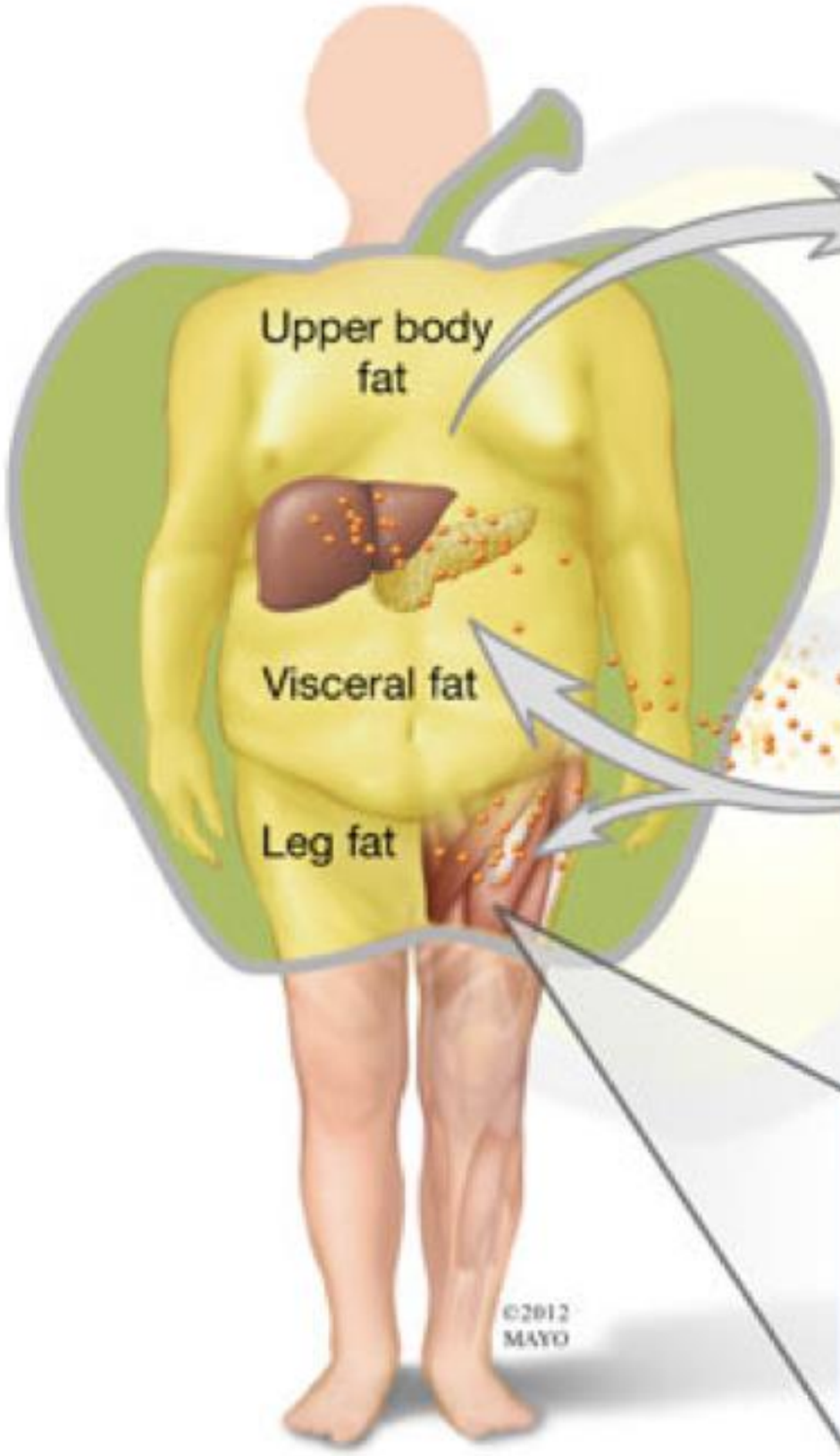


Figure 2. Obesity is a multifactorial disease characterized by expansion of adipose tissue occurring through adipocyte hypertrophy (enlargement of pre-existing cells) or adipocyte hyperplasia (generation of new cells through adipogenesis). Limited expandability of adipose tissue through hyperplasia leads to increases in FCS (adipocyte hypertrophy), which represents a critical marker of central adiposity, adipose tissue dysfunction and concomitant metabolic disease risk.

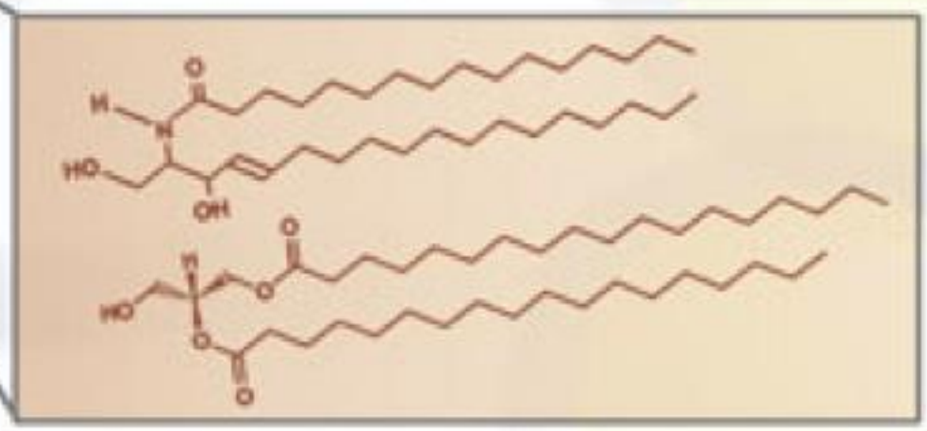
Not all fat cells are alike



In upper body subcutaneous fat, cells increase in size with weight gain.

When they become overly large and surrounded by inflammatory cells, they release too many free fatty acids.

Fatty acids build up in muscle, liver, and pancreatic islet cells, where they form diglycerides and ceramides that can lead to metabolic dysfunction.



Hyperplasia

↑ Adiponectin

↓ Inflammatory Adipokines

Hypertrophy

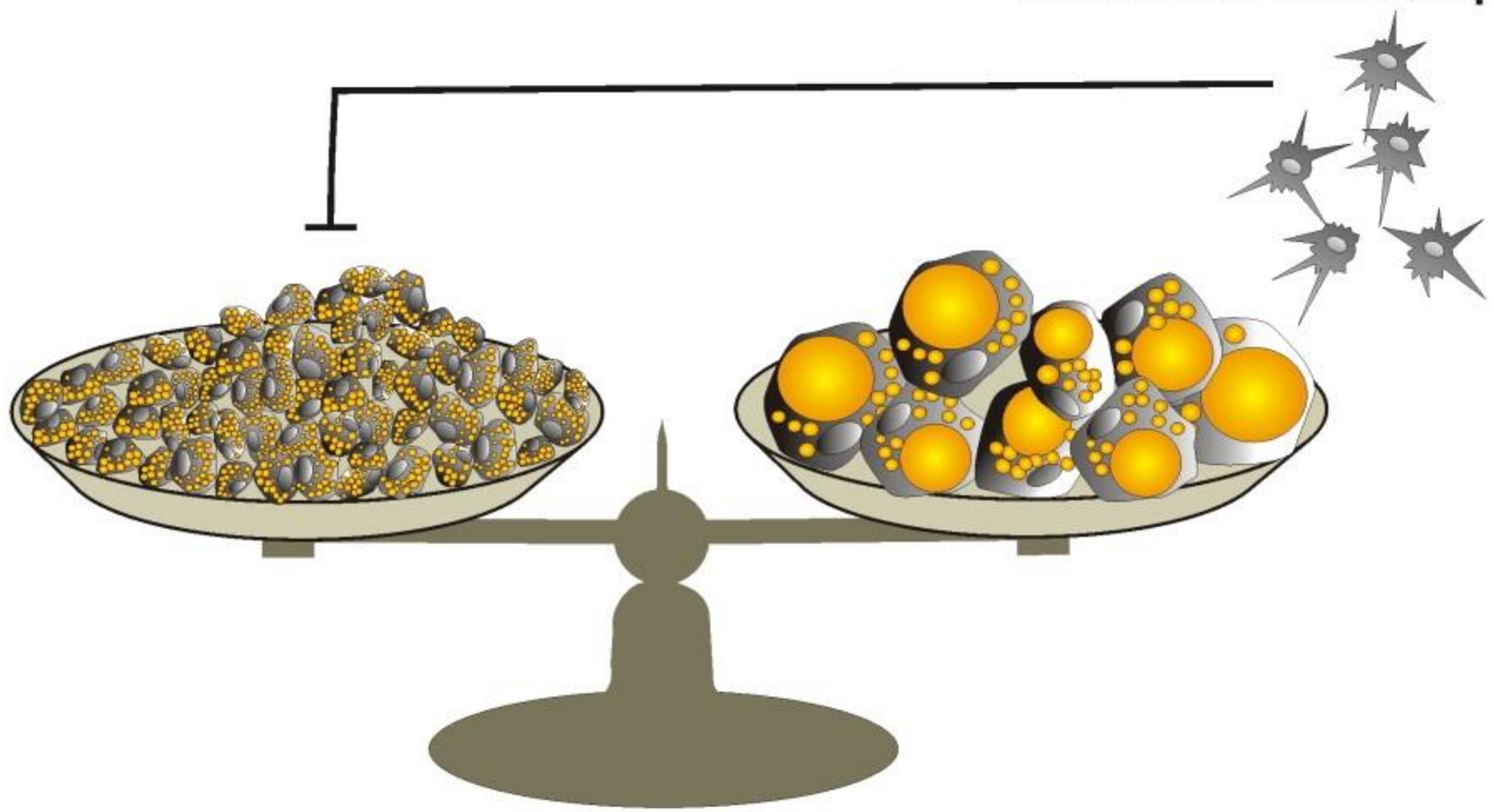
↓ Adiponectin

↑ Inflammatory Adipokines

↓ Blood Flow → Hypoxia

↓

Infiltration of Macrophages



Obesity

Adipose Tissue Expandability in the Maintenance of Metabolic Homeostasis

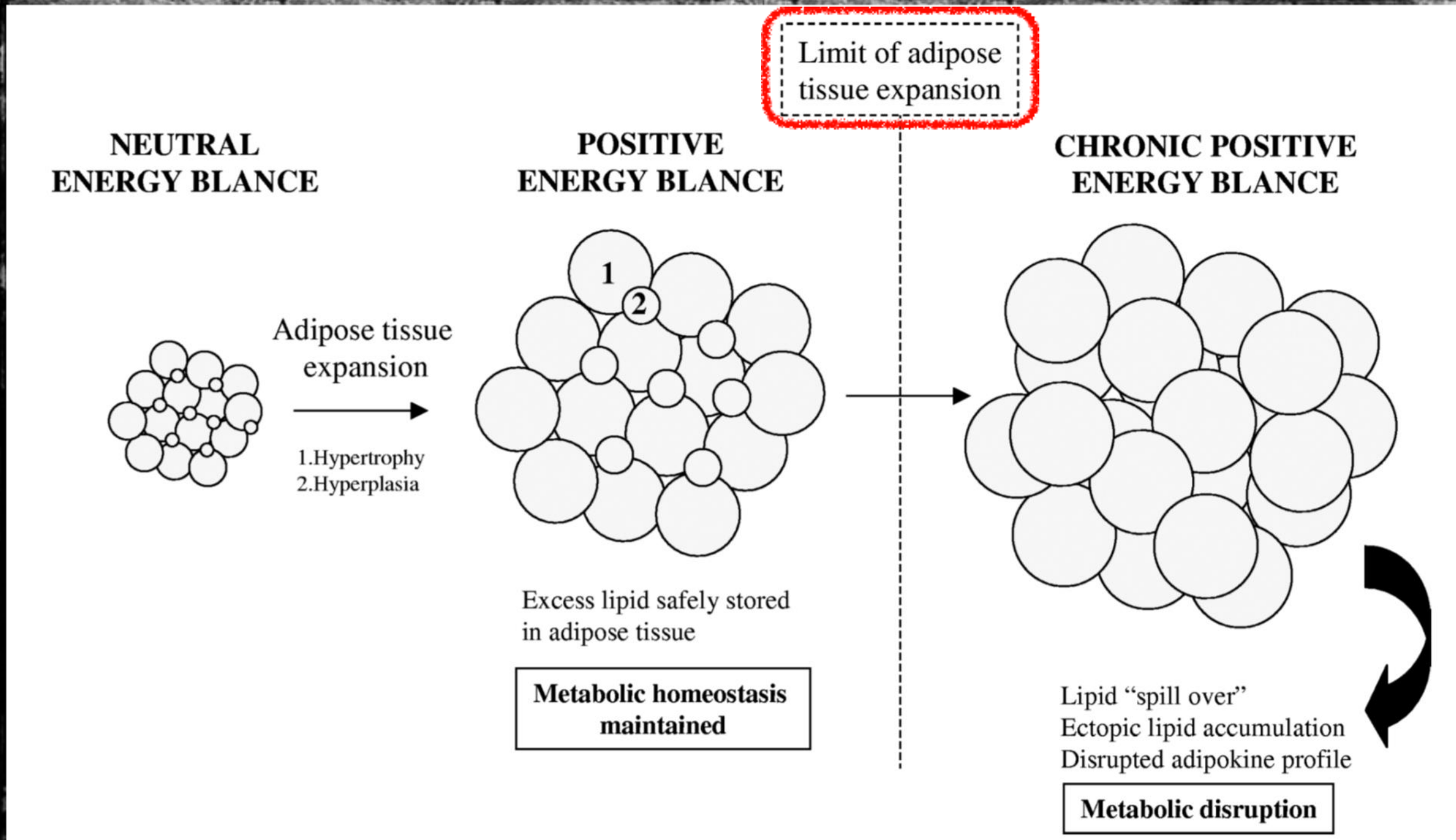
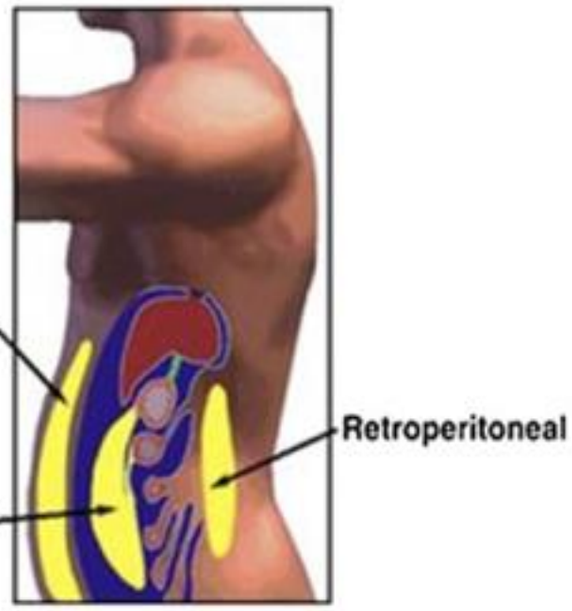


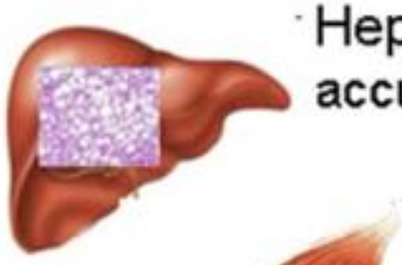
Figure 1. Adipose tissue expandability as an important factor in preventing lipotoxicity and associated metabolic complications.

Excess calories
(increased intake +/-
reduced energy expenditure)

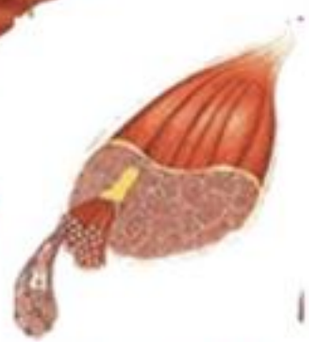


Subcutaneous stores overwhelmed
(genes, ethnicity, ageing)

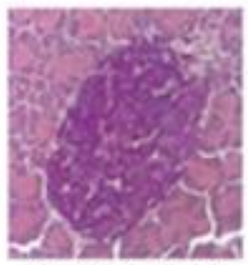
FAT
'Spill over'



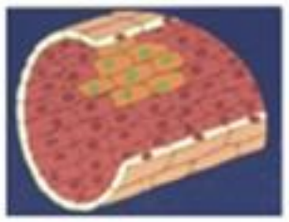
Hepatic lipid accumulation



muscle



pancreatic beta cell



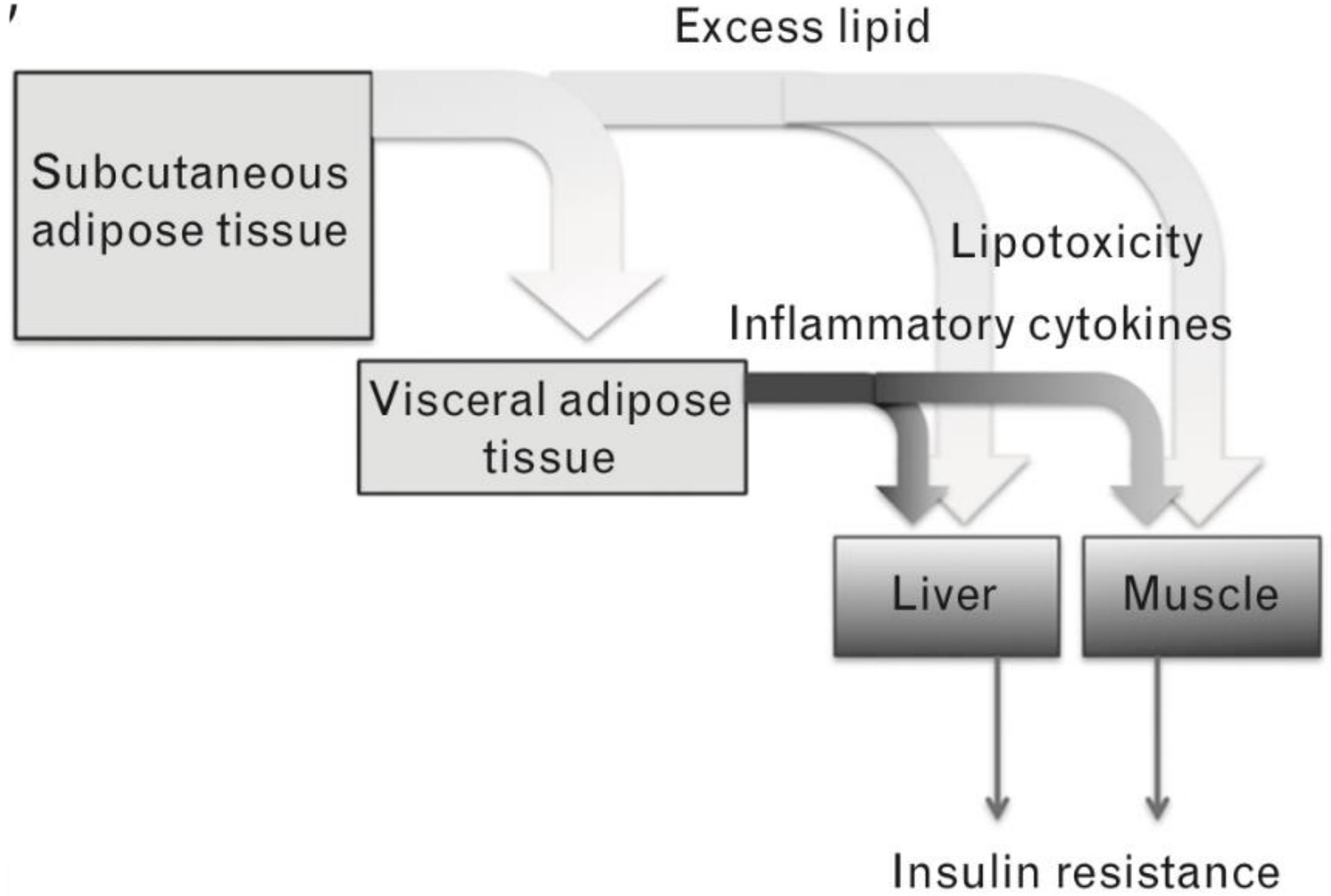
Perivascular fat ⇒
Endothelial dysfunction (altered blood flow)

Insulin resistance

β cell dysfunction?

Hyperglycaemia

What causes the insulin resistance underlying obesity?



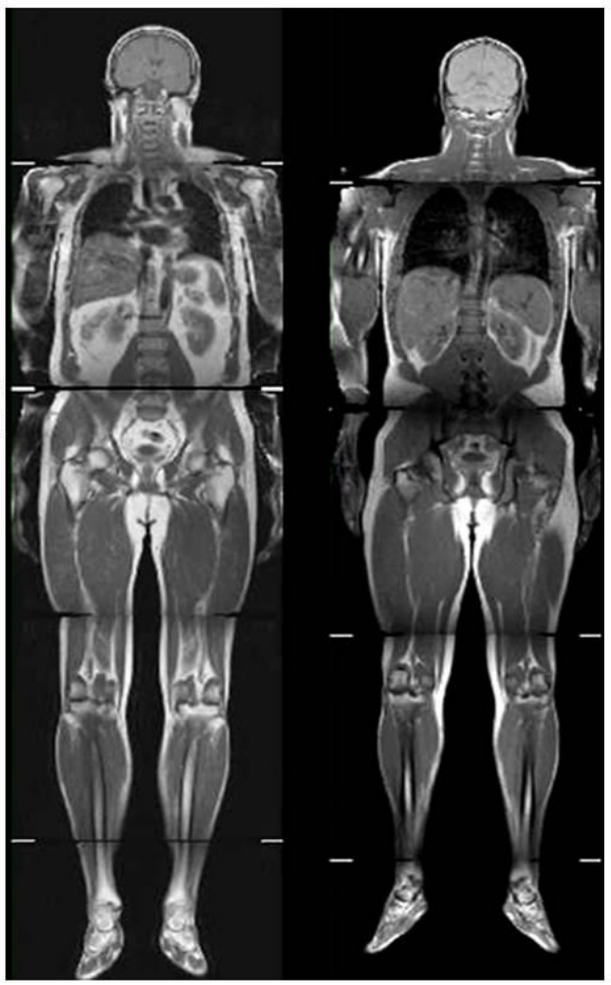
Normal weight individuals who develop Type 2 diabetes: the personal fat threshold

Roy Taylor* and Rury R. Holman†

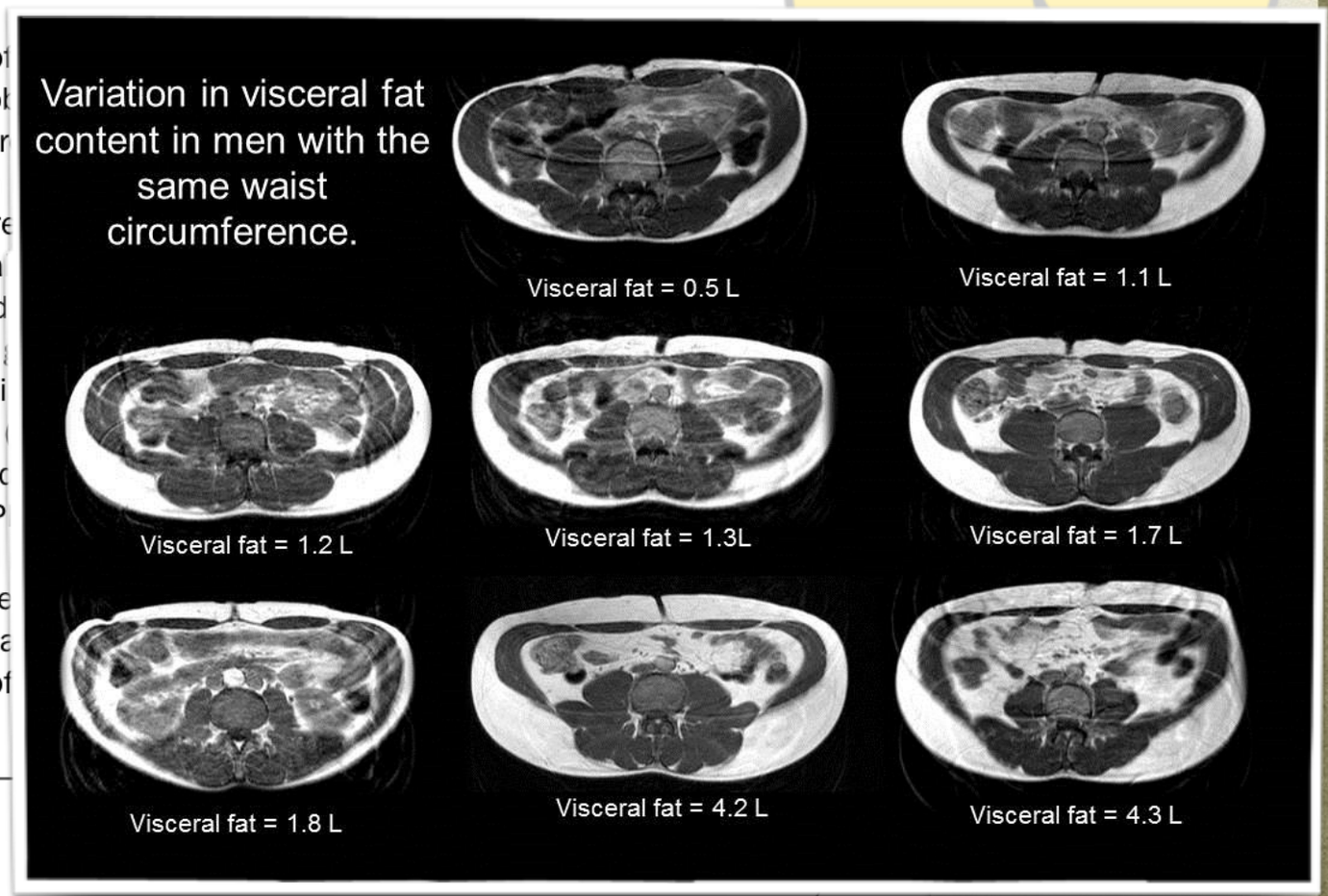
ersity, Newcastle upon Tyne, U.K.

