# Hidden faces of diabetes and insulin resistance


## Prof. Elsayed Abdel Fattah Eid

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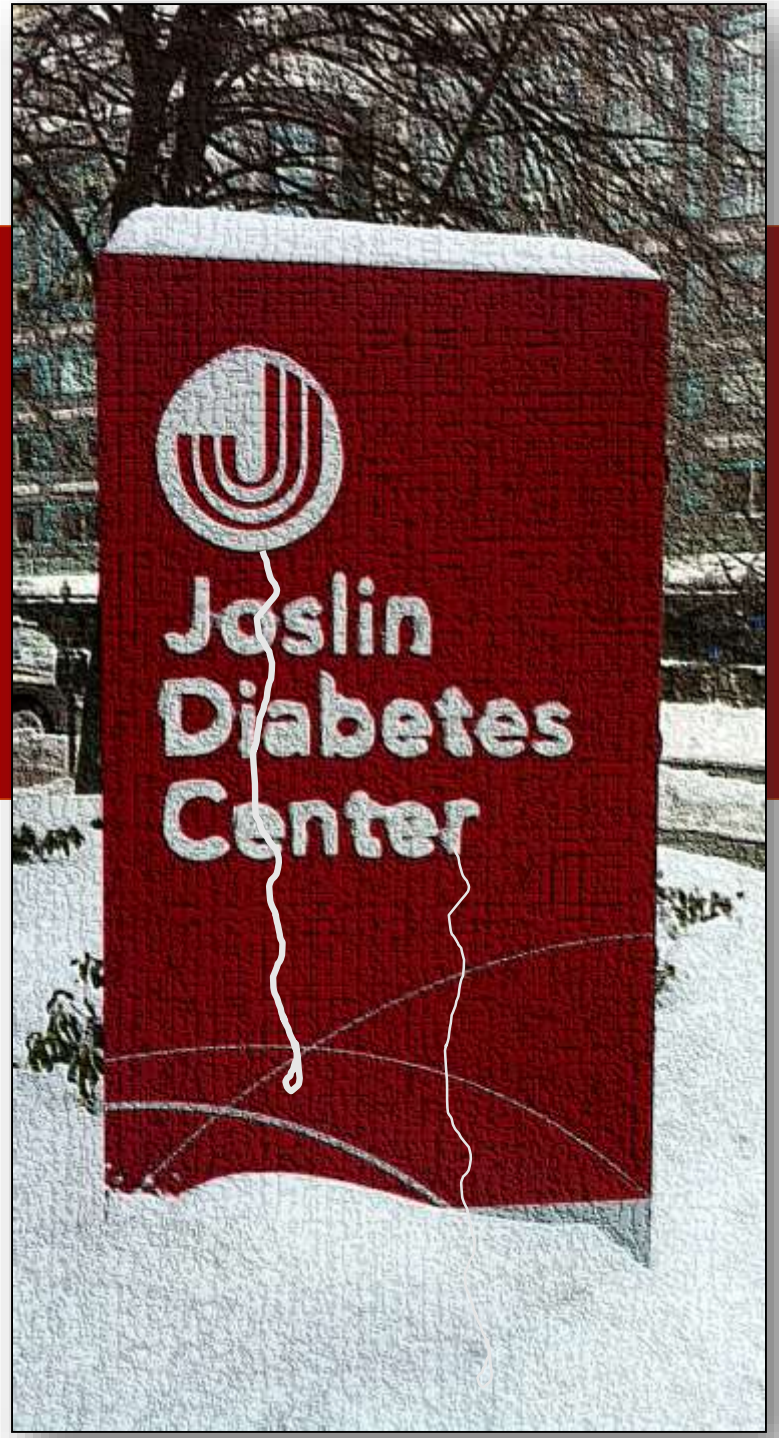
**Delta university**

# Road Map to Diabetes:

## Selecting the Optimal Time for Intervention to Prevent and Reverse Diabetes

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