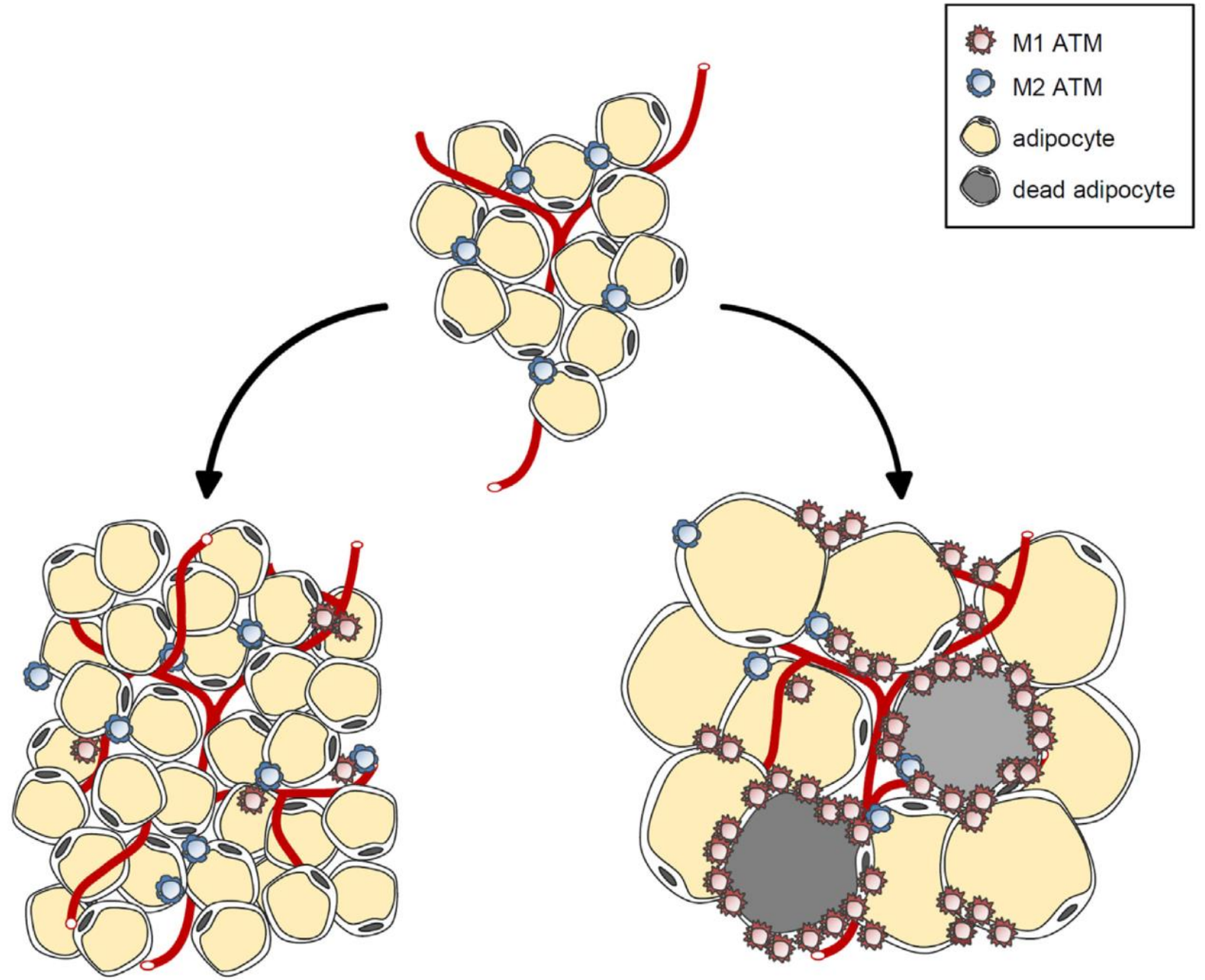
Similar Age, Gender, BMI and Same % Body Fat

Different levels of Internal Fat = Different Disease Risks



EL Thomas and JD Bell 2008



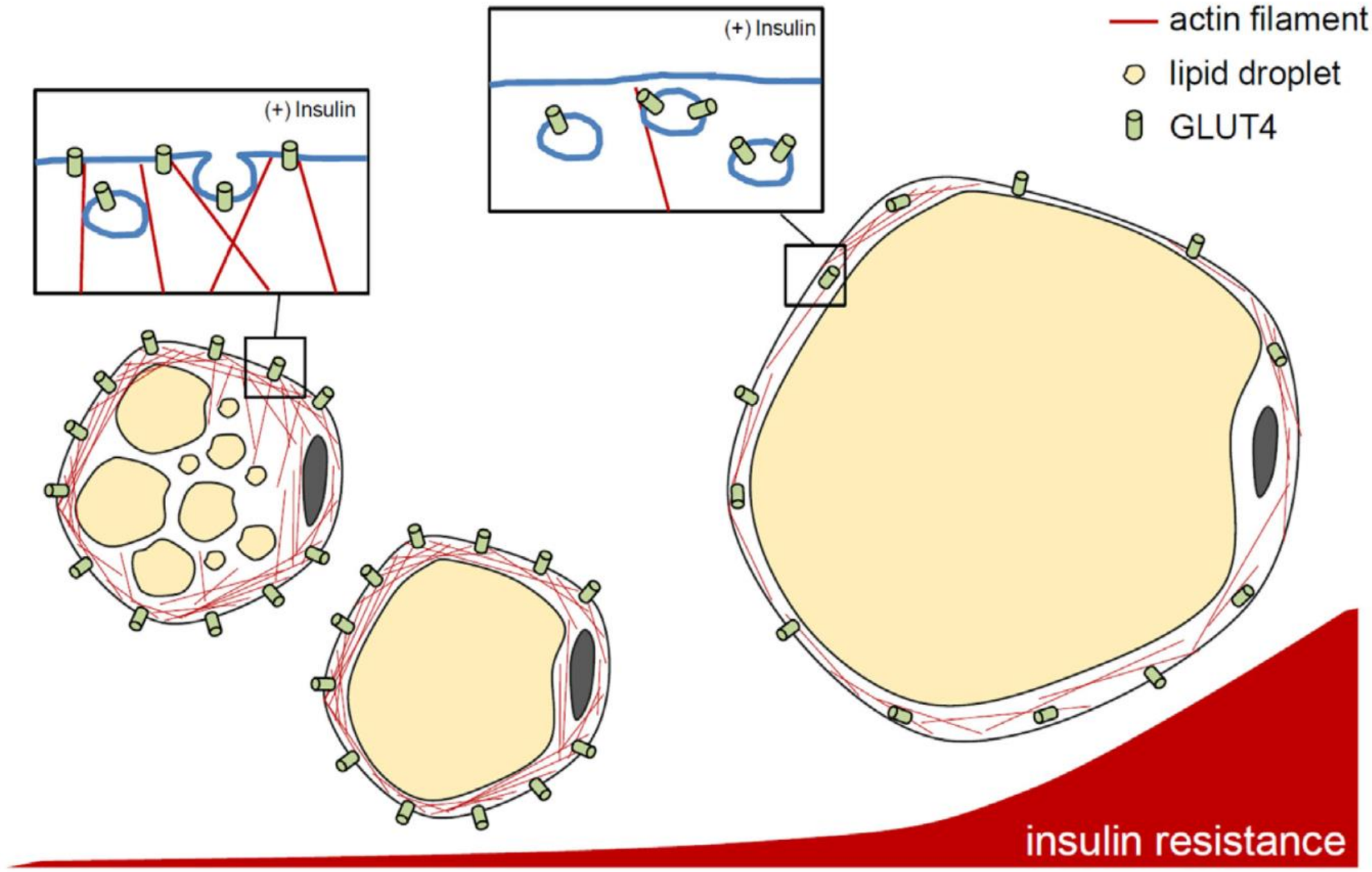


Hyperplasia

- 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 ↓



Small adipocyte

- small cell size
- multilocular lipid droplets
- organized cortical actin
- intact GLUT4 translocation

Hypertrophic adipocyte

- large cell size
- unilocular-like lipid droplet
- disorganized cortical actin
- impaired GLUT4 translocation

Viewpoints on the Way to the Consensus Session

Where does insulin resistance start? The adipose tissue

PATRICIA

two variables.

The primacy of defective subcutaneous fat storage versus visceral fat enlargement in the development of metabolic complications is supported by evidence in patients with total lipodystrophy, who experience severe insulin resistance despite the lack of visceral fat. In addition, treatments that selectively augment the ability of subcutaneous tissue to take up and

PLAUSIBILITY: ADIPOSE TISSUE CAN CAUSE INSULIN RESISTANCE — Adipose tissue releases a variety of factors known to modulate insulin sensitivity, and their effects are summarized in Fig. 1.

myocardium and skeletal muscle, and in the liver in states of insulin resistance and/or in steatosis (8–10), and recent evidence supports a role of β-cell oxidative stress in mediating FA-induced β-cell dysfunction (11). Local production of re-

levels are predictive of hepatic steatosis and insulin resistance. However, the observation that weight loss has a dramatic effect on insulin sensitivity without change in the plasma adiponectin concentration mitigates against a causal role

Priscilla Lopes-Schliep

gin with co
oss of fat f
in the neck
eveloped
melitus at 13 years of age. He had a homozygous mutation in the *BS* ne. (*B*) A
old white woman with FPLD caused by heterozygous missense mutation in the *LMN*
She had loss of fat from the extremities and trunk beginning at puberty and had ex
accumulation in the face and neck region. She had surgical removal of fat from the chin, neck,
axillae, and mons pubis. She had acanthosis nigricans in the axillae and groin.

Lipodystrophy: metabolic insights from a rare disorder

Isabel Hu **ge**[1]

[1]Metabolic Re Cambridge,
Hills Road, Ca
(Corresponde

Abstract

Obesity, in hy patients
are among model for
mortality . Indeed, as
understand ndromes is
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extreme p evelopment
similarities in adipose
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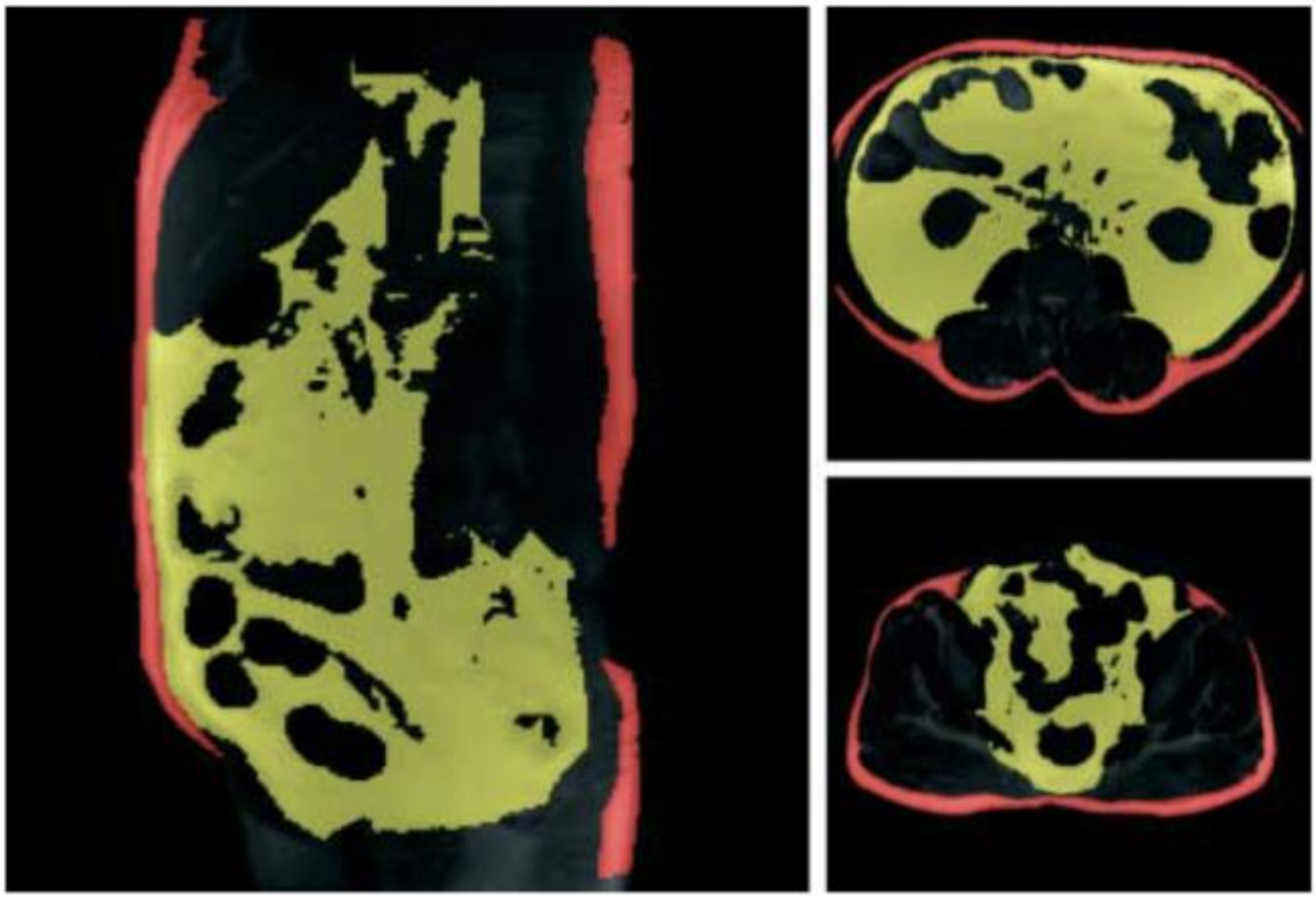

Figure 1 Fat distribution in a patient with familial partial lipodystrophy (FPLD) due to a heterozygous R482W *LMNA* mutation. Note the striking paucity of subcutaneous fat (highlighted in red) and abundant visceral fat (highlighted in yellow). The image on the left is a sagittal T1-weighted MRI image, whereas those on the right are transverse abdominal (upper right panel) and gluteal (lower right panel) images.

Mouse models of inherited lipodystrophy

David B. Savage[1]

Insulin resistance is a major
between obesity and diabet
remarkably similar to those
a rare disease. In both cases
muscle, where it plays a cen
lipodystrophies are characte
Genetically engineered mice
including hyperphagia, fatty
tractable model of the huma
humans has been more diffi
generalised lipodystrophy, i
studies have been instrume
lipid accumulation and insu
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difficulties in generating mo
fat depots and the apparent
dramatic differences presen

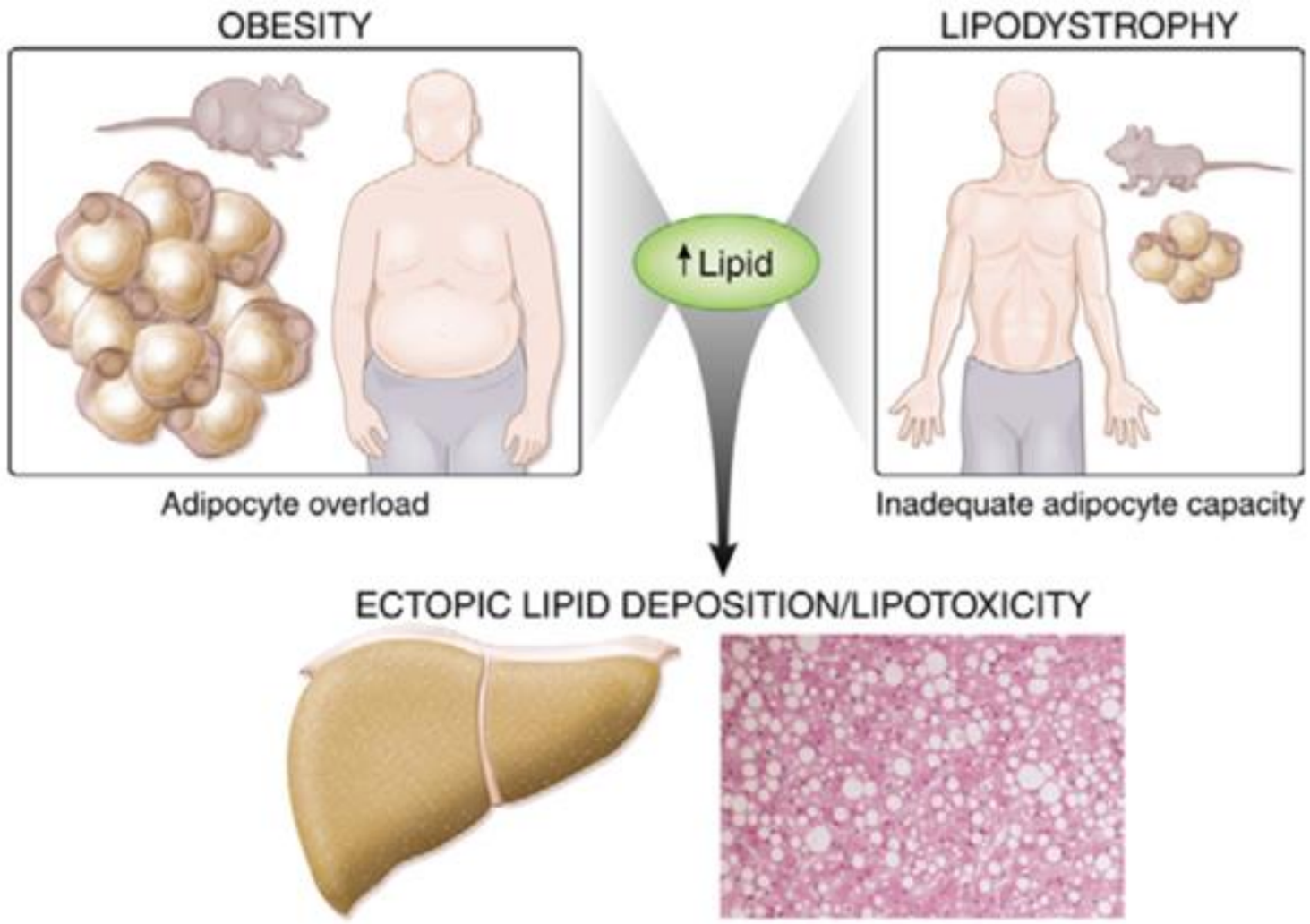
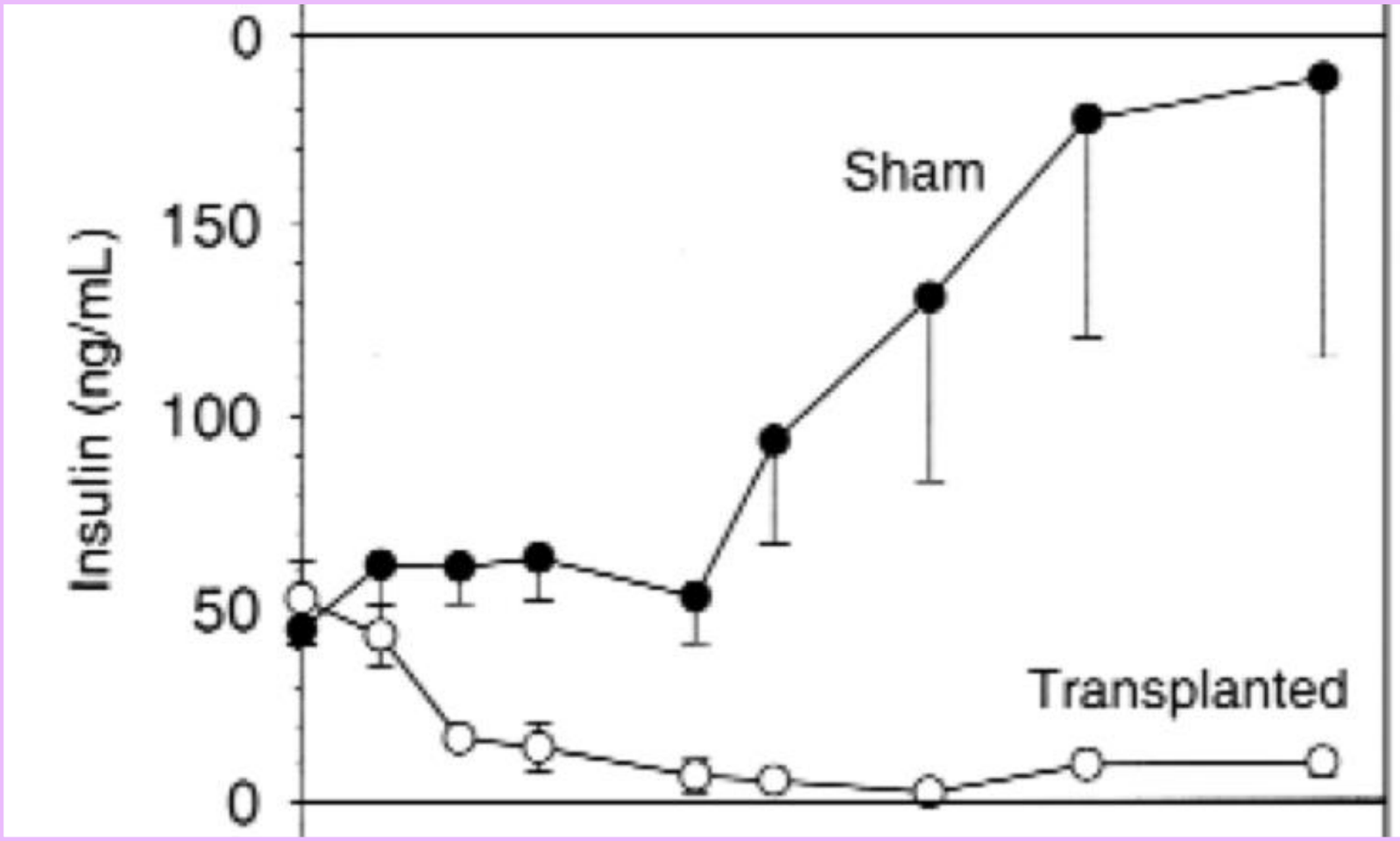
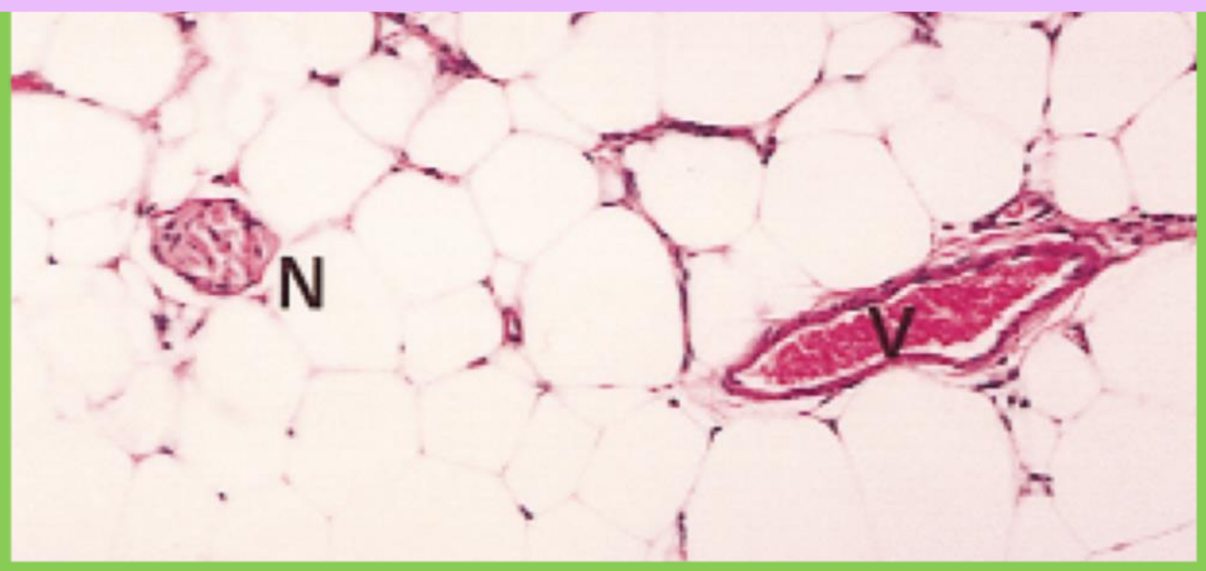


Fig. 1. Schematic illustration of the 'lipid overflow' hypothesis. The 'lipid overflow' hypothesis proposes that the capacity of adipose tissue to accommodate excess energy in the form of triglyceride is finite. Exceeding this limit leads to ectopic lipid accumulation and insulin resistance. This scenario occurs typically in obesity-associated insulin resistance. Lipodystrophy is an extreme example of reduced adipose tissue 'capacity' and is characterised by severe ectopic lipid accumulation/insulin resistance.

Surgical implantation of adipose tissue rev
diabetes in lipoatrophic mice





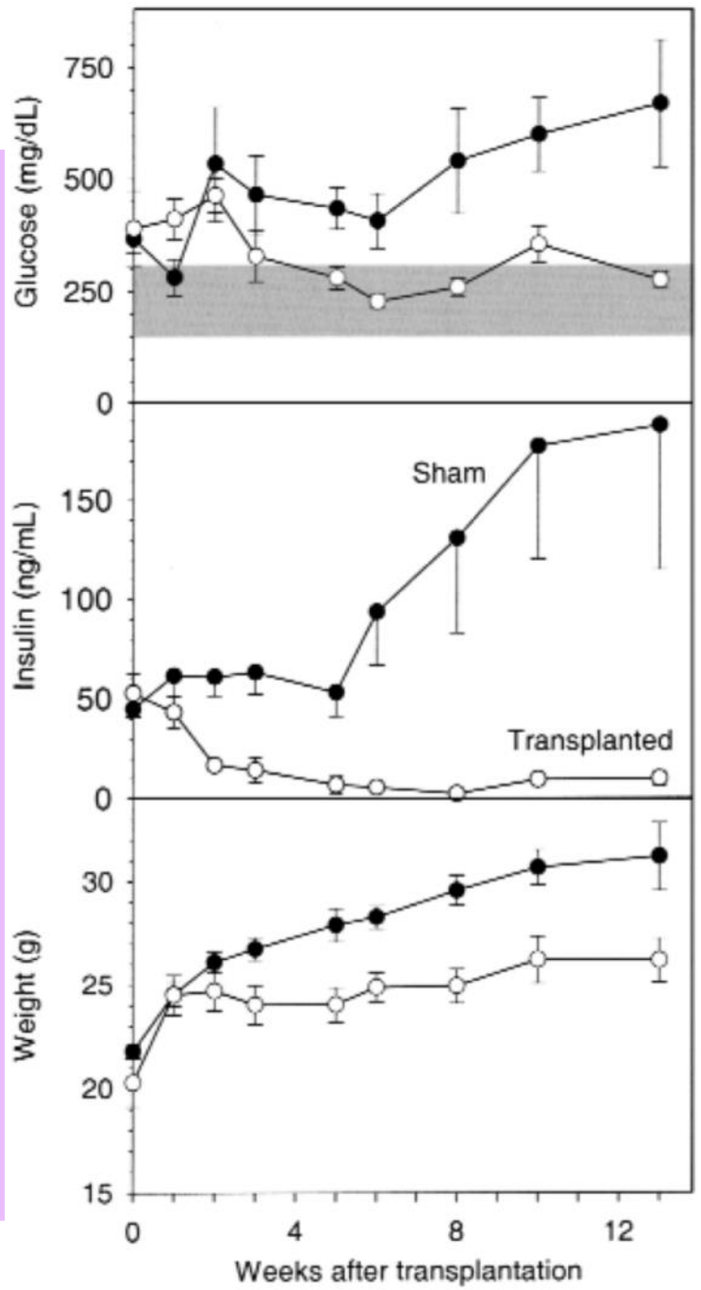


Figure 2
Fat transplantation improves plasma glucose and insulin levels and reduces postweaning growth in A-ZIP/F-1 mice. The sham-operated (filled circles [*n* = 5, except *n* = 3 at 13 weeks]) and transplanted animals (open circles [*n* = 6], 900 mg of parametrial fat) were significantly different beginning 5 weeks after transplantation for glucose, 2 weeks for insulin, and 3 weeks for body weight. The shaded region is the normal range for plasma/serum glucose for fed FVB/N mice (mean ± 2 SD; 150–306 mg/dL; *n* = 84).

Viewpoints on the Way to the Consensus Session

Where does insulin resistance start? The adipose tissue

PATRICIA IOZZO, MD, PHD

Adipose tissue is a heterogeneous organ with respect to embryonic origin, body distribution, and function. In addition to playing a major role in the regulation of nutrient and energy homeostasis, it is involved in the modulation of the immune response, reproductive function, hemostasis, mechanical support, bone mass growth, and thermogenesis.

To postulate that insulin resistance starts in adipose tissue, there should be evidence of *1*) potential mechanisms for such a causal relationship, 2) the manifestation of such mechanisms in insulin-resistant individuals, and *3*) their early occurrence in the development of insulin resistance.

PLAUSIBILITY: ADIPOSE TISSUE CAN CAUSE INSULIN RESISTANCE — Adipose tissue releases a variety of factors known to modulate insulin sensitivity, and their effects are summarized in Fig. 1.

Fatty acids

The concept that fatty acids (FAs) provoke cardiac, skeletal muscle, and hepatic insulin resistance and impair β-cell function has been extensively confirmed in humans, and mechanisms are reviewed in detail elsewhere (1). A sustained pharmacologic inhibition of lipolysis, with reduction in the plasma FA concentration, reverses these defects (2–4). Elevated FA levels also promote the synthesis and release of VLDL by the liver by *1*) increasing substrate availability, *2*) inhibiting insulin-mediated apoB degradation (5), and *3*) reducing hepatic insulin clearance, contributing to hyperinsulinemia. In the brain, excessive FA uptake and its response to weight loss have been documented in subjects with the metabolic syndrome (6), and FAs are implicated in the central regulation of glucose production (7).

FA overflow from adipocytes to skeletal muscle and other tissues may result in free radical formation during oxidative phosphorylation, the intramyocellular accumulation of triglyceride, and the production of toxic lipid metabolites (fatty-acyl CoAs, diacylglycerol, and ceramides) and metabolic intermediates, which reflect oxidative damage (4), both of which can interfere with the insulin signaling cascade. Consistent with this hypothesis, lipid oxidation is increased systemically and regionally, i.e., in the myocardium and skeletal muscle, and in the liver in states of insulin resistance and/or in steatosis (8–10), and recent evidence supports a role of β-cell oxidative stress in mediating FA-induced β-cell dysfunction (11). Local production of reactive oxygen species within adipose tissue likely initiates lipotoxicity and insulin resistance at the immediate site of FA release (12). Oxidative damage is amplified by peroxidation of lipid stores and could, in turn, impair mitochondrial function and insulin sensitivity and produce inflammation in different target organs.

Adipokines

Adipose tissue is the largest endocrine organ in the body and generates multiple signals that regulate metabolism in other tissues. Leptin acts centrally to enhance the resting metabolic rate and decrease appetite, thus reducing tissue triglyceride accumulation. In lipodystrophic humans with severe insulin resistance, the administration of leptin restores insulin sensitivity and reduces organ steatosis and hyperglycemia (13). However, leptin deficiency and resistance are rare causes of disease in humans. Interestingly, leptin receptors have been identified in the vessel wall, and leptin infusion increases arterial blood pressure (14). Adiponectin is produced by adipose tissue in inverse amounts to the fat mass and is one relevant mediator of the action of peroxisome proliferator–activated receptor-γ (PPAR-γ) agonists. Administration of adiponectin reverses the insulin resistance associated with obesity or lipodystrophy by reducing FA and triglyceride levels (15). Plasma adiponectin concentrations typically are reduced in obese normal glucose tolerant, insulin-resistant and lean, and obese type 2 diabetic subjects, and decreased plasma adiponectin levels are predictive of hepatic steatosis and insulin resistance. However, the observation that weight loss has a dramatic effect on insulin sensitivity without change in the plasma adiponectin concentration mitigates against a causal role of this hormone in the pathogenesis of insulin resistance (16). The role of resistin, which is elevated in animal models of obesity and diabetes, and of visfatin and omentin (which are produced by visceral fat) in the development of insulin resistance remains controversial.

Adipocytokines

Tumor necrosis factor (TNF)-α stimulates adipose tissue lipolysis, promotes VLDL production (17), interferes with insulin signaling and expression of adiponectin, and increases the expression of interleukins. In humans, tissue expression, rather than circulating levels of TNF-α, correlates with obesity and insulin resistance (18). Interleukin (IL)-6 also is associated with insulin resistance, increased fat mass, and elevated circulating FA levels, consistent with the lipolytic action of this cytokine. IL-6 interferes with the insulin signaling pathway in hepatocytes, skeletal muscle, and adipose tissue (19) and inhibits the production of adiponectin.

From the Institute of Clinical Physiology, National Research Council (CNR), Pisa, Italy.
Corresponding author: Patricia Iozzo, patricia.iozzo@ifc.cnr.it.
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DOI: 10.2337/dc09-S304

namic features, and this could explain the relatively weak correlation between the two variables.

The primacy of defective subcutaneous fat storage versus visceral fat enlargement in the development of metabolic complications is supported by evidence in patients with total lipodystrophy, who experience severe insulin resistance despite the lack of visceral fat. In addition, treatments that selectively augment the ability of subcutaneous tissue to take up and store fat (including glitazones in humans and subcutaneous fat re-implantation in animals [43]) have a major impact to reverse insulin resistance and normalize metabolic risk factors without modifying (or even increasing) the total mass of ectopic fat depots. Conversely, liposuction fails to correct the metabolic disturbances, i.e., insulin resistance and glucose intolerance, in obese humans (44); this

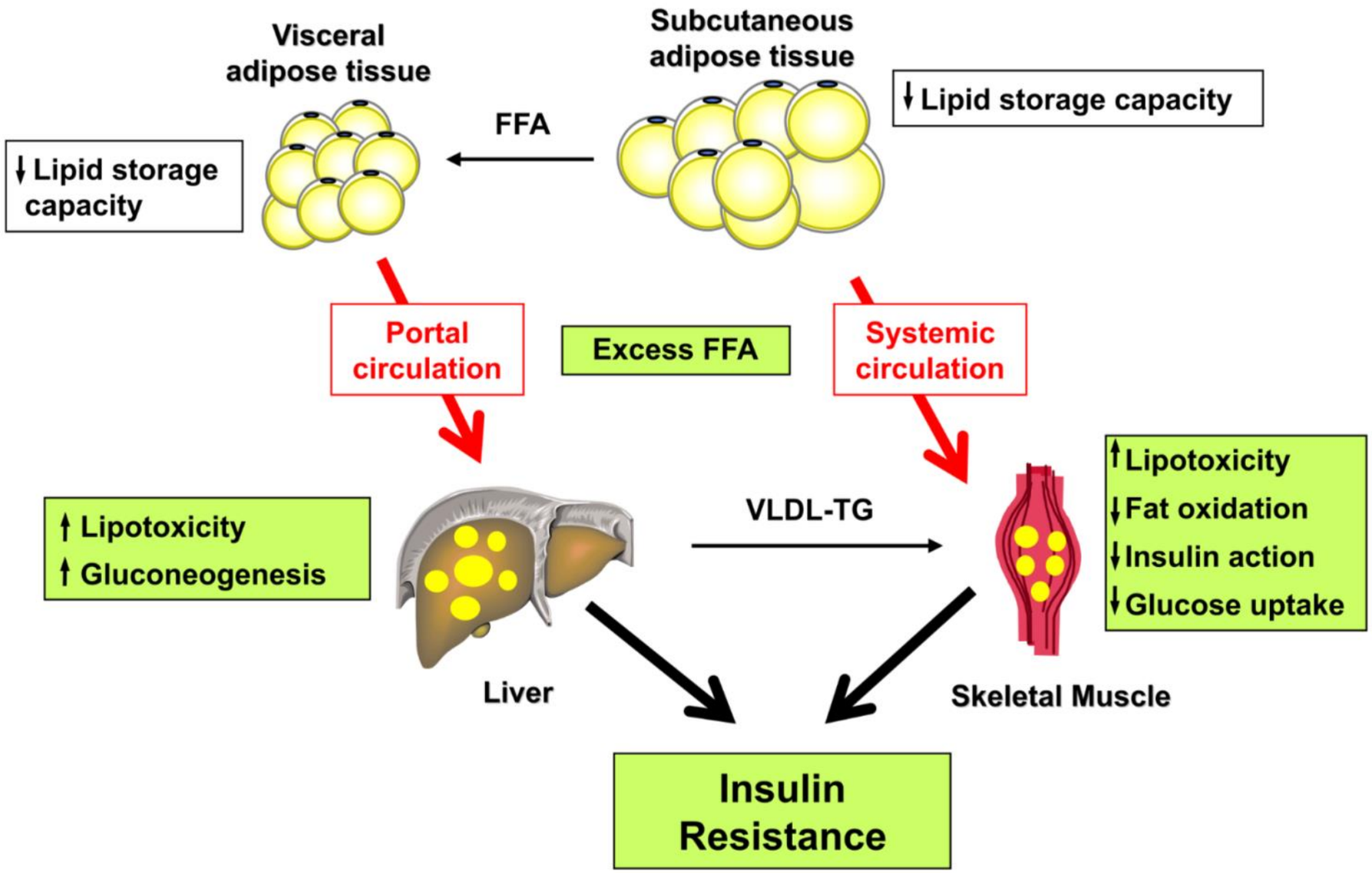
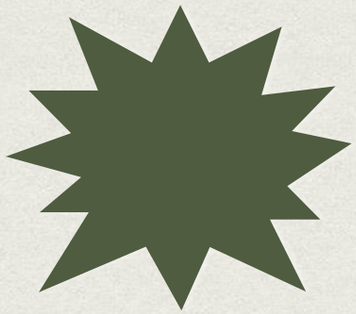
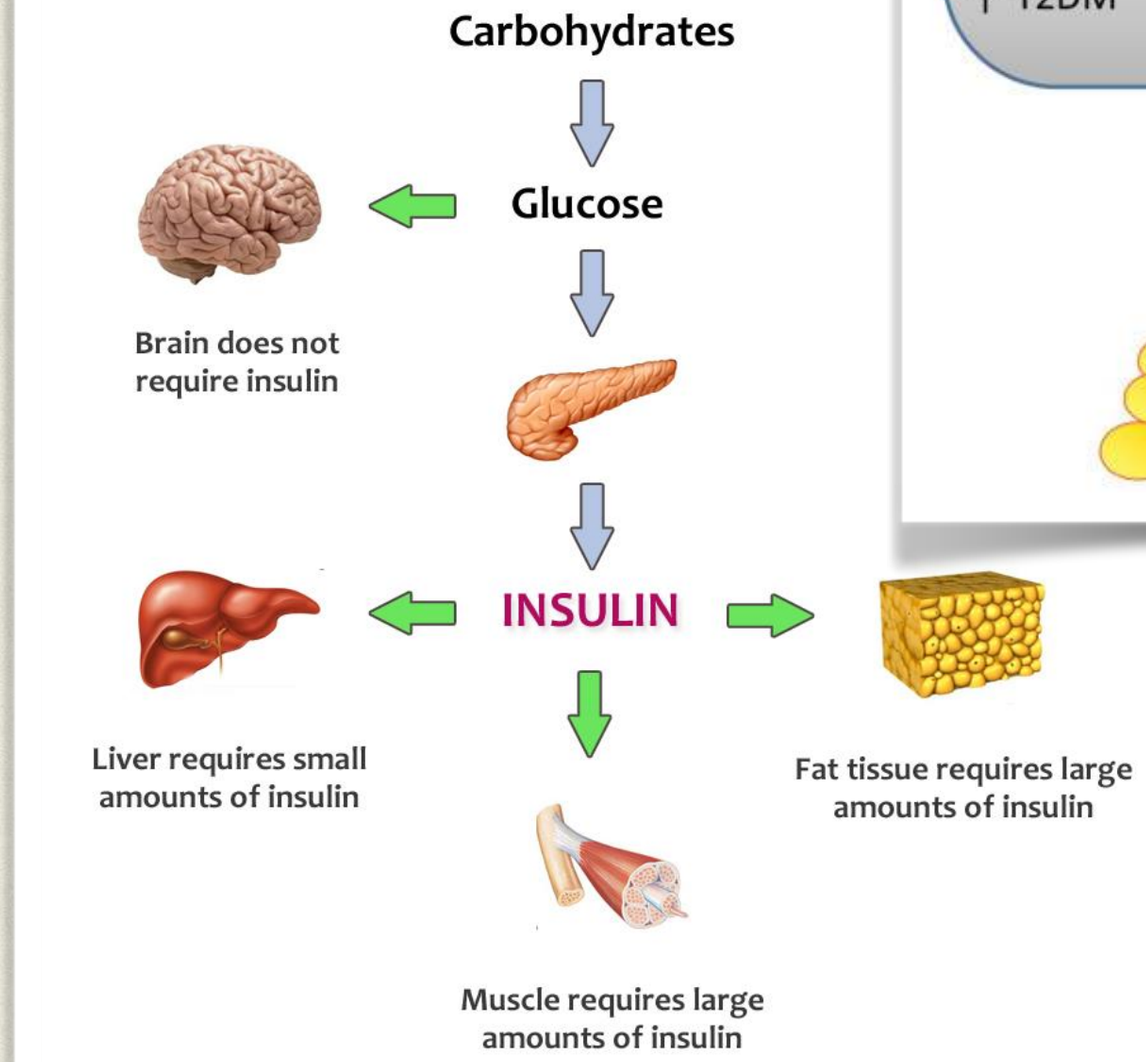
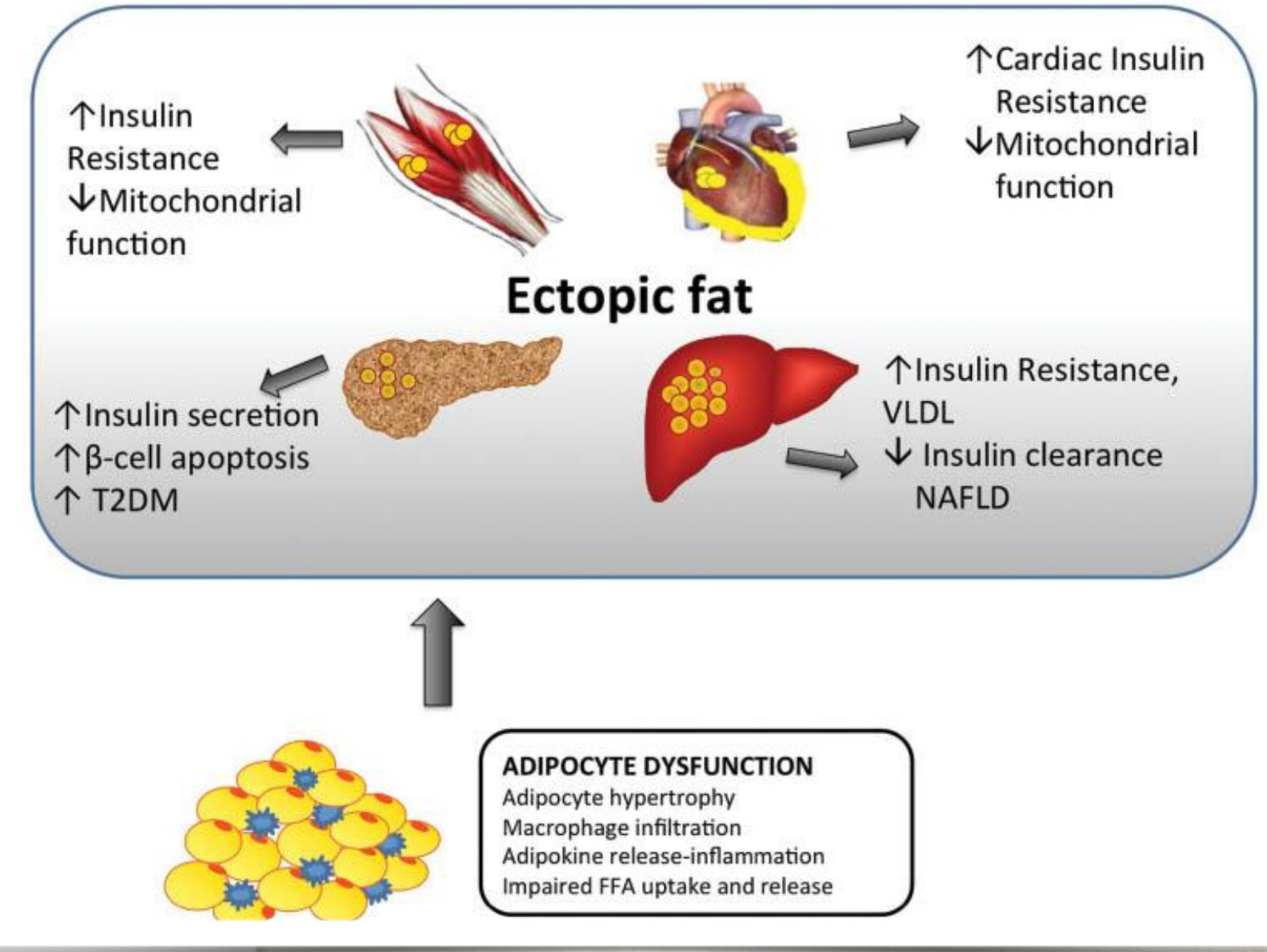
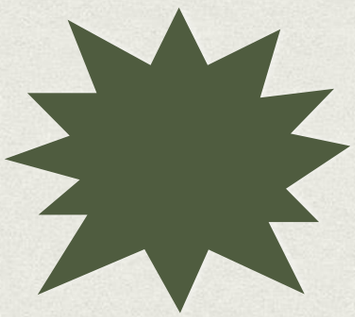


Fig. 1. Model for fat-induced insulin resistance describing how a failure to appropriately store lipids into subcutaneous adipose tissue (quantitatively predominant) will lead to ectopic lipid deposition into visceral fat and insulin-sensitive tissues such as liver and skeletal muscle. These tissues will progressively develop a state of lipotoxicity, altering insulin signaling and action and contributing to whole body insulin resistance and deterioration of glucose tolerance.

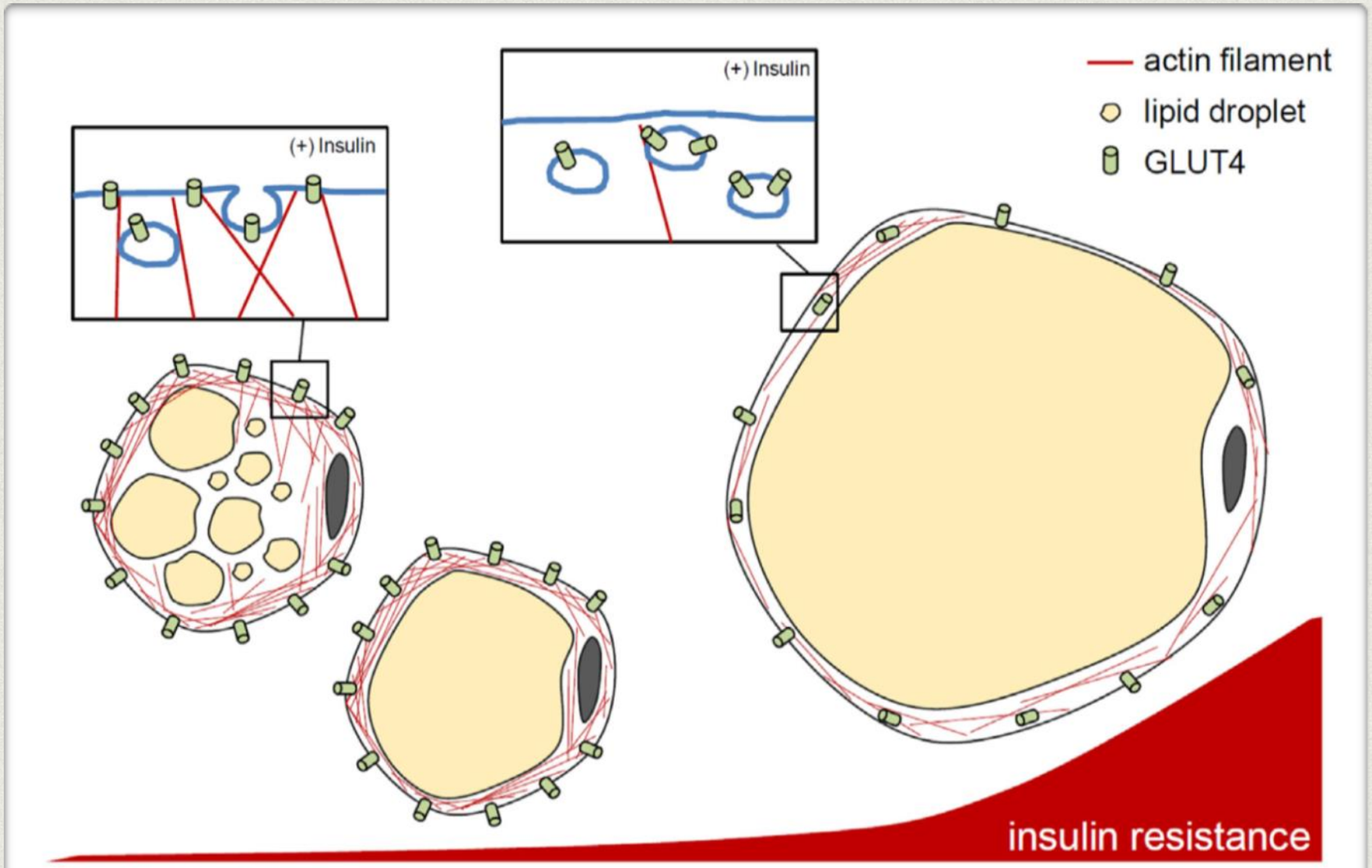



Carbohydrates
Glucose
Brain does not require insulin
INSULIN
Liver requires small amounts of insulin
Fat tissue requires large amounts of insulin
Muscle requires large amounts of insulin


↑Insulin Resistance
↓Mitochondrial function
↑Cardiac Insulin Resistance
↓Mitochondrial function
Ectopic fat
↑Insulin secretion
↑β-cell apoptosis
↑ T2DM
↑Insulin Resistance, VLDL
↓ Insulin clearance
NAFLD
ADIPOCYTE DYSFUNCTION
Adipocyte hypertrophy
Macrophage infiltration
Adipokine release-inflammation
Impaired FFA uptake and release



YOU ARE INSULIN RESISTANT BECAUSE YOU FILLED UP YOUR ADIPOCYTES.



Small adipocyte

- small cell size
- multilocular lipid droplets
- organized cortical actin
- intact GLUT4 translocation

Hypertrophic adipocyte

- large cell size
- unilocular-like lipid droplet
- disorganized cortical actin
- impaired GLUT4 translocation

Role of a critical visceral adipose tissue threshold (CVATT) in metabolic syndrome: implications for controlling dietary carbohydrates: a review

Eric S Freedland*

Address: Boston Universi

Email: Eric S Freedland*

* Corresponding author

Published: 05 November 2

Nutrition & Metabolism 20

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enzymes that normally are involved in fat oxidation

[231]. The net effect could prevent further weight gain and might even encourage weight regain beyond the initial baseline [232], which could contribute to VAT.

Implications of Controlling Dietary Carbohydrates

Reduced fat oxidation and carbohydrates

Frisancho points out that an important contributing factor for obesity in modern as well as developing nations is a reduced fat oxidation and increased metabolism of carbohydrate. This has been brought about by a shift toward the body's preference toward oxidizing carbohydrate rather than fat – resulting in an increased deposition of body fat. In developing nations, obesity can co-exist with developmental undernutrition, which can result in obesity with short stature [233].

A solution to reducing the ectopic fat, as well as VAT, burden would be to enhance its oxidation in nonadipose tissues, e.g., liver, pancreas, and skeletal muscle. This will

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Ectopic Fat in Insulin Resistance, Dyslipidemia, and Cardiometabolic Disease

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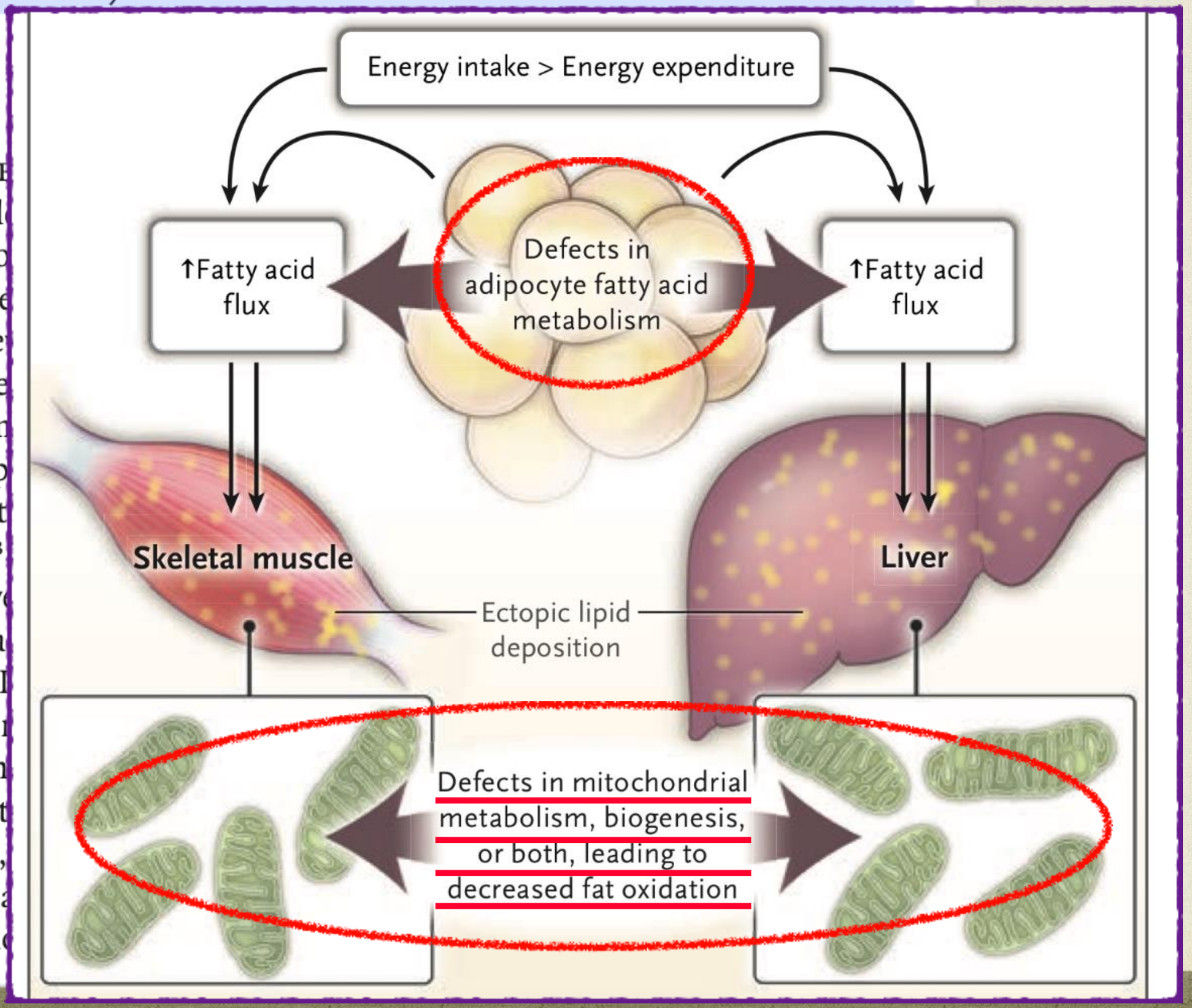

Minireview: Mitochondrial Energetics and Insulin Resistance

Anthony E. Civitarese and Eric Ravussin

Pennington Biomedical Research Center, Baton Rouge, Louisiana 70808

Obesity, insulin resistance, type 2 diabetes mellitus, and aging are associated with impaired skeletal muscle oxidation capacity, reduced mitochondrial content, and lower rates of oxidative phosphorylation. Several studies have reported ultrastructural abnormalities in mitochondrial morphology and reductions in mitochondrial mass in insulin-resistant individuals. From lower organisms to rodents, mitochondrial membrane structure, function, and programmed cell death are regulated in part by the balance between the opposing forces of mitochondrial fusion and fission, suggesting they may also play an important role in human physiology. (*Endocrinology* 149: 950–954, 2008)

Healthy

Age-Diminished

Family History of Diabetes Links Impaired Substrate Switching and Reduced Mitochondrial Content in Skeletal Muscle

Barbara Ukropcova, Olga Sereda, Lilian de Jonge, Iwona Bogacka, Tuong Nguyen, Hui Xie, George A. Bray, a

Insulin resistance i
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acids to glucose in
to fat oxidation in
hypothesized to co
jective of this study
in substrate switchi
linked to reduced
fore the developme
measured in young
(n = 34) a famil
hyperinsulinemic cl
idation measured i
HFD. Muscle mitoc
subjects with high
uted 49% of the va
diabetes were infle
oxidation and mus
differ in the amou
inflexibility, lower
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family history of di
sic metabolic defec
of insulin resistanc

endocrine signal(s) necessary to

might be delayed or absent. Our results do not support this view, since adaptation to a HFD was not associated with changes in adiponectin, leptin, or FFAs, factors that are known to influence fat oxidation in skeletal muscle (43).

Mitochondrial mass, structure, and function are altered in insulin resistance (44,45). Defects of mitochondria are believed to contribute to impaired fat oxidation and to the accumulation of intramyocellular lipid intermediates, which contribute to the pathogenesis of insulin resistance (16). Mitochondrial dysfunction in the elderly and in the offspring of diabetic patients is well documented (24,46,47). Ritov et al. (45) demonstrated a reduction in mtDNA content in skeletal muscle in obese and type 2 diabetic subjects. Similarly, we show that mtDNA content in skeletal muscle is inversely correlated with BMI and body fat and is positively associated with insulin sensitivity, metabolic flexibility, aerobic capacity, and maximal HFD-induced fat oxidation, measured as sleep RQ, in healthy young adults. Skeletal muscle mitochondrial content may link these metabolic phenotypes, supporting the hypothesis that reduced mitochondrial mass is a common underlying disorder of inflexible/inadaptable/insulin-resis-

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HFD is
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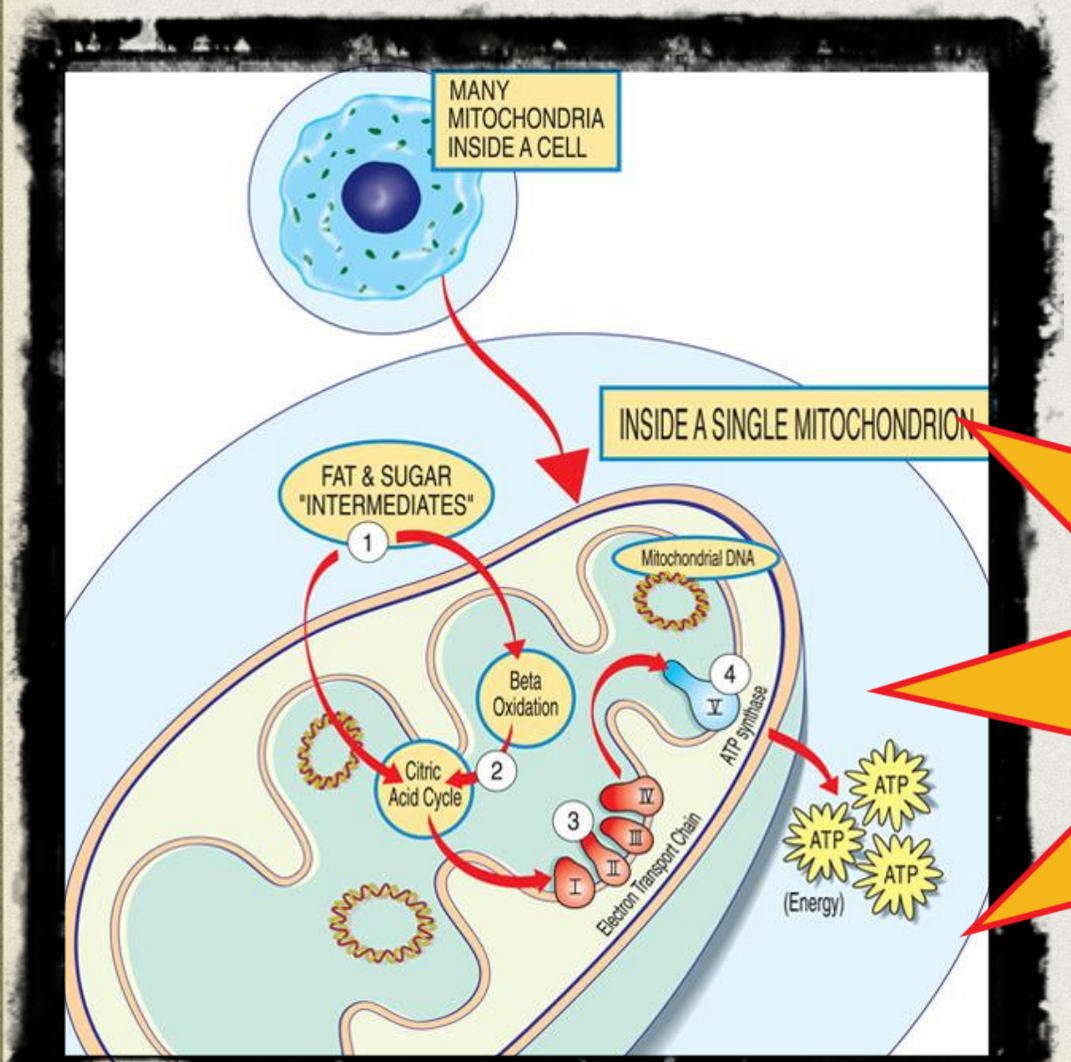
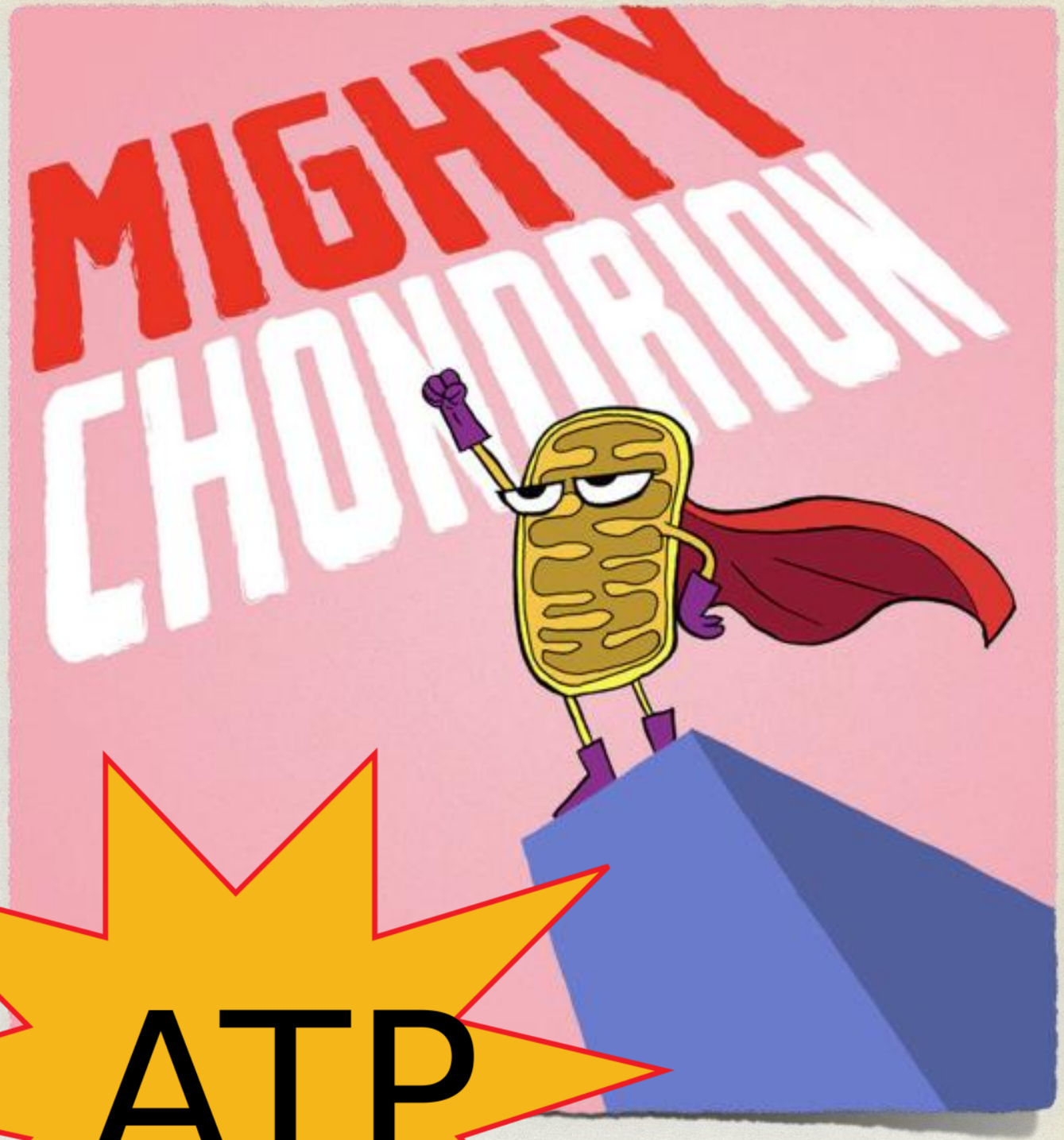
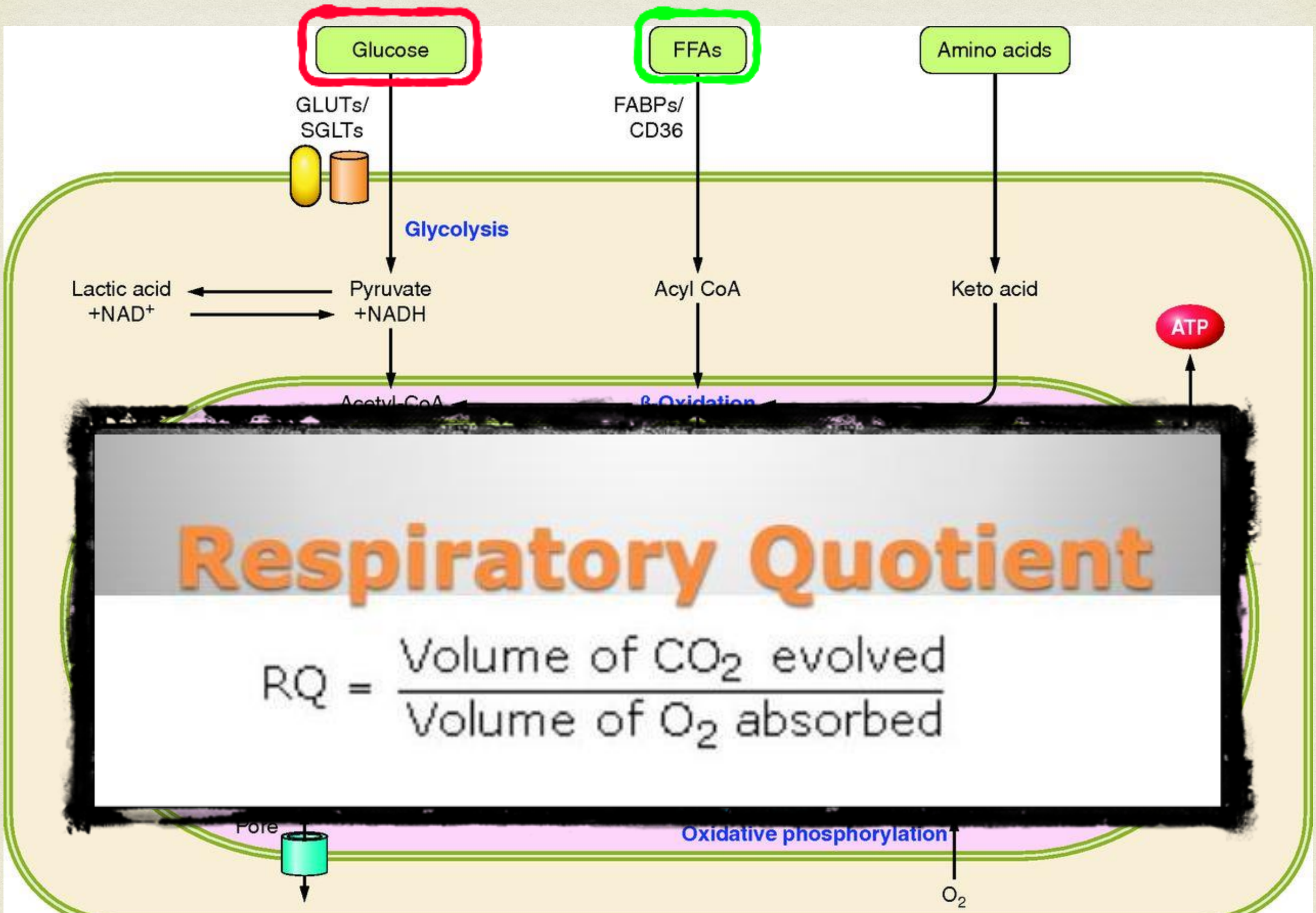

MANY
MITOCHONDRIA
INSIDE A CELL
INSIDE A SINGLE MITOCHONDRION
FAT & SUGAR
"INTERMEDIATES"
1
Mitochondrial DNA
Beta
Oxidation
4
V
ATP synthase
Citric
Acid Cycle
2
3
IV
III
II
I
Electron Transport Chain
ATP
ATP
ATP
ATP
(Energy)

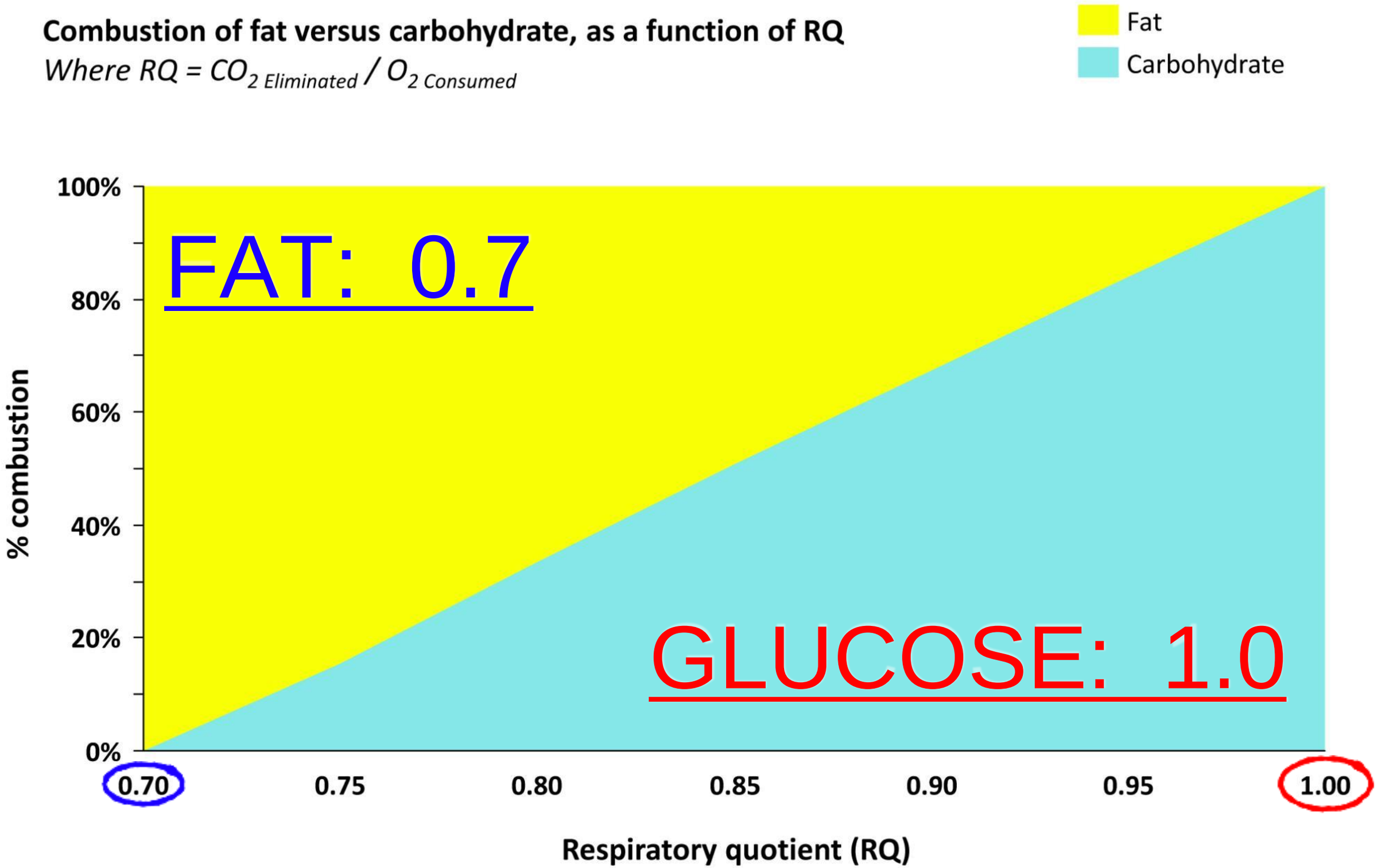

MIGHTY
CHONDRION

ATP


Glucose
FFAs
Amino acids
GLUTs/
SGLTs
FABPs/
CD36
Glycolysis
Lactic acid
+NAD+
Pyruvate
+NADH
Acyl CoA
Keto acid
ATP
Acetyl-CoA
β-Oxidation
Respiratory Quotient
RQ = Volume of CO2 evolved / Volume of O2 absorbed
Pore
Oxidative phosphorylation
O2

Combustion of fat versus carbohydrate, as a function of RQ

Where RQ = $CO_{2\ Eliminated}$ / $O_{2\ Consumed}$



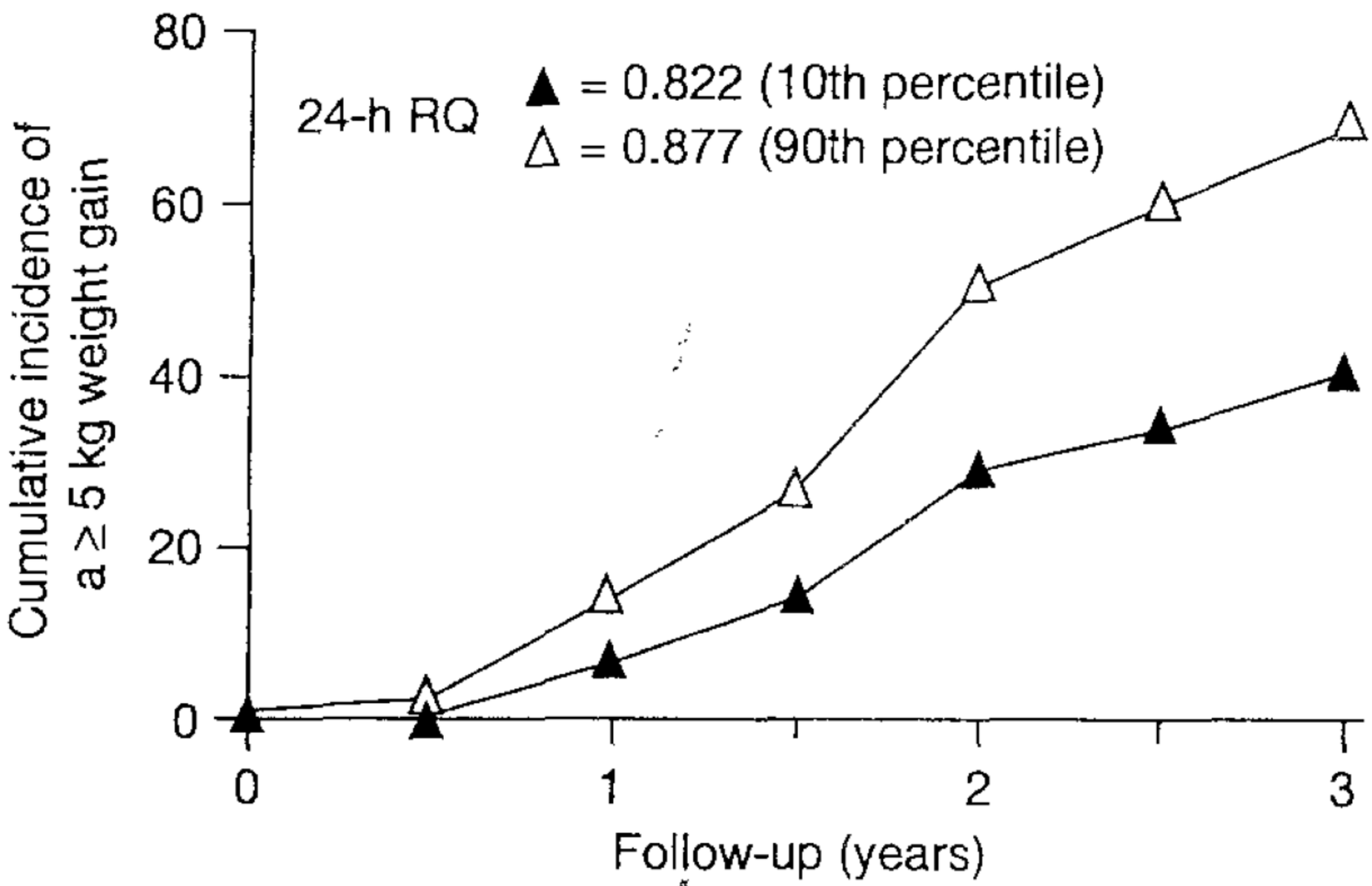


Fig 2. High 24-hour RQ as a predictor of body weight gain.

Fasting respiratory quotient as a predictor of weight changes in non-obese women

Conclusion

Our results support the hypothesis that post-absorptive RQ may be a predictor of weight changes in non-obese women studied in free living conditions. Although energy balance and diet composition immediately prior to RQ measurement were not strictly controlled in the present study, defective fat oxidation remains a likely explanation for this finding.

Article

Individuals with Metabolically Healthy Overweight/Obesity Have Higher Fat Utilization than Metabolically Unhealthy Individuals

5. Discussion

In this investigation, we find that fasting RQ, an index of nutrient utilization assessed by indirect calorimetry, is significantly lower in individuals with metabolically healthy overweight/obesity than in those with MS and T2DM. This suggests that individuals who are healthy overweight/obese are still able, to some extent, to utilize fat in the fasting state while fat utilization is significantly reduced in individuals with unhealthy obesity (Table 2). These results could help to hypothesize that new factors are involved in the pathogenesis of T2DM and potential new therapeutic goals exist. Furthermore, in this population, we demonstrated the association between RQ and HOMA-IR, which is widely utilized as an insulin resistance index (Table 4). This result could have important implications in predicting diabetes, which must be confirmed by longitudinal studies. The mechanisms underlying

individuals with unhealthy obesity (Table 2). These results could help to hypothesize that new factors are involved in the pathogenesis of T2DM and potential new therapeutic goals exist. Furthermore, in this population, we demonstrated the association between RQ and HOMA-IR, which is widely utilized as an insulin resistance index (Table 4). This result could have important implications in predicting diabetes, which must be confirmed by longitudinal studies. The mechanisms underlying

6. Conclusions

We find that fasting fat utilization is significantly lower in individuals who are metabolically healthy overweight/obese than in those who are metabolically unhealthy. These results can help to hypothesize the factors involved in the pathogenesis of T2DM.

Fasting substrate oxidation in relation to habitual dietary fat intake and insulin resistance in non-diabetic women: a case for metabolic flexibility?

Madelaine
and Estelle

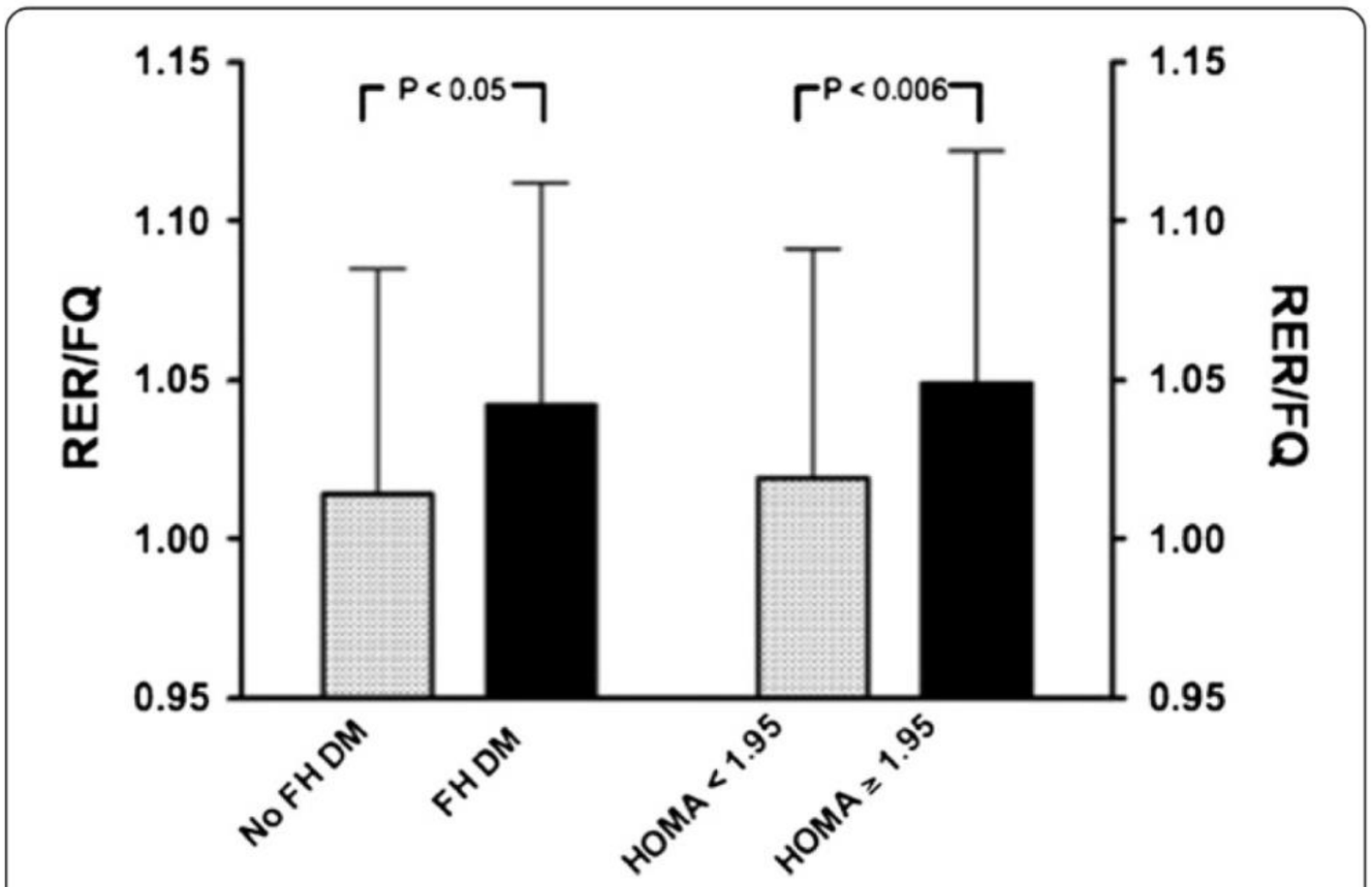


Figure 1 Fat oxidation in relation to dietary fat was lower (represented by a higher RER/FQ ratio) in persons with a family history of diabetes, and in those who were insulin resistant.

Abstract

Backgrou ... availability" has been ... macronut ... family history of ...

Methods ... se tissue area (VAT ... s], insulin resistance ... physical activity in ... assess energy in ... included (N=140). ...

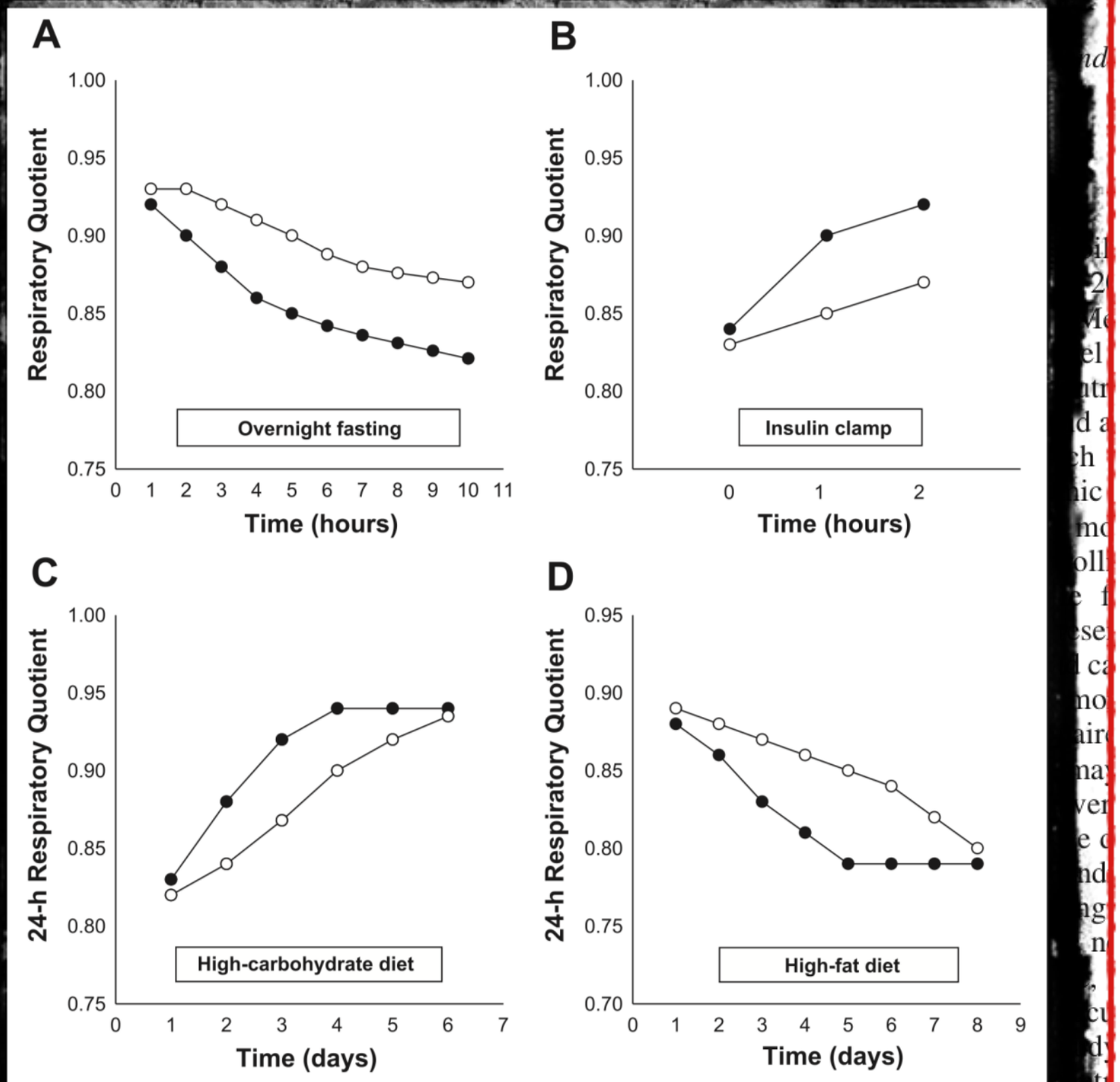
Results: ... nd lower PA levels ... veen groups. H ... and FH DM (adju ... than their counterpa ...

Conclusi ... iated with ...

Conclusion: In these apparently healthy, weight-stable women, insulin resistance and FH DM were associated with lower fat oxidation in relation to dietary fat intake, suggesting lower metabolic flexibility.

Am J Physiol Endocrinol Metab 295: E1009–E1017, 2008.
First published September 2, 2008; doi:10.1152/ajpendo.90558.2008.

Metabolic flexibility and insulin resistance



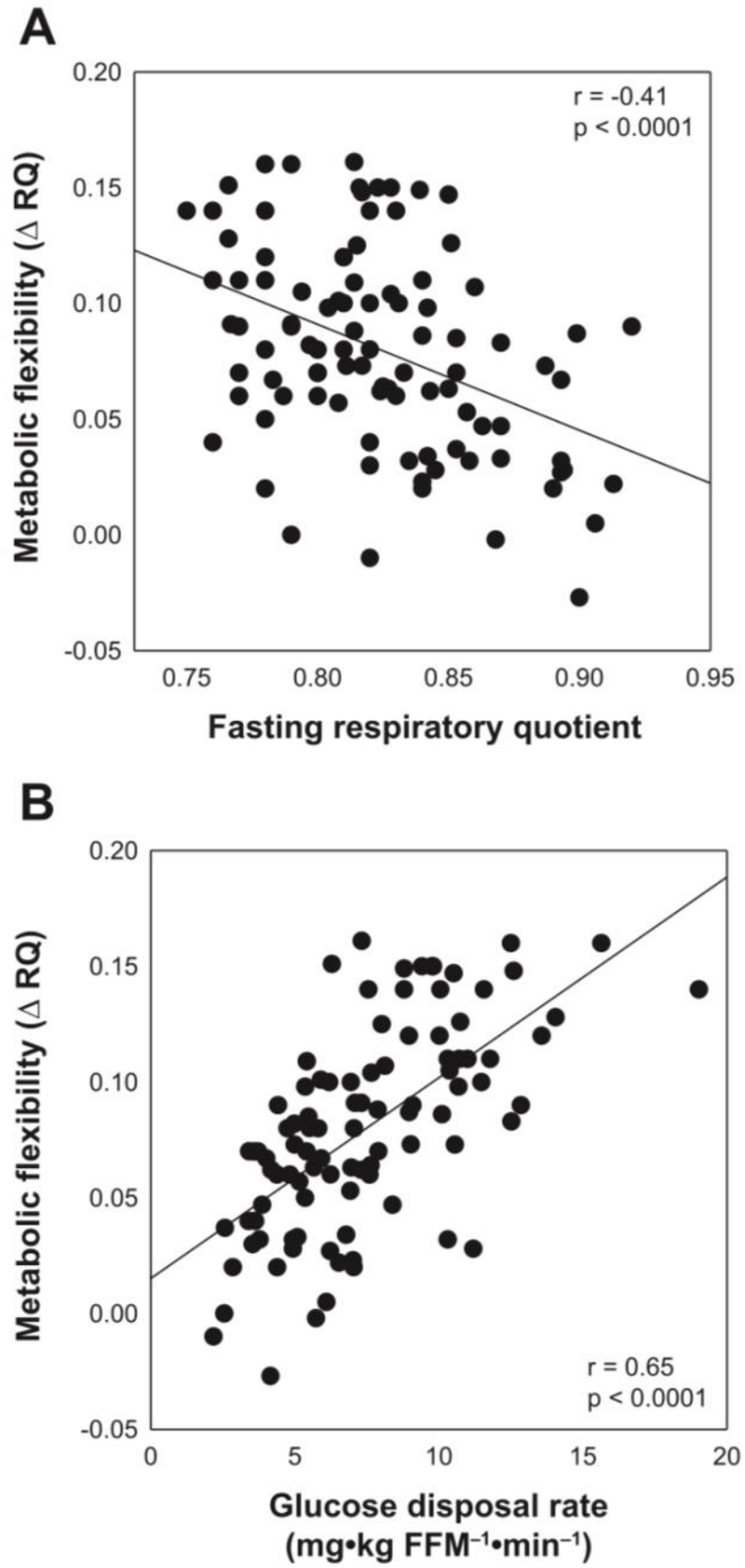
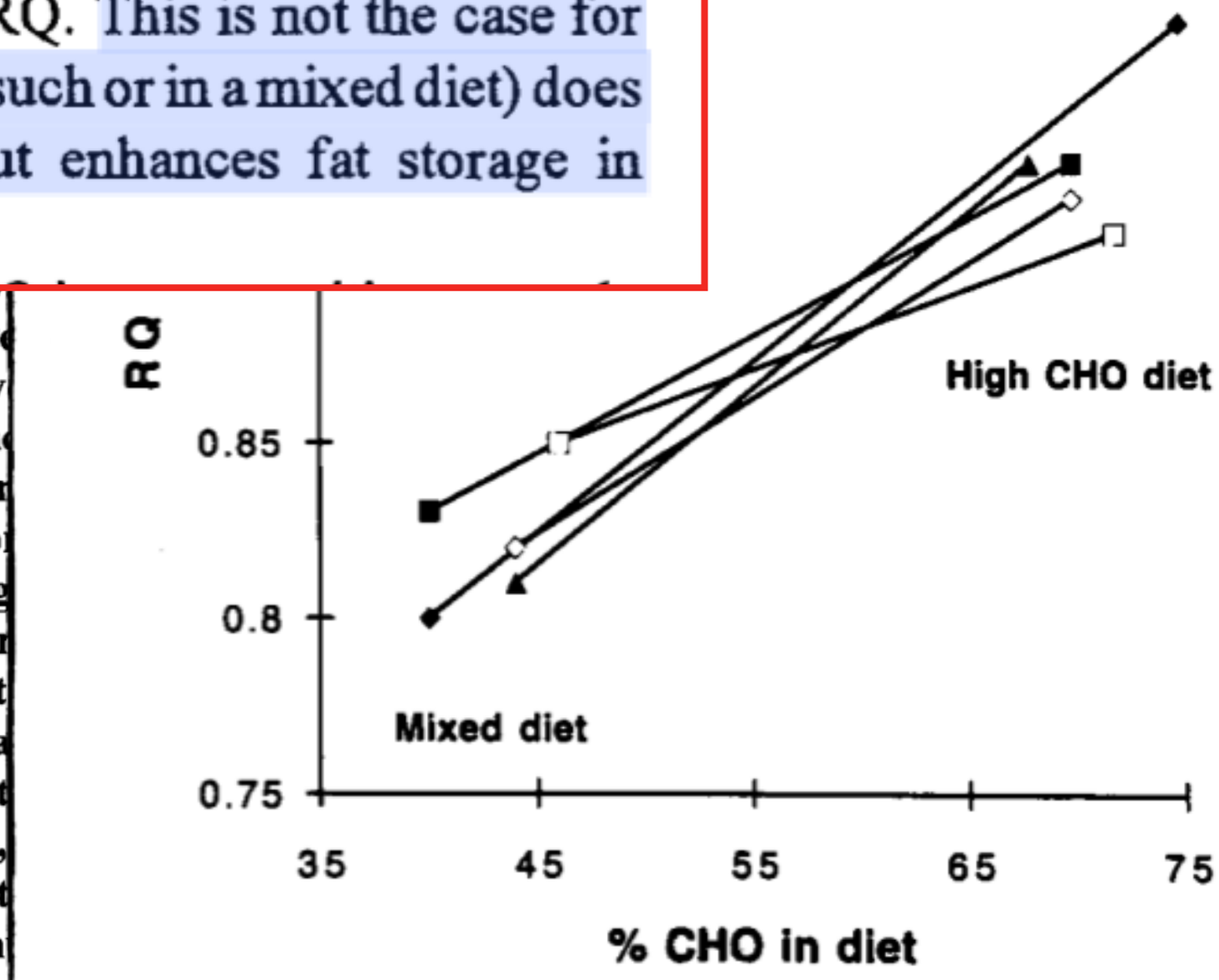


Fig. 3. Correlation between metabolic flexibility [steady-state respiratory quotient (RQ) − fasting RQ = ΔRQ] and fasting RQ (*A*) and insulin-stimulated glucose disposal rate (*B*).

Abnormalities of Fuel Utilization as Predisposing to the Development of Obesity in Humans

drate balance was reached again (15). Therefore, a surfeit of carbohydrate (as such or in a mixed diet) results in an increased carbohydrate oxidation and a lower fat oxidation, as evidenced by an increased RQ. This is not the case for fat; i.e., an excess fat intake (as such or in a mixed diet) does not stimulate fat oxidation but enhances fat storage in adipose tissue (5,19).

in post-obese European women investigat
the cessation of a hypocaloric diet. It is w
numerous exogenous and endogenous fa
the RQ at rest such as: the level of feedi
negative energy balance), the compositio
(high vs. low carbohydrate), the size of the g
the amount of adipose tissue as well as ge
should be stressed that some nutritional sit
exist during which a low ratio of fat to ca
observed (i.e., a high RQ) despite weight
more, in most studies mentioned above,
carbohydrate oxidation ratio explains less t
variance in weight gain, suggesting that n
tional factors also play a substantial role
weight gain.



Glucose and insulin-induced inhibition of fatty acid oxidation: the glucose-fatty acid cycle reversed

(14). In this circumstance the increase in FFA availability far exceeds the decrease in glucose availability, and as a consequence the percent FFA taken up by tissues that are oxidized falls dramatically (14).

The notion that the availability of glucose, rather than FFA, primarily controls substrate oxidation helps to explain a variety of physiological and pathological responses. For example, it is well established that excessive carbohydrate intake increases triglyceride concentration (20), yet recent studies have revealed a limited capacity for the de novo synthesis of fatty acids in the liver (11). We propose that hypertriglyceridemia occurs because of the increased intracellular hepatic availability of fatty acids for triglyceride formation, stemming from the inhibition of their oxidation by the high glucose intake. In response to exercise, fatty acid

lipid and heparin infusion during a hyperinsulinemic-

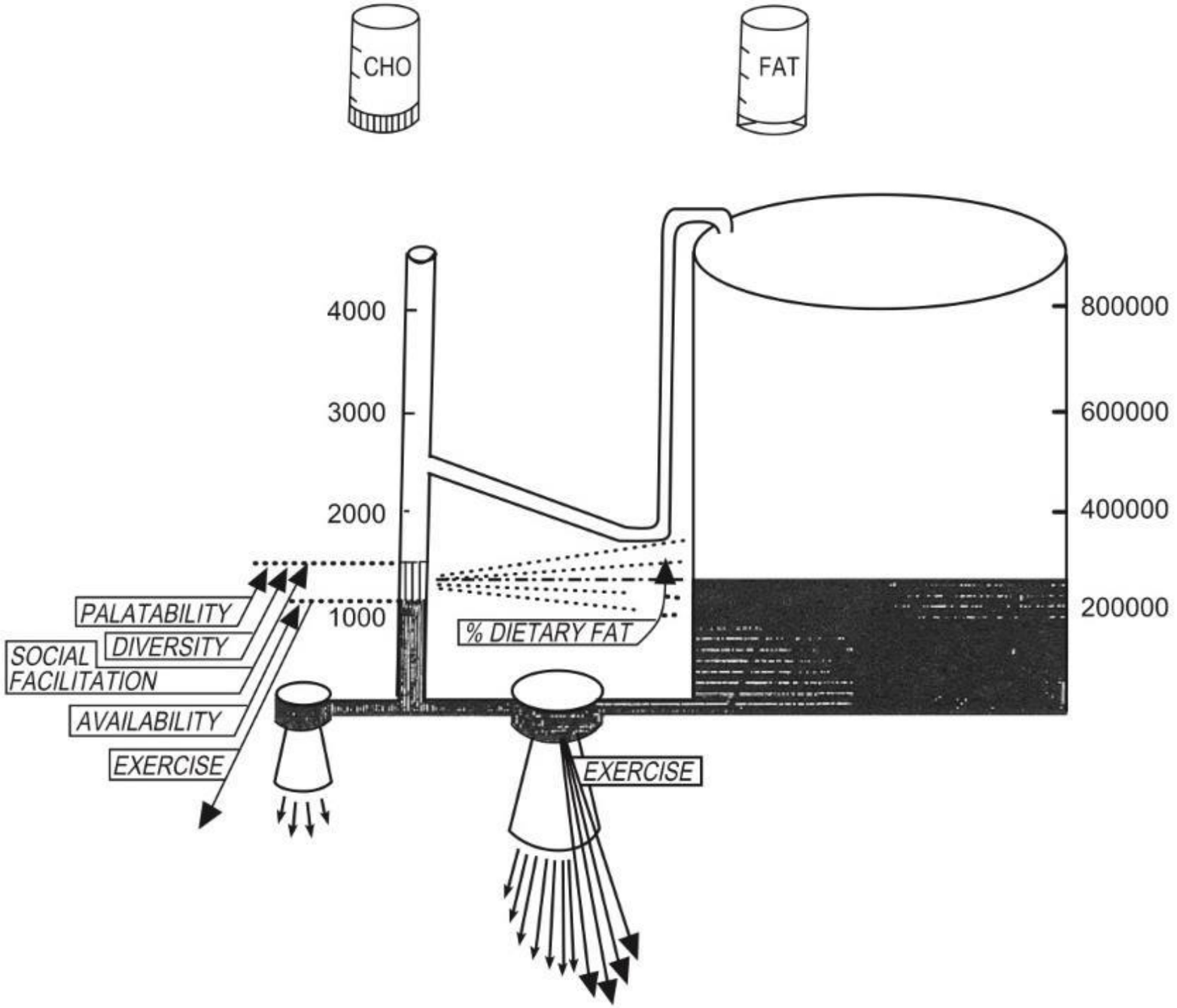
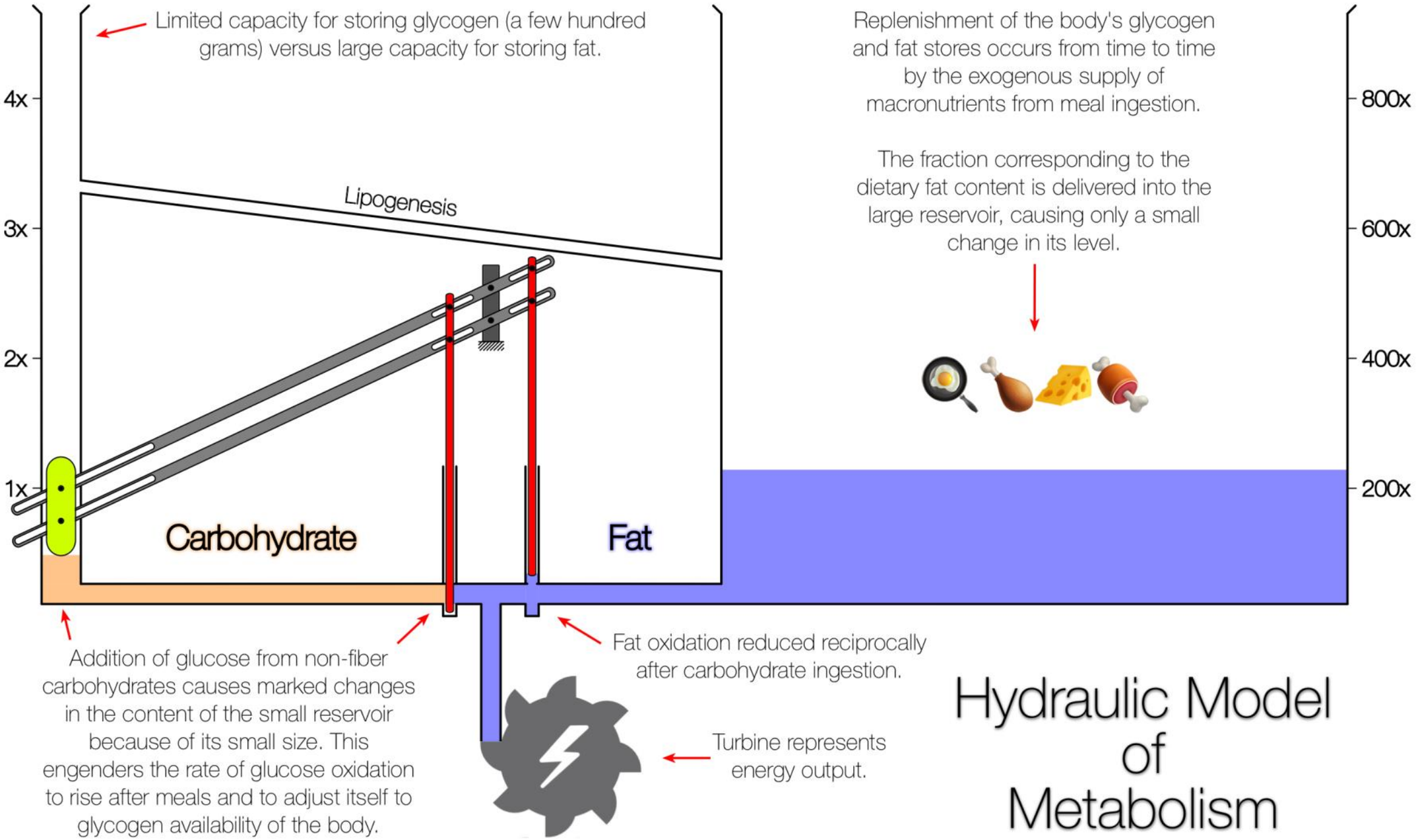


Fig. 4. Hydraulic model of Flatt [9,10], which is constituted by 2 reservoirs, a small and large one, describing that limited capacity of the body for storing glycogen (a few hundred grams) and the large capacity for storage fat (a few decakilos), respectively. There is a small turbine, which represents the exclusive use of glucose by the brain (approximately 100 g/day). The relative proportions of glucose and fatty acids used by the body (brain excluded) is represented by the large turbine and is assumed to be influenced by the proportional availability of glucose and free fatty acids. Replenishment of the body's glycogen and fat stores occurs from time to time by the exogenous supply of macronutrients (meal ingestion). The fraction corresponding to the dietary fat content is therefore delivered into the large reservoir. Addition of fuel from the meals to the large reservoir cause only a small change in its level, whereas marked changes in the content of the small reservoir occurs because of its small size. This engenders the rate of glucose oxidation to rise after meals and to adjust itself to glycogen availability of the body.


Limited capacity for storing glycogen (a few hundred grams) versus large capacity for storing fat.
Lipogenesis
4x
3x
2x
1x
800x
600x
400x
200x
Carbohydrate
Fat
Replenishment of the body's glycogen and fat stores occurs from time to time by the exogenous supply of macronutrients from meal ingestion.
The fraction corresponding to the dietary fat content is delivered into the large reservoir, causing only a small change in its level.
Addition of glucose from non-fiber carbohydrates causes marked changes in the content of the small reservoir because of its small size. This engenders the rate of glucose oxidation to rise after meals and to adjust itself to glycogen availability of the body.
Fat oxidation reduced reciprocally after carbohydrate ingestion.
Turbine represents energy output.
Hydraulic Model of Metabolism

Glucose Hysteresis as a Mechanism in Dietary Restriction, Aging and Disease

Charles V. Mobbs, **Jason Mastaitis**, **Minhua Zhang**, **Fumiko Isoda**, **Hui Cheng**, and **Kelvin Yen**
Departments of Neuroscience and Geriatrics, Mount Sinai School of Medicine, New York, N.Y., USA

Abstract

Elevated blood glucose associated with diabetes produces progressive and apparently irreversible damage to many cell types. Conversely, reduction of glucose extends life span in yeast, and dietary restriction reduces blood glucose. Therefore it has been hypothesized that cumulative toxic effects of glucose drive at least some aspects of the aging process and, conversely, that protective effects of dietary restriction are mediated by a reduction in exposure to glucose. The mechanisms mediating cumulative toxic effects of glucose are suggested by two general principles of metabolic processes, illustrated by the *lac* operon but also observed with glucose-induced gene expression. First, metabolites induce the machinery of their own metabolism. Second, induction of gene expression by metabolites can entail a form of molecular memory called hysteresis. When applied to glucose-regulated gene expression, these two principles suggest a mechanism whereby repetitive exposure to postprandial excursions of glucose leads to an age-related increase in glycolytic capacity (and reduction in β-oxidation of free fatty acids), which in turn leads to an increased generation of oxidative damage and a decreased capacity to respond to oxidative damage, independent of metabolic rate. According to this mechanism, dietary restriction increases life span and reduces pathology by reducing exposure to glucose and therefore delaying the development of glucose-induced glycolytic capacity.

Masoro et al. [1] proposed that 'dietary restriction retards the aging processes by altering the characteristics of fuel use'. Similarly, on the basis of a large-scale analysis of gene expression, Lee et al. [2] concluded that 'aging was associated with transcriptional alterations consistent with a metabolic shift from fatty acid to carbohydrate metabolism' and that dietary restriction 'resulted in alterations in gene expression consistent with preserved fatty acid metabolism' through 'transcriptional reprogramming' (see also Anderson and Weindruch in this volume). Indeed, life span in yeast is increased simply by reducing glucose concentrations which, interestingly, actually increases metabolic rate [3]. In the present review we extend these concepts and propose a specific mechanism by which a cumulative toxic effect of glucose drives at least some aspects of the aging process, reduction in which mediates protective effects of caloric restriction.

Glucose Increases Glycolysis and Inhibits Alternative Metabolic Pathways, Including β-Oxidation of Free Fatty Acids

A general feature of metabolic regulation is that substrates typically induce the metabolic machinery necessary for their own metabolism. The classic example of this phenomenon is the *lac* operon, in which lactose induces both the activity and gene expression of β-galactosidase,

"A general feature of metabolic regulation is that substrates typically induce the metabolic machinery necessary for their own metabolism."

Glucose-Fatty Acid Interaction in Skeletal Muscle and Adipose Tissue in Insulin Resistance

M. CAHOVÁ, H. VAVŘÍNKOVÁ, L. KAZDOVÁ

Institute for Clinical and Experimental Medicine, Prague, Czech Republic

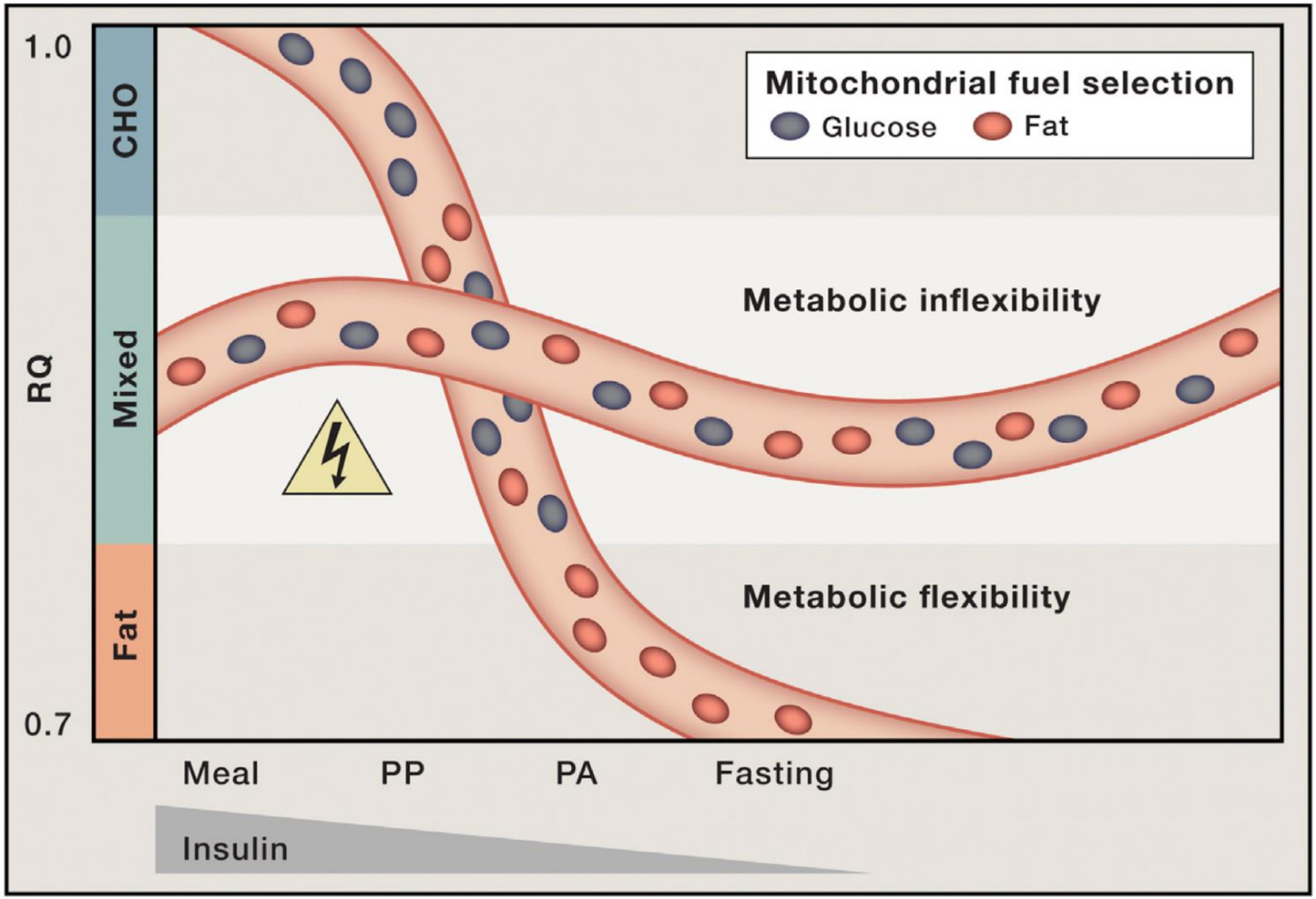
energy rich substrates (glucose, lipids) and energy output. The defects in the metabolism of glucose in IR and type 2 diabetes are closely associated with the disturbances in the metabolism of lipids. In this review, we have summarized the evidence indicating that one of the important mechanisms underlying the development of IR is the impaired ability of skeletal muscle to oxidize fatty acids as a consequence of elevated glucose oxidation in the situation of hyperglycemia and hyperinsulinemia and the impaired ability to switch easily between glucose and fat oxidation in response to homeostatic signals. The decreased fat oxidation results into the accumulation of intermediates of fatty acid metabolism that are supposed to interfere with the insulin signaling cascade and in consequence negatively influence the glucose utilization. Pathologically elevated fatty acid concentration in serum is now accepted as an important risk factor leading to IR. Adipose tissue plays a crucial role in the regulation of fatty acid homeostasis. The adipose tissue may be the primary site where the early metabolic disturbances leading to the development of IR take place and the

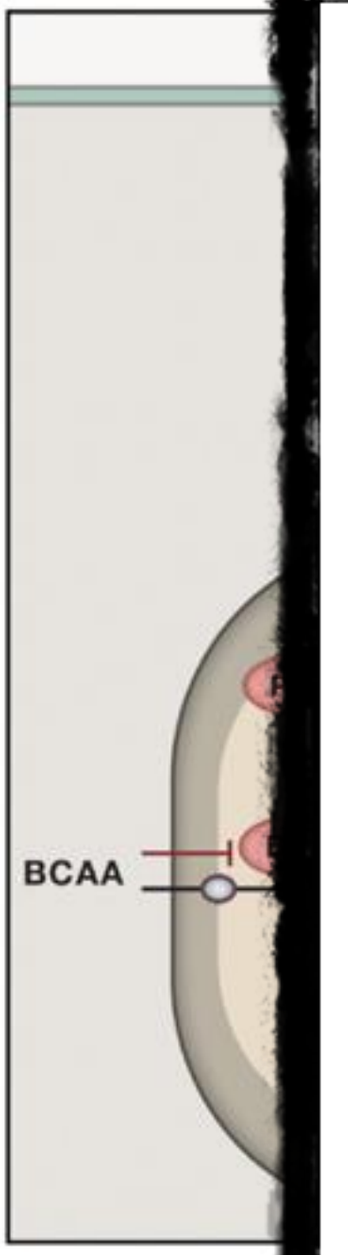
diabetes are closely

the evidence indicating that one of the important mechanisms underlying the development of IR is the impaired ability

of skeletal muscle to oxidize fatty acids as a consequence of elevated glucose oxidation in the situation of hyperglycemia and hyperinsulinemia and the impaired ability to switch easily between glucose and fat oxidation in response to homeostatic signals. The decreased fat oxidation results into the accumulation of intermediates of fatty acid metabolism that are supposed to interfere with the insulin signaling cascade and in consequence negatively influence the glucose utilization. Pathologically elevated fatty acid concentration in serum is now accepted as an important risk factor leading to IR. Adipose tissue plays a crucial role in the regulation of fatty acid homeostasis. The adipose tissue may be the primary site where the early metabolic disturbances leading to the development of IR take place and the

Metabolic Inflexibility: When Mitochondrial Indecision Leads to Metabolic Gridlock





BCKD kinase; CL, cit
chain acylcarnitine;
kinase. Red indicate

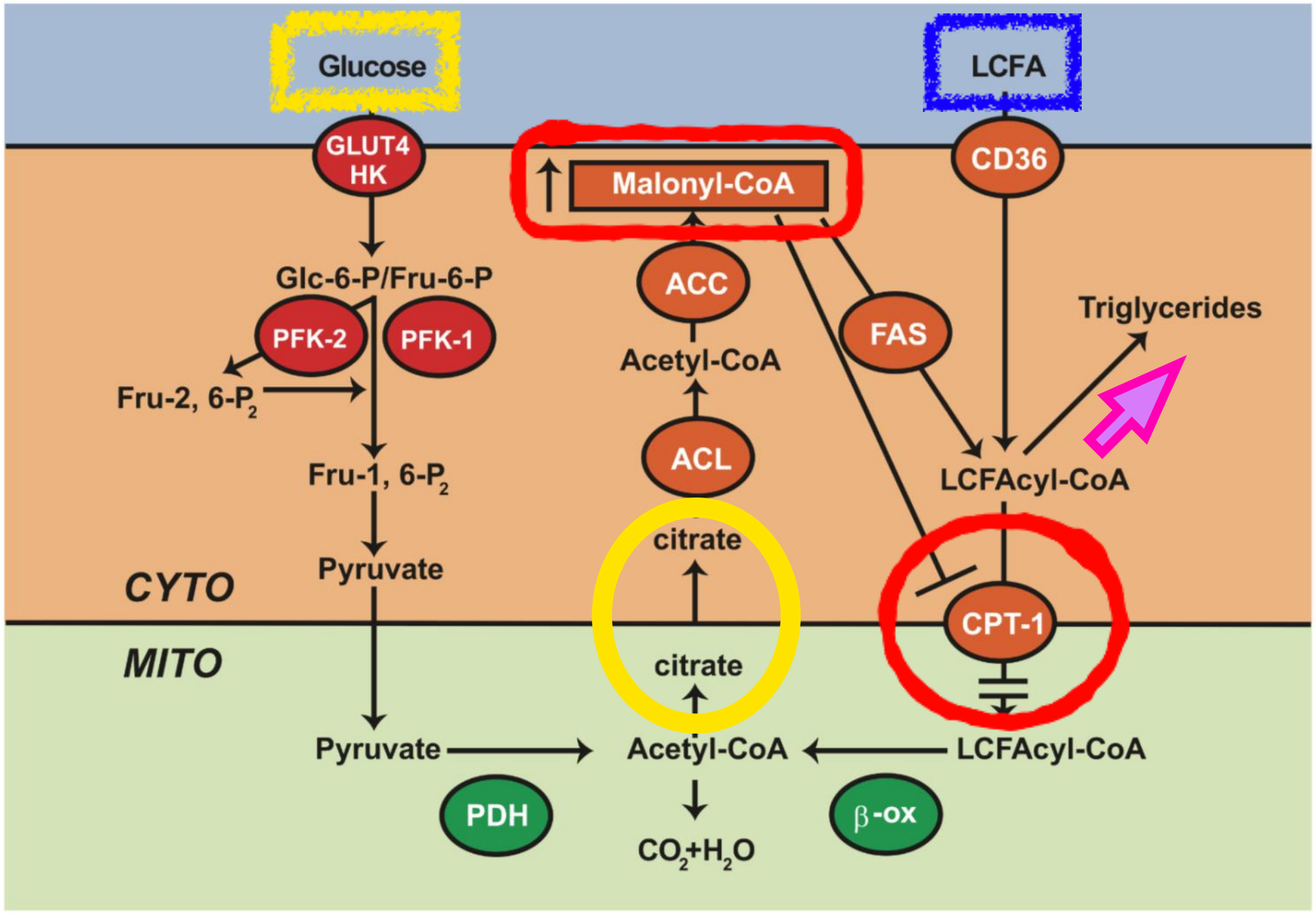


Fig. 5. Mechanism of inhibition of fatty acid oxidation by glucose. This mechanism is mediated by malonyl-CoA, the concentration of which depends on ACC activity and which inhibits the entry of long-chain fatty acyl (LCFAcyl-CoA) moieties into mitochondria. This effect reroutes fatty acids toward esterification. In extrahepatic tissues, the effect of glucose is stimulated by insulin. See text for further details. ACL, ATP-citrate lyase; FAS, fatty acid synthase.

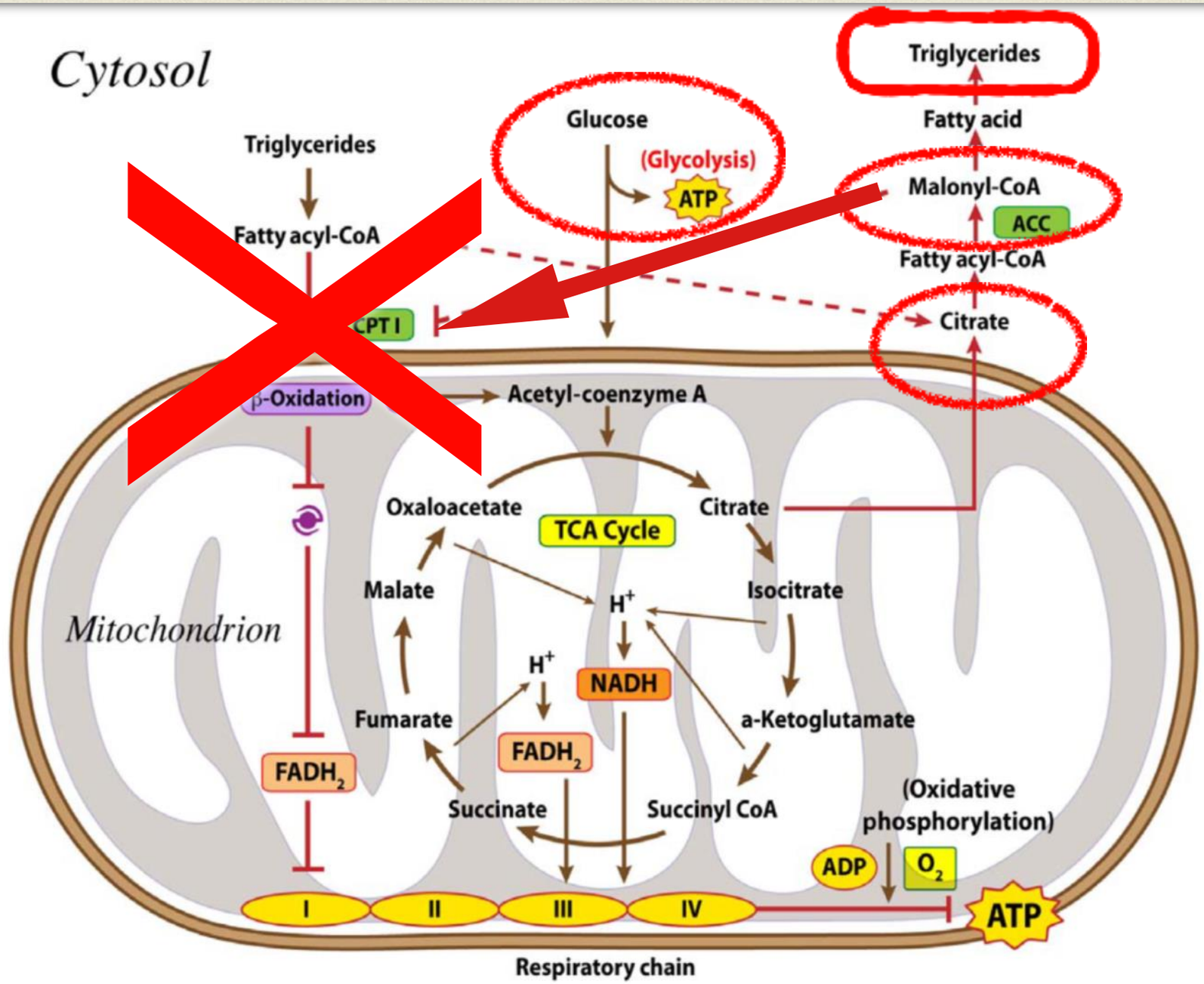
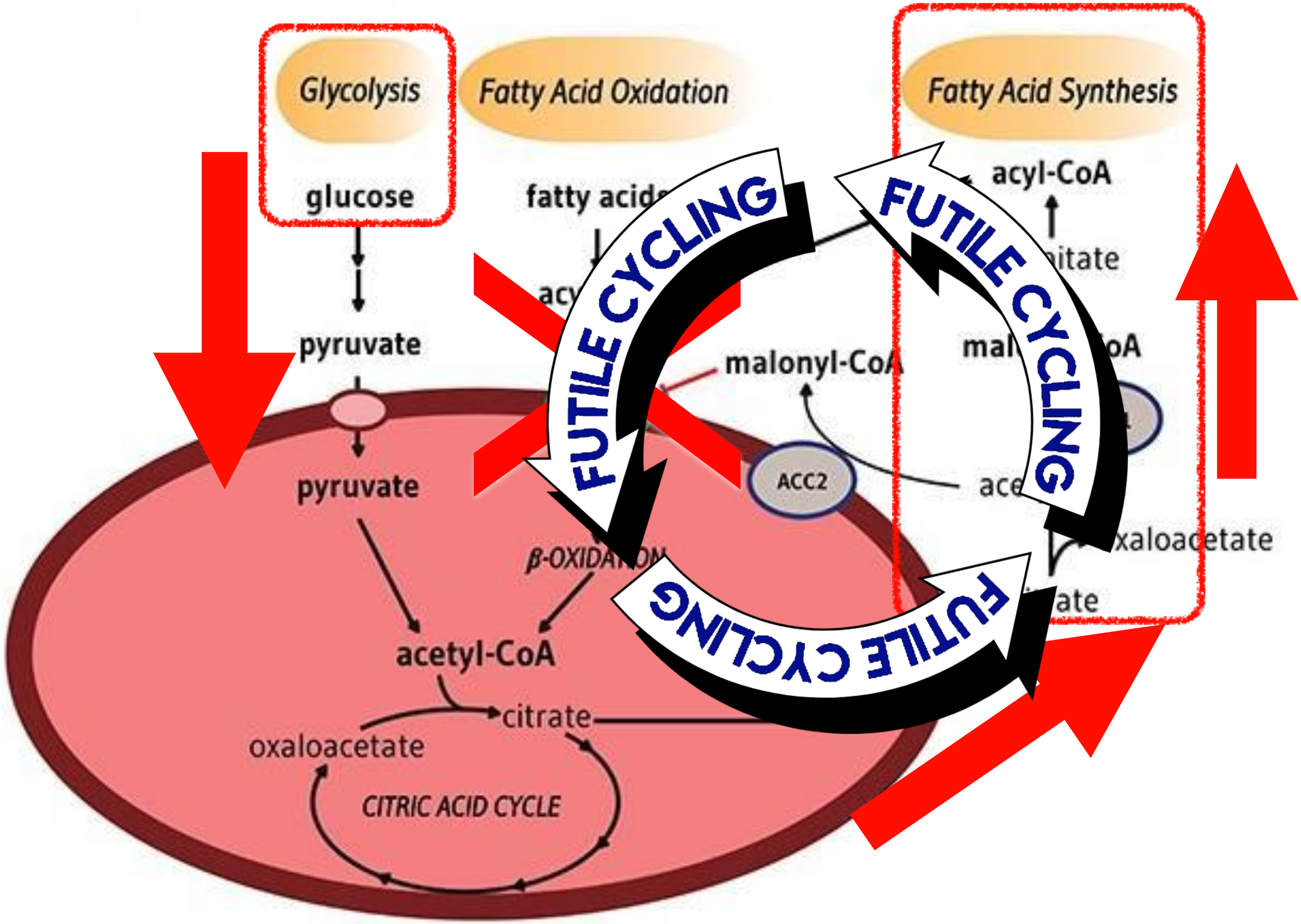


Figure 2. Impaired mitochondrial energy production. In obesity, impaired glucose tolerance, and type 2 diabetes, mitochondrial β-oxidation is decreased in skeletal muscles cells. Carnitine palmitoyltransferase 1 (CPT1) activity, necessary for the transport of long-chain fatty acids into the cell, is diminished, leading to the accumulation of fatty acyl-CoA within the cytosol. Under the influence of the enzyme acetyl-CoA carboxylase (ACC), unmetabolized fatty acyl-CoA is converted to malonyl-CoA and committed to the re-synthesis of fatty acids, which can accumulate within the cell or be transported to other tissues as triglycerides. The reduced ability to use fatty acids for ATP production increases obese individuals' reliance on glycolysis and decreases their exercise capacity. NOTE: ADP = adenosine diphosphate; ATP = adenosine triphosphate; $FADH_2$ = flavin adenine dinucleotide; NADH = nicotinamide adenine dinucleotide; O_2 = oxygen; H^+ = hydrogen ion.


Glycolysis
Fatty Acid Oxidation
Fatty Acid Synthesis
glucose
pyruvate
fatty acids
acyl-CoA
malonyl-CoA
ACC2
FUTILE CYCLING
FUTILE CYCLING
FUTILE CYCLING
β-OXIDATION
acetyl-CoA
citrate
oxaloacetate
CITRIC ACID CYCLE

Glucose and insulin-induced inhibition of fatty acid oxidation: the glucose-fatty acid cycle reversed

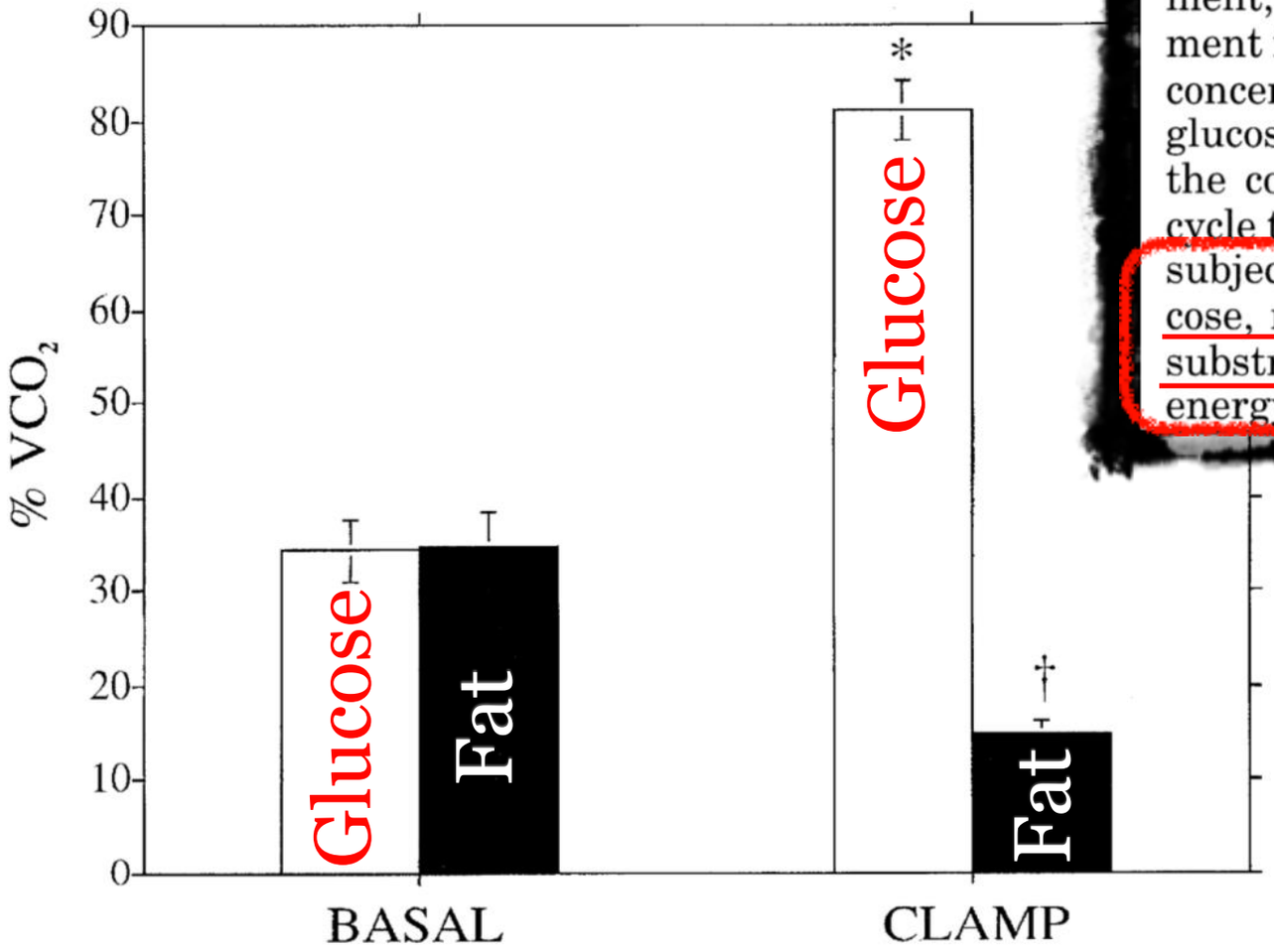
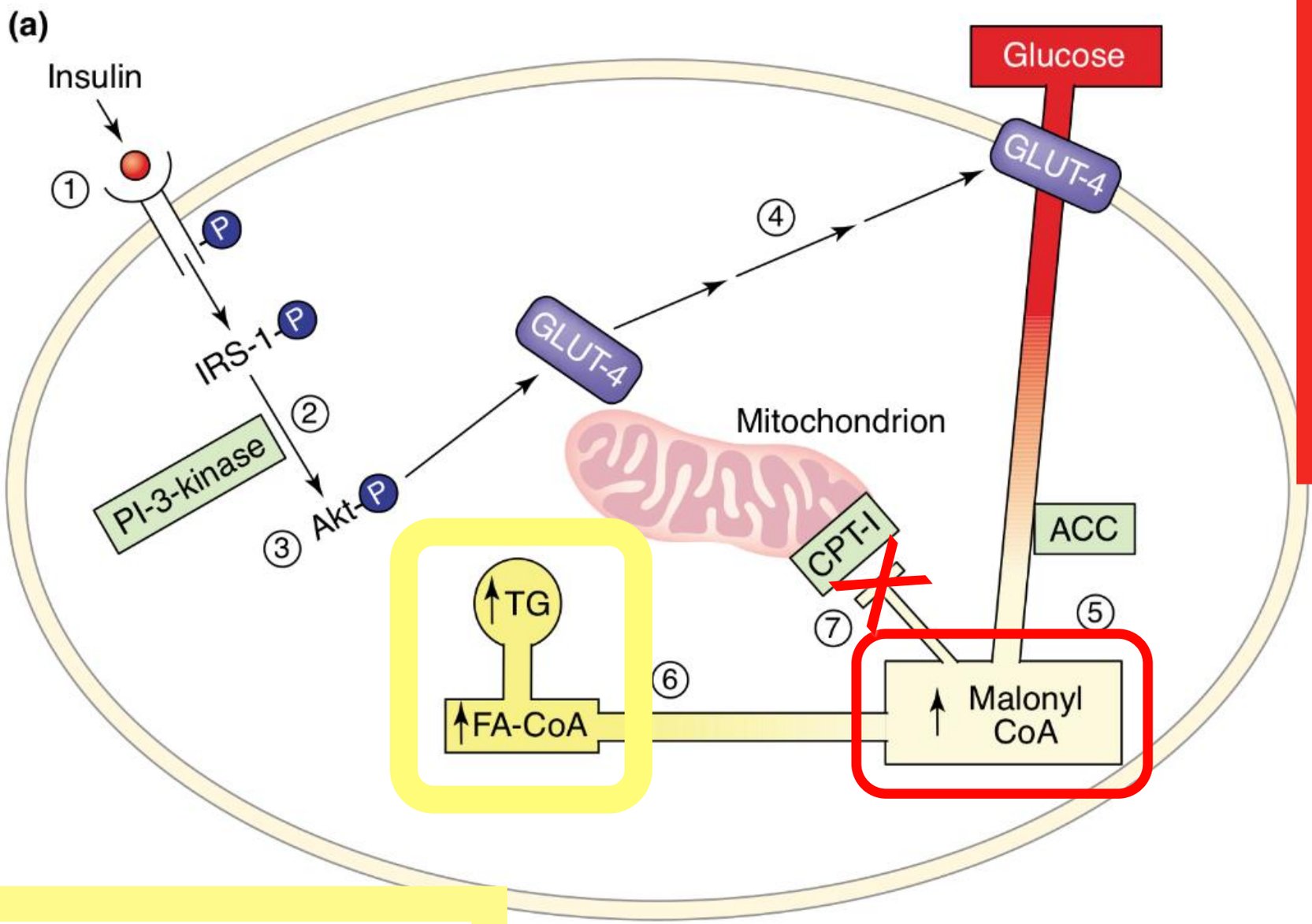


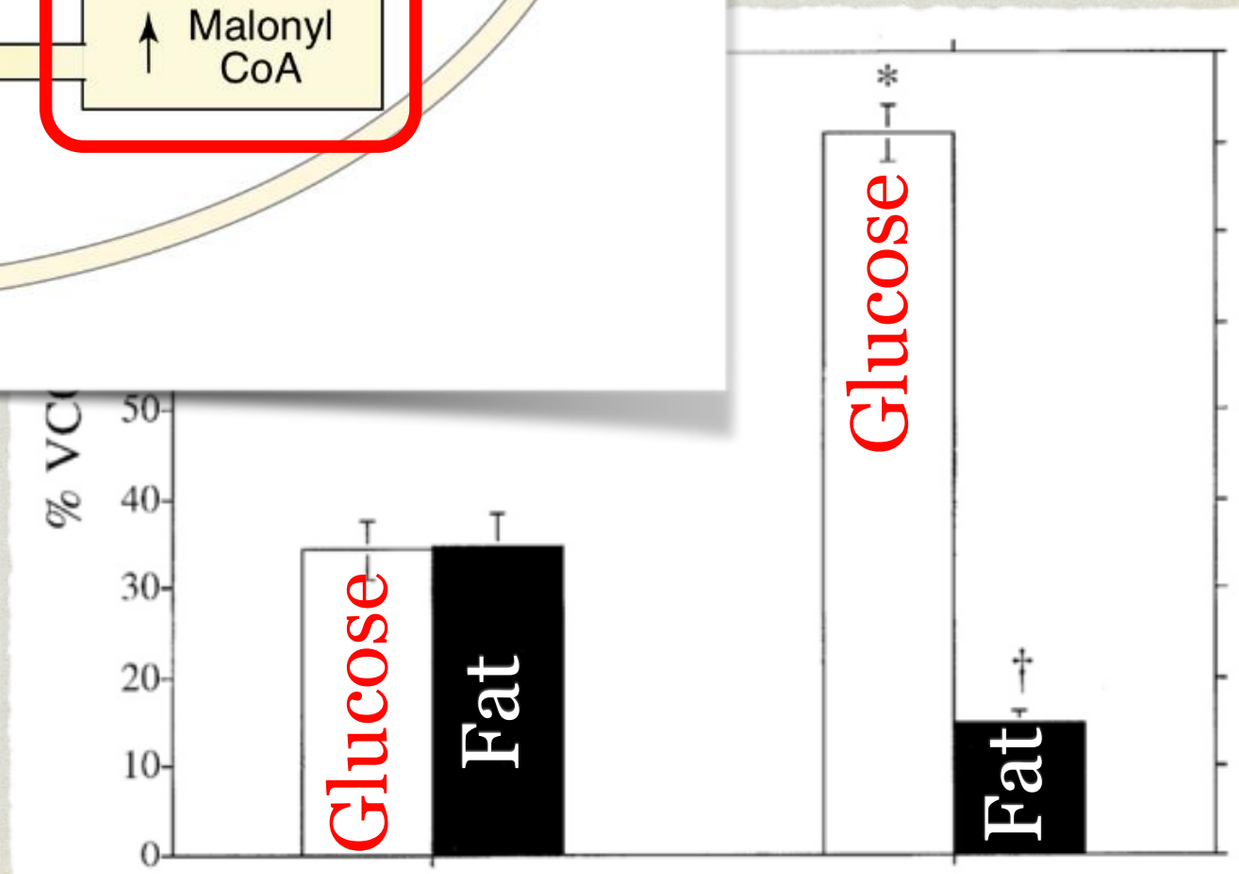
Fig. 2. Percentage of carbon dioxide production ($\dot{V}CO_2$) derived from oxidation of fatty acids (filled bars) and glucose (open bars) in the basal state and during hyperinsulinemic-hyperglycemic clamp. Values are means ± SE for 5 volunteers. $^*P < 0.01$ vs. basal glucose oxidation; $\dagger P < 0.01$ vs. basal fatty acid oxidation.

G-6-*P* concentration, which in turn inhibits glucose uptake (18). However, the results of the current experiment, coupled with the results of our previous experiment in which we showed that an increase in fatty acid concentration did not affect glucose oxidation when glucose uptake was maintained constant (27), lead to the conclusion that the traditional glucose-fatty acid cycle theory is not applicable to the situation in human subjects. Rather, the intracellular availability of glucose, not fatty acids, is the prime determinant of the substrate mix (i.e., glucose vs. fat) that is oxidized for energy.

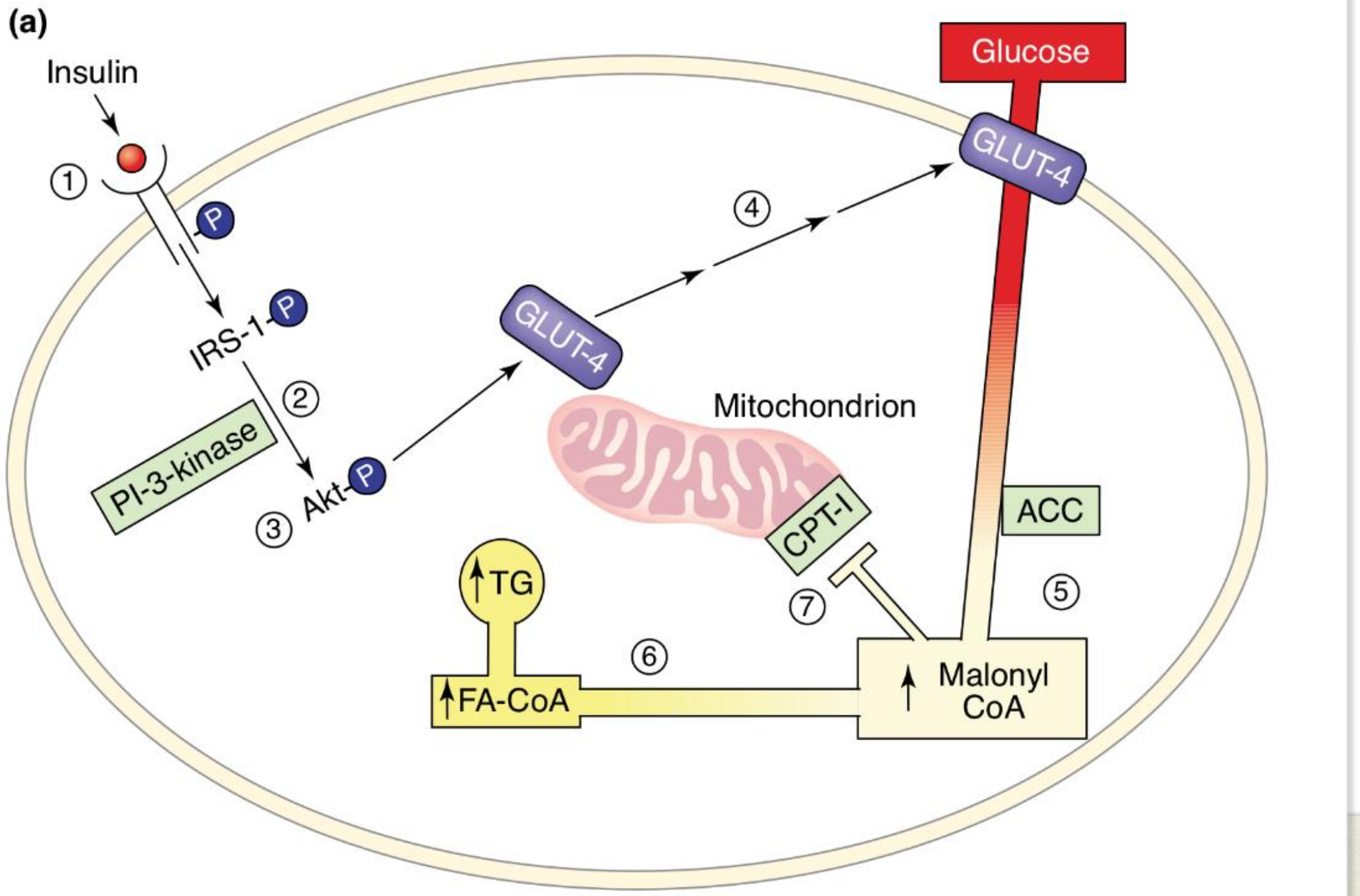
xidation, which in turn should
e and oxidation (i.e., insulin resis-

of time since the initial publica-
he glucose-fatty acid cycle and its
e (see, e.g., Refs. 3, 4, 12), defini-
existence in human subjects is
aspect of the theory is that fatty
s glucose oxidation by increasing
nd subsequently G-6-*P* concentra-
ies in which FFA concentrations
e generally failed to demonstrate
nge in either muscle citrate or
(see, e.g., Refs. 3, 4, 8, 10).
pporting the inhibitory effect of
ation comes from a number of

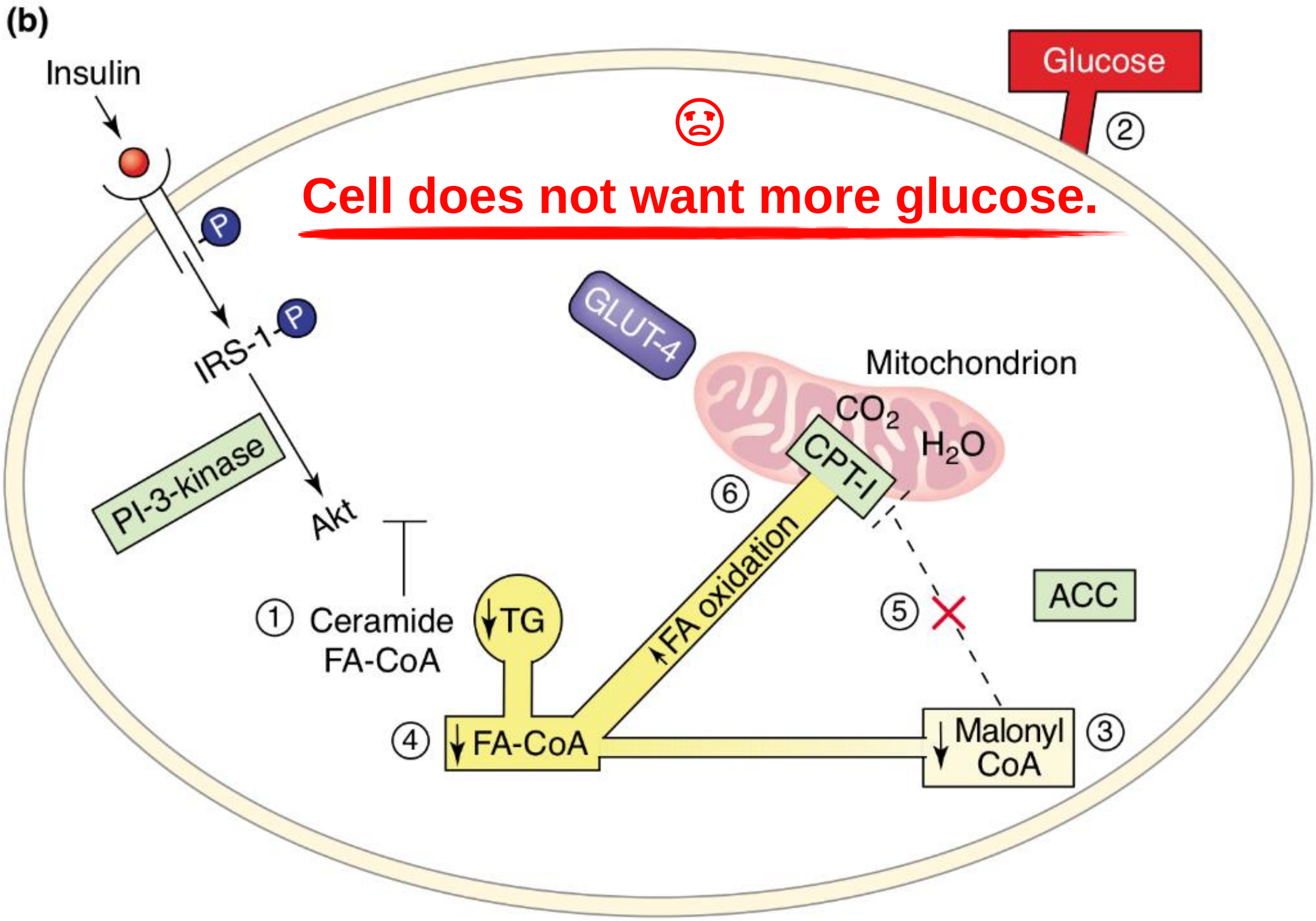

(a)
Insulin
①
P
IRS-1
P
②
PI-3-kinase
③ Akt
P
④
GLUT-4
GLUT-4
Glucose
Mitochondrion
CPT-I
ACC
⑤
⑦
⑥
TG
FA-CoA
Malonyl CoA

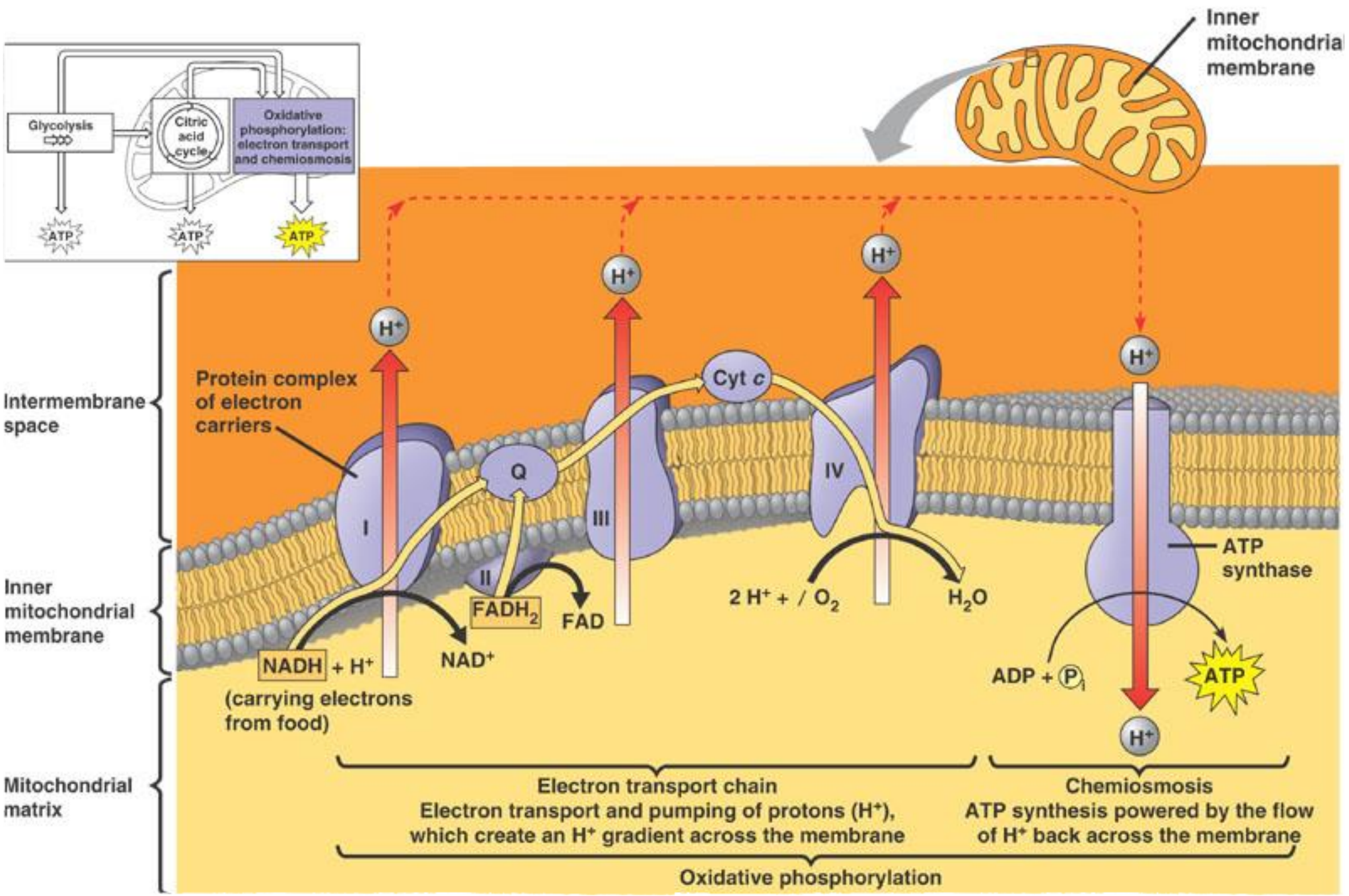

% VC
50
40
30
20
10
0
Glucose
Fat
*
†
Glucose
Fat

Lipid overload and overflow: metabolic trauma and the metabolic syndrome



Insulin resistance: cell protection?




Glycolysis
Citric acid cycle
Oxidative phosphorylation: electron transport and chemiosmosis
ATP
ATP
ATP
Inner mitochondrial membrane
Intermembrane space
Inner mitochondrial membrane
Mitochondrial matrix
Protein complex of electron carriers
H+
H+
H+
H+
Cyt c
Q
I
II
III
IV
FADH2
FAD
NADH + H+
NAD+
(carrying electrons from food)
2 H+ + 1/2 O2
H2O
ATP synthase
ADP + Pi
ATP
H+
Electron transport chain
Electron transport and pumping of protons (H+), which create an H+ gradient across the membrane
Chemiosmosis
ATP synthesis powered by the flow of H+ back across the membrane
Oxidative phosphorylation

Mitochondrial Complex II Promotes Longevity, Other Mitochondrial Complexes Reduce Longevity

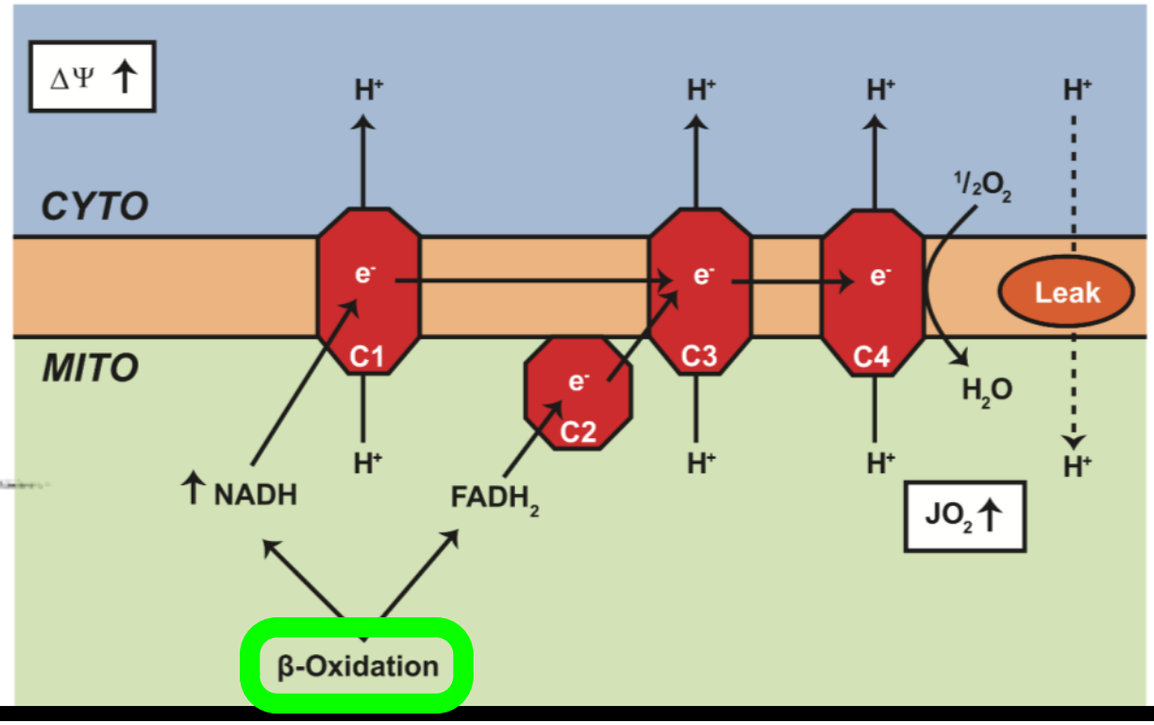
The fact that diabetes accelerates many age-related pathologies, especially cardiovascular pathologies, suggests that diabetes and aging may share common pathological mechanisms. Certainly this is clear for yeast, in which reducing glucose concentration is sufficient to increase life span [3]. A role for glucose metabolism in determining life span is also suggested by examination of the role of specific complexes of the mitochondrial electron transport chain (ETC) in determining longevity. Genome-wide screening studies have demonstrated that genes coding for mitochondrial functions constitute possibly the most conspicuous single class of 'senescence assurance genes', ablation of which increases life span [23,24]. Almost all of these life-span-limiting mitochondrial genes code for proteins in mitochondrial complexes I, III, IV or V [23-26]. For example, of 23 genes discovered in an exhaustive genome-wide screen whose inhibition increased life span [26], 12 were genes coding for proteins in mitochondrial (ETC) complexes I, III, IV or V, and one gene coded for a key enzyme in glycolysis, glucose-6-

Glucose toxicity. High values of $\Delta\Psi$ lead to proton leak, reversed electron flow, and ROS production (Fig. 7). As described above, active fatty acid oxidation induces such a state. Flooding the system with glucose on top of fatty acids is expected to induce considerable damage to the mitochondria if energy demand is not concomitantly increased. An overabundant diet rich in carbohydrates and fat (184) should force-feed electrons from glucose into the respiratory chain, in which the already prevailing high $\Delta\Psi$ prevents electron flow. This excessive energy supply, not matched by energy demand, will further worsen the jamming of electrons in the respiratory chain and eventually result in massive ROS production and mitochondrial damage (Fig. 7). In addition, a saturated flux

complexes. While such a pattern of fuel use might or might not reduce ATP synthesis, the actual mechanism extending life span would be, according to this hypothesis, reduced production of reactive oxygen species due to relatively increased utilization of complex II.

Reduced Complex I Activity Is Associated with Increased Life Span in Worms, Mice and Humans

As indicated above, genome-wide screening revealed that RNA-interference-mediated reduction in complex I activity increases life span in *Caenorhabditis elegans* [25,26]. Furthermore, classic genetic screens had previously identified that mutations in the *clk-1* gene [33], which also influences mitochondrial function [34], increase life span. This gene codes



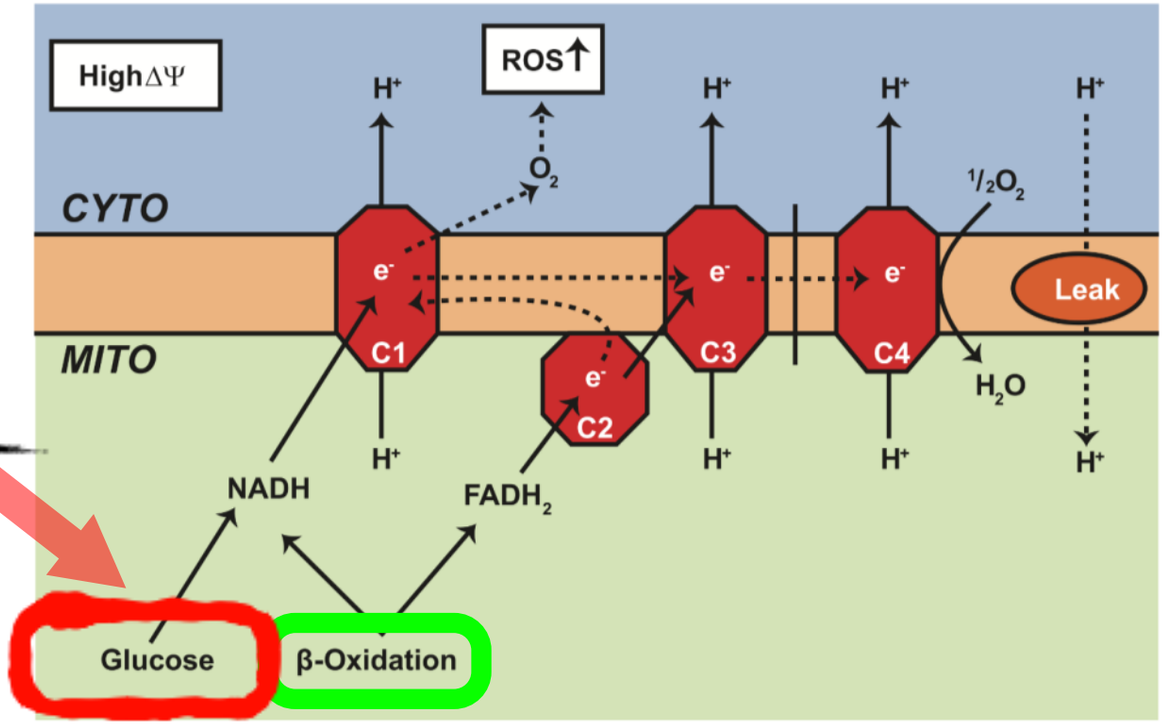


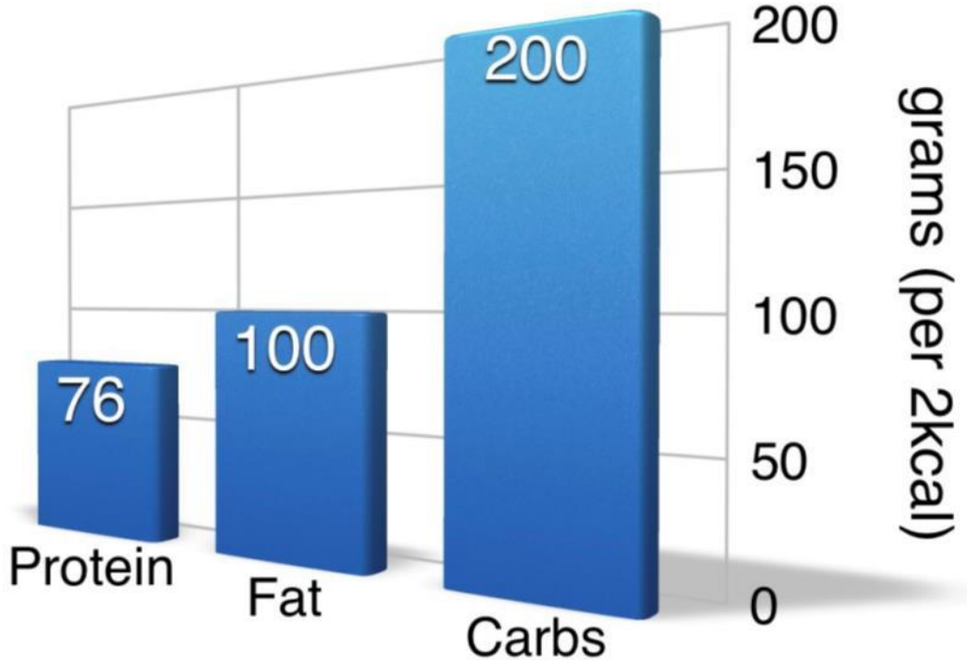
Fig. 7. Proton leaks, reverse electron flow, and reactive oxygen species (ROS) production. High values of $\Delta\Psi$ prevent electron flow, favor proton leaks, and lead to reverse electron flow and eventually enhanced production of ROS. This process is worsened by the concomitant oxidation of glucose and probably contributes to glucose toxicity. See text for further details.


++++
ENVIGO
Teklad
TEKLAD GLOBAL DIETS®
2018
18% Protein
Rodent Diet
Teklad
18% Protein Rodent Diet
2018

45F30S TD.08811	15%	40%	45%	"Western Diet" with ~45% of kcal fat using primarily milk fat and with ~30% kcal from

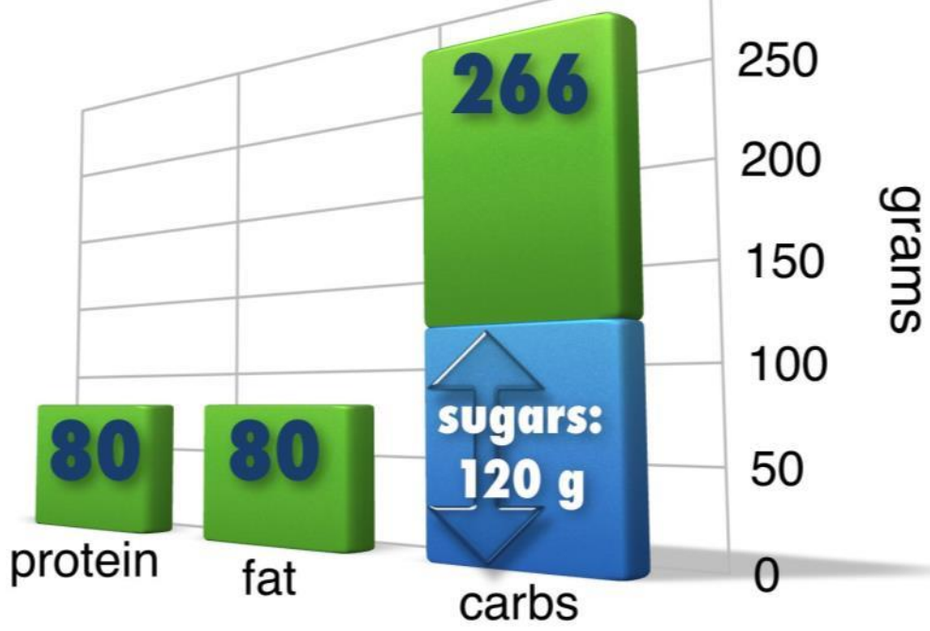
Obesogenic Rodent Chow

Protein: 15%
Fat: 45%
Carbohydrate: 40%



American Daily Intake

protein: 80 grams
fat: 80 grams
carbohydrates: 266 grams
(sugars: 120 grams)



Authors: JB Flowers and BD Mickelson

40% Refined Carbs (sugar/starch)

+

40% Vegetable Oil

=

=

Specially designed obesogenic rat chow

40% Refined Carbs (sugar/starch)

+

40% Vegetable Oil

=

Doughnut

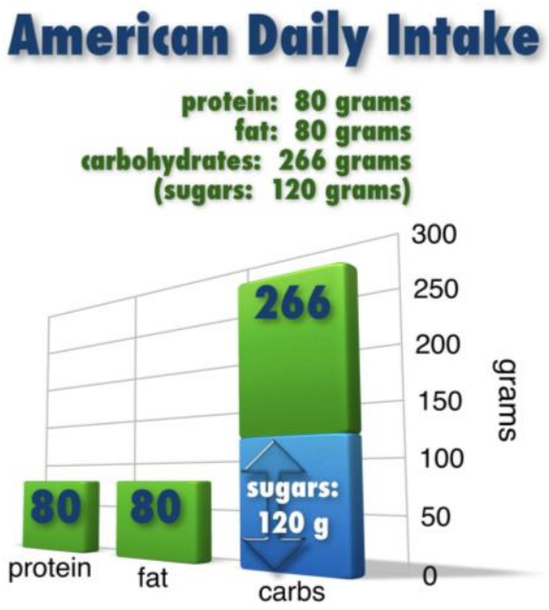
	45F30S TD.08811	15%	40%	45%	"Western Diet" with ~45% of kcal fat using primarily milk fat and with ~30% kcal from sucrose.

Worst Body Composition:

Highest FAT Mass — Lowest LEAN Mass

Diet: low protein, high carb AND high fat

Activity: sedentary



High carb AND
High fat

Low protein
Low fiber
Low nutrient

Best Body Composition:

Lowest FAT Mass — Highest LEAN Mass

Diet: high protein, low carb AND low fat

Activity: resistance

High protein
High fiber
High nutrient

Low carb AND
Low fat

The Effects of Intensive Weight Reduction on Body Composition and Serum Hormones in Female Fitness Competitors

females (27.2 ± 4.1 years) dieting for a competition and 23 (27.7 ± 3.7 years) acting as weight-stable controls. The energy deficit of the diet group was achieved by reducing carbohydrate intake and increasing aerobic exercise while maintaining a high level of protein intake and resistance training in addition to moderate fat intake. The diet led to a ~12% decrease in body weight ($P < 0.001$) and a ~35–50% decrease in fat

Reviewed by:
Matteo Maria Pecchiari,
University of Milan, Italy
Eric Helms,
Auckland University of Technology,
New Zealand

***Correspondence:**
Juha J. Hulmi
juha.hulmi@jyu.fi

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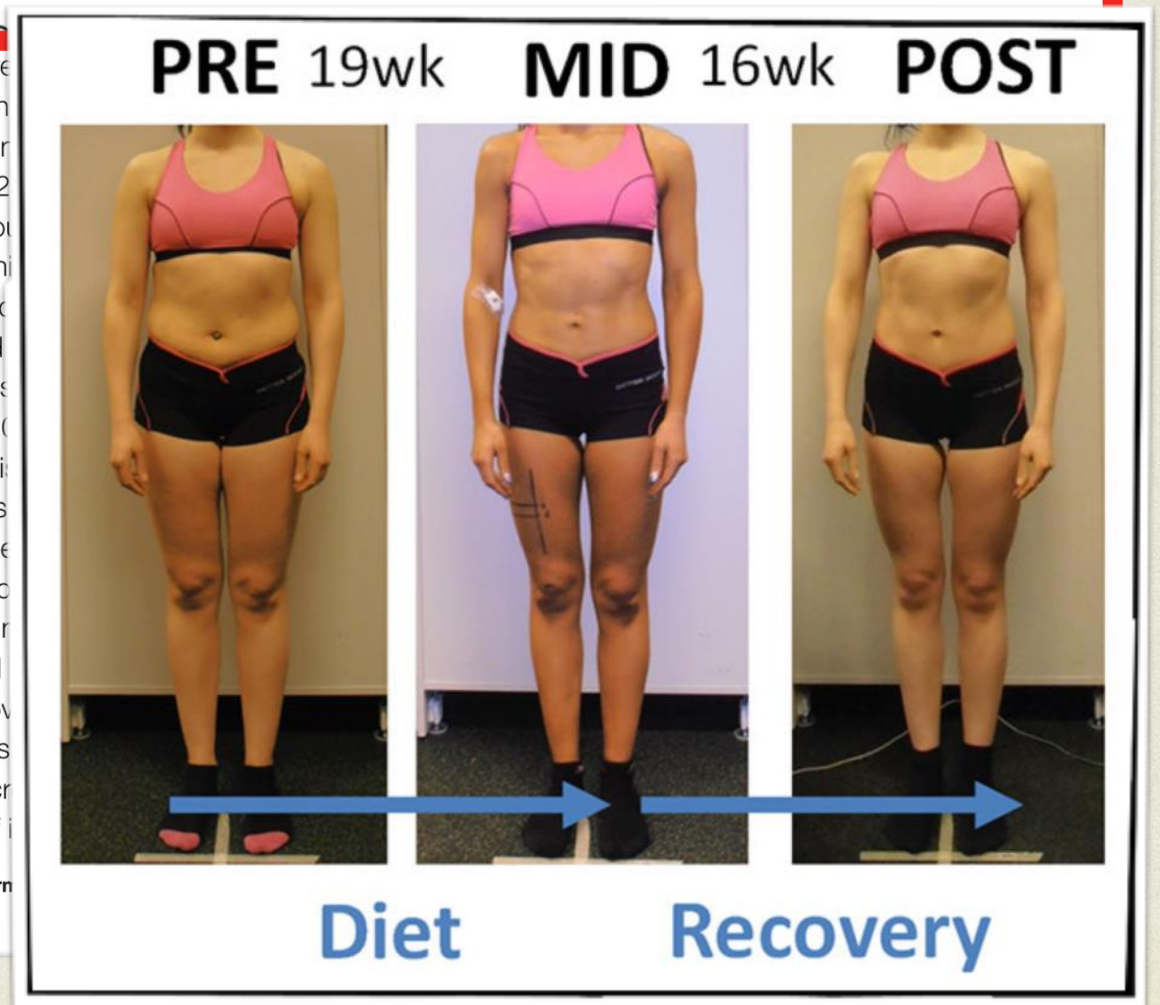
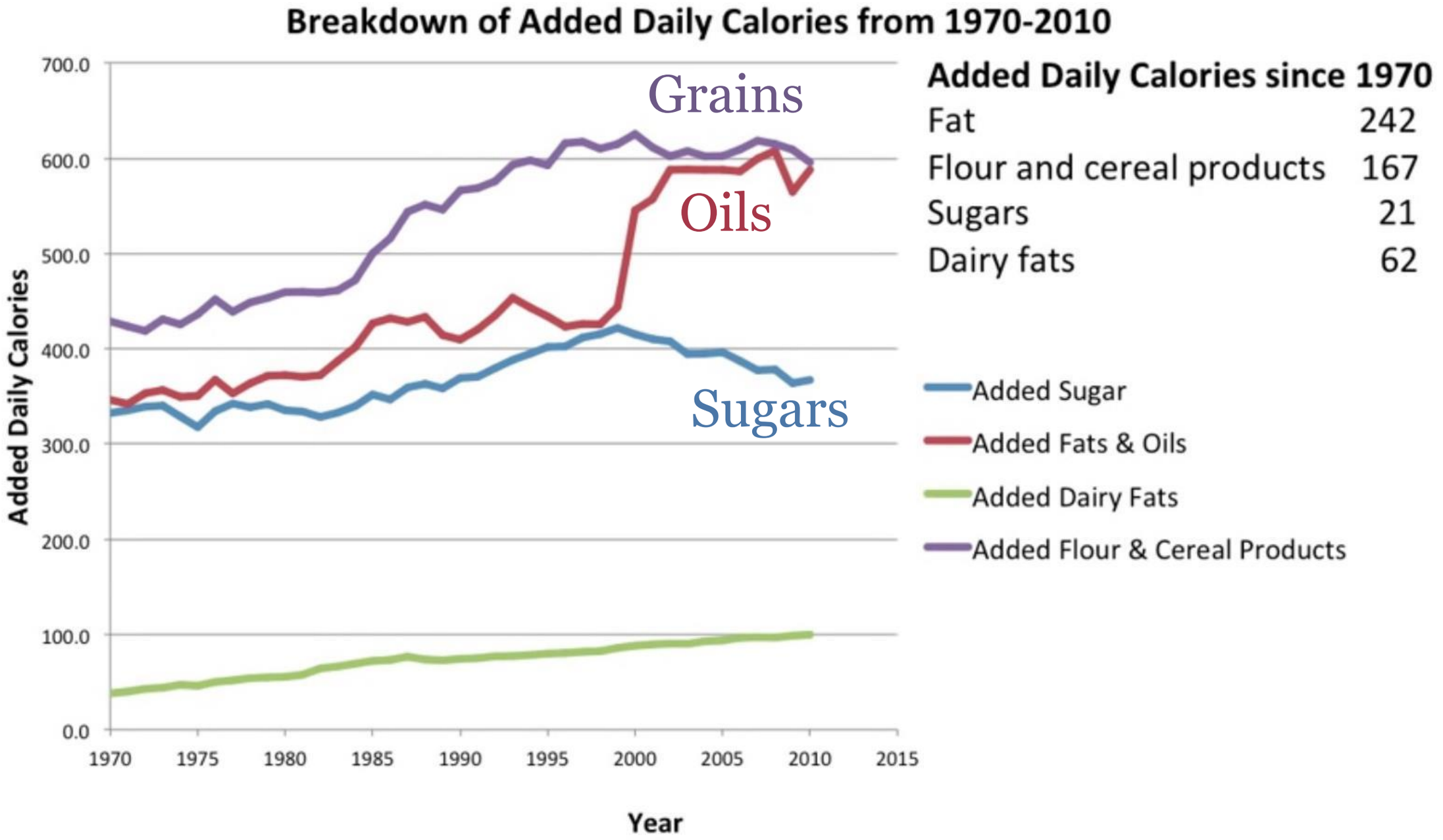
longitudinal studies investigating these kinds of diets are
present study was to investigate the effects of a 4-month
females competing in fitness-sport. In total 50 participar
females (27.2 ± 4.1 years) dieting for a competition and 2
weight-stable controls. The energy deficit of the diet grou
carbohydrate intake and increasing aerobic exercise whi
protein intake and resistance training in addition to mod
to a ~12% decrease in body weight ($P < 0.001$) and
mass (DXA, bioimpedance, skinfolds, $P < 0.001$) whereas
their body and fat mass (diet × group interaction $P < 0.0$
mass (bioimpedance and skinfolds) and in vastus lateralis
(ultrasound) were observed in diet ($P < 0.05$), whereas
(DXA: lean mass, ultrasound: triceps brachii thickness). The
during the diet with decreased serum concentrations o
testosterone ($P < 0.001$), and estradiol ($P < 0.01$) coincidir
of menstrual irregularities ($P < 0.05$). Body weight and
testosterone returned to baseline during a 3–4 month recov
energy intake and decreased levels aerobic exercise. This
that most of the hormonal changes after a 35–50% decr
normal-weight females can recover within 3–4 months of

Keywords: fat loss, exercise, nutrition, fitness, body composition, sex horn



Breakdown of Added Calories

- USDA data revealing breakdown of added daily calories

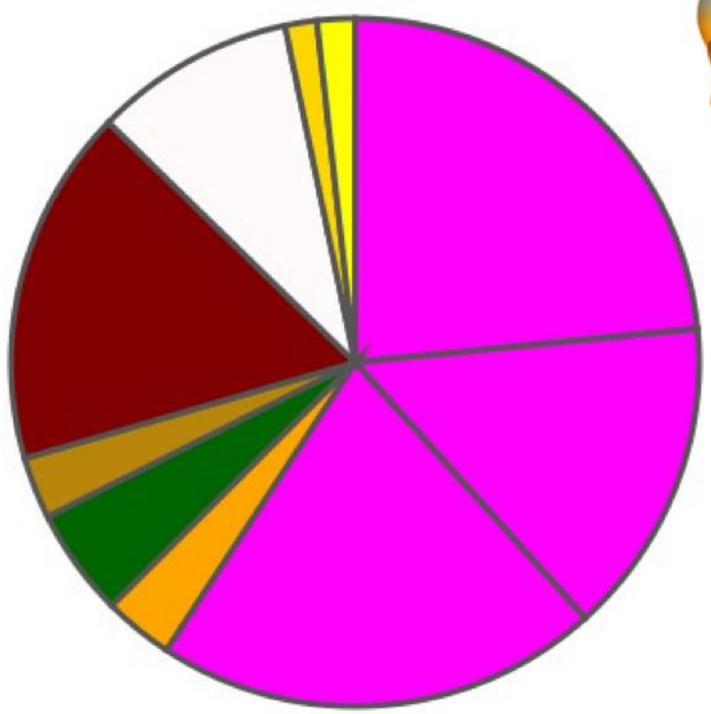


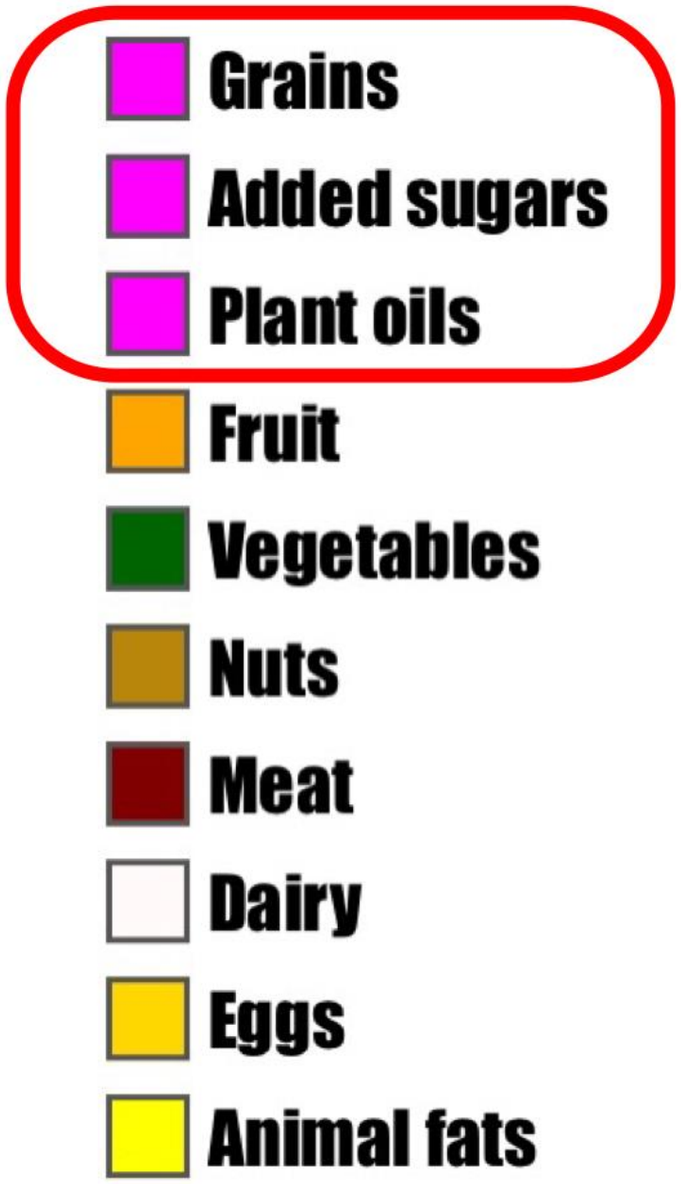
AVOID THE

PROCESSED FOOD TRIFECTA:

FLOUR, SUGAR, & OIL

Calories in America, 2010





Adipose tissue as a buffer for daily lipid flux

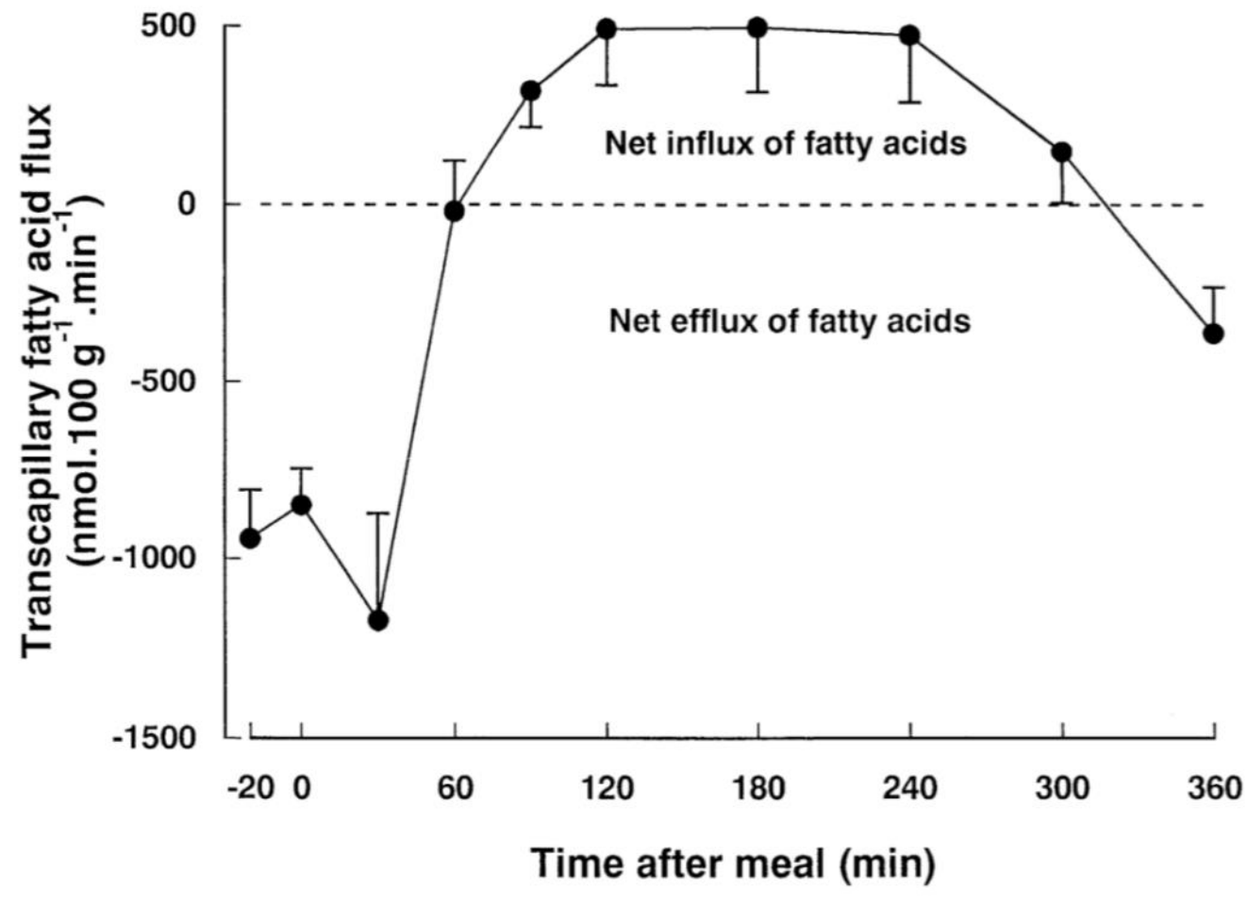
K. N. Frayn

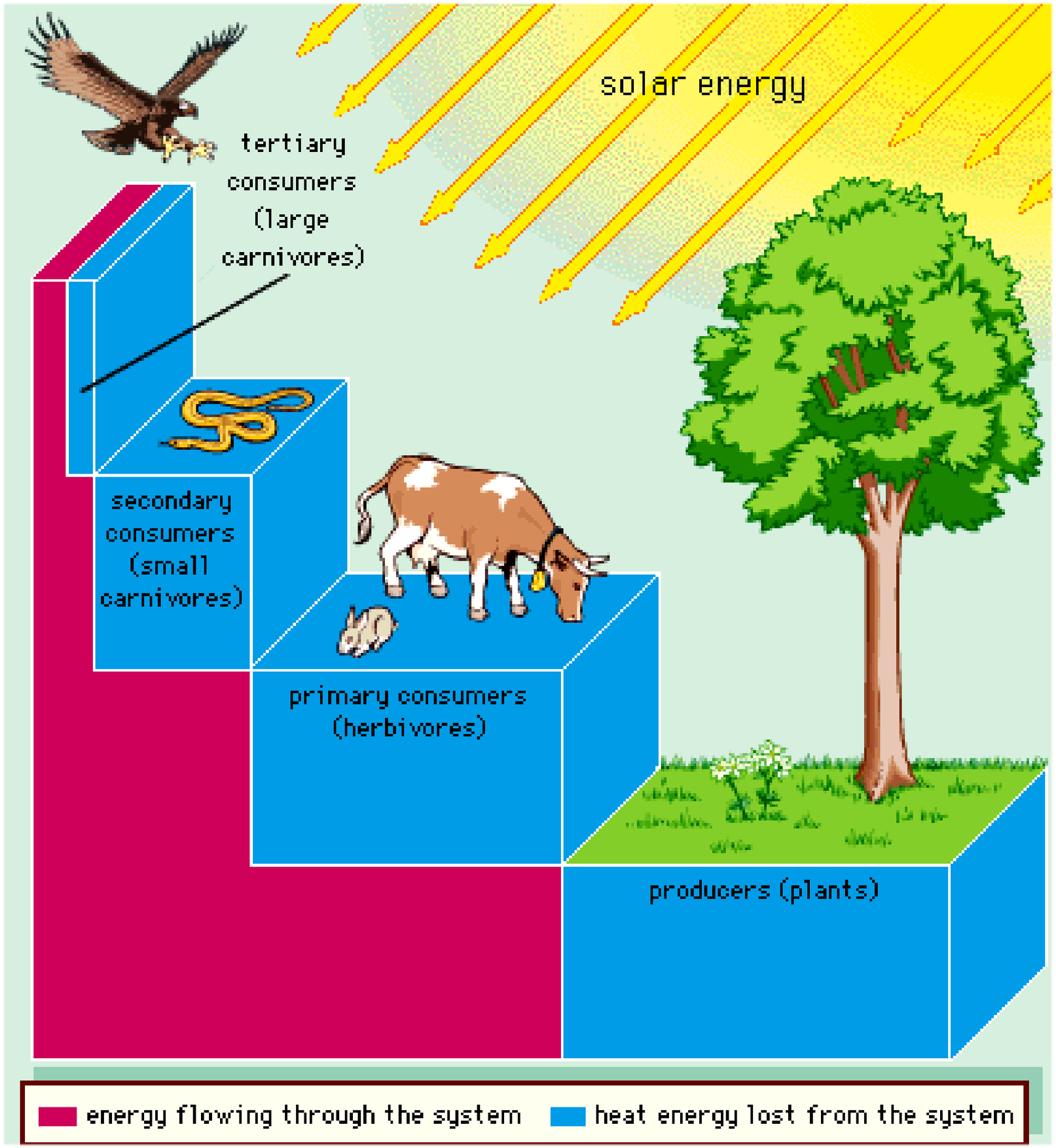
Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Radcliffe Infirmary, Oxford, UK

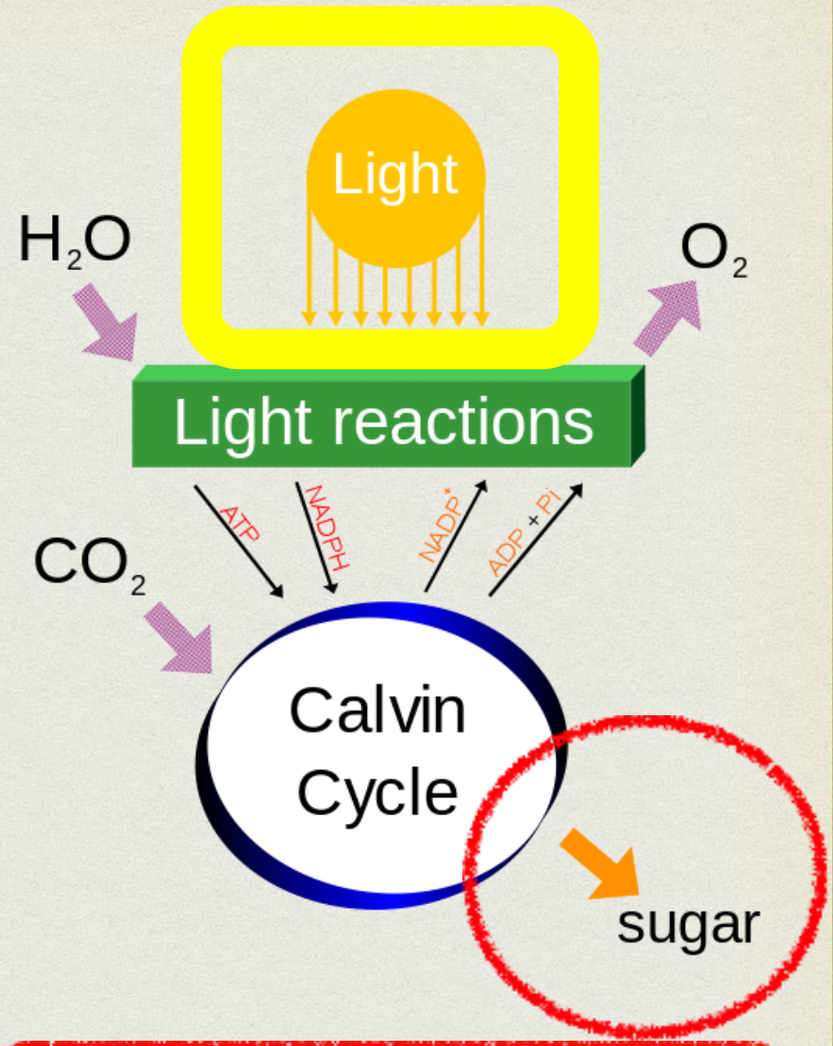
Abstract

Insulin resistance occurs in obesity and Type II (non-insulin-dependent) diabetes mellitus, but it is also a form of triacylglycerol, leading to insulin resistance. These tissues will include liver, skeletal muscle and the pancreatic beta cell, where the long term effect is to impair insulin secretion. Adipose tissue buffering of

K. N. Frayn: Adipose tissue as a buffer for daily lipid flux



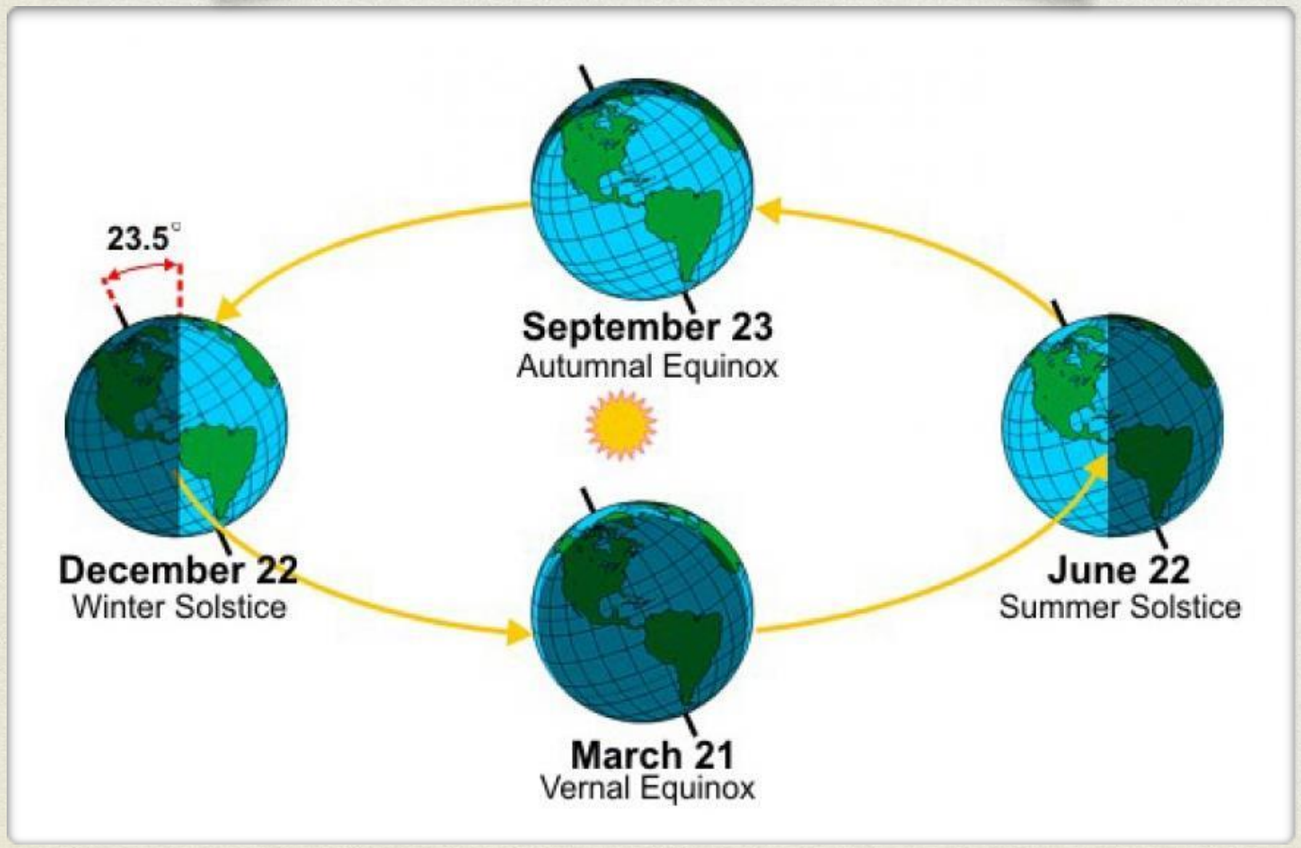




Herbivore Summer: More sugar.

Carnivore Summer: More fat.

Omnivore Summer: More sugar AND fat.



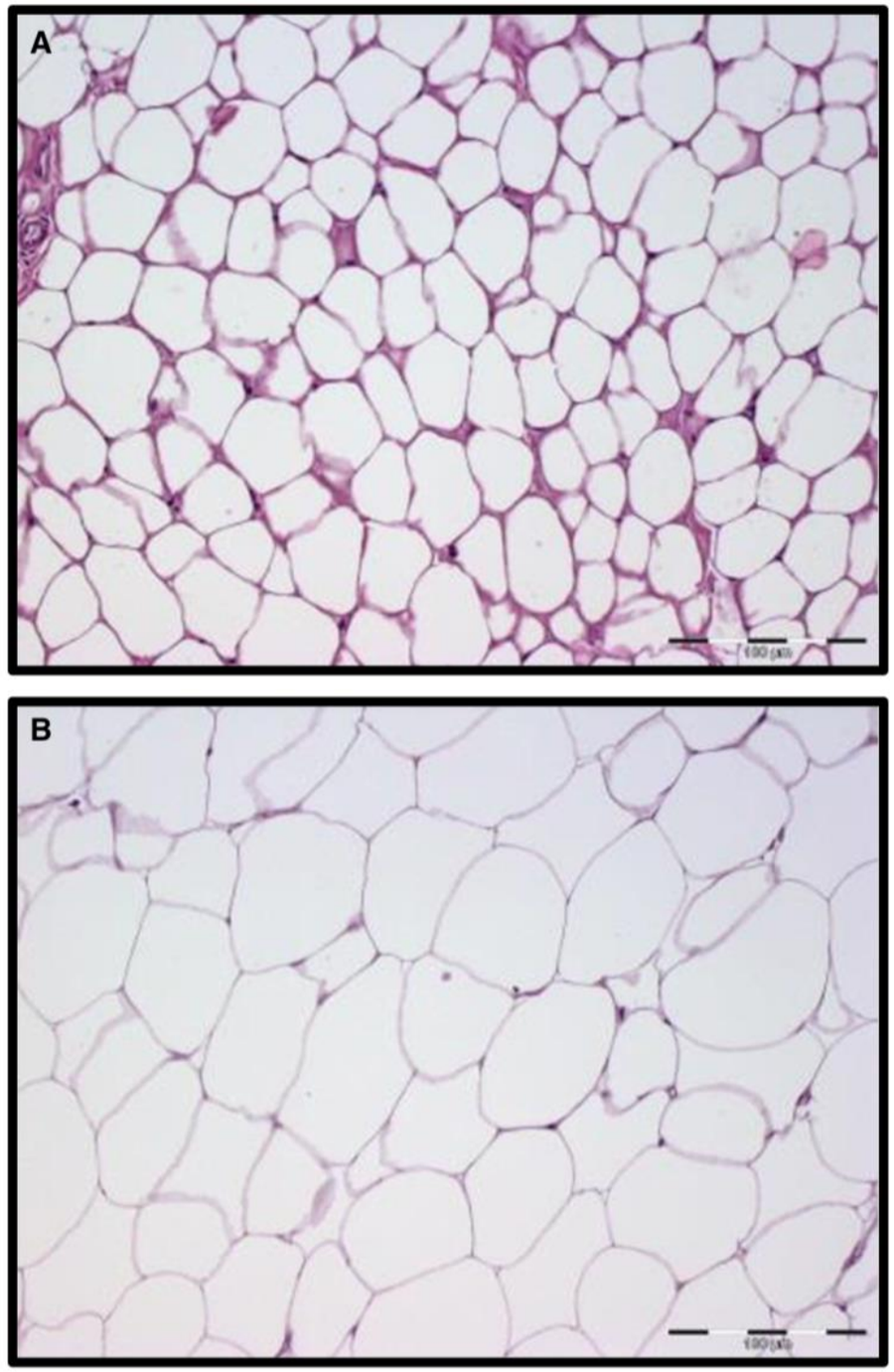


Figure 1. Hematoxylin and eosin staining of adipose tissue biopsies taken from the inguinal fat pad from the same immobilized free-ranging brown bear (fitted with GPS-collars) during summer (A) and during hibernation in winter (B) from Dalarna, Sweden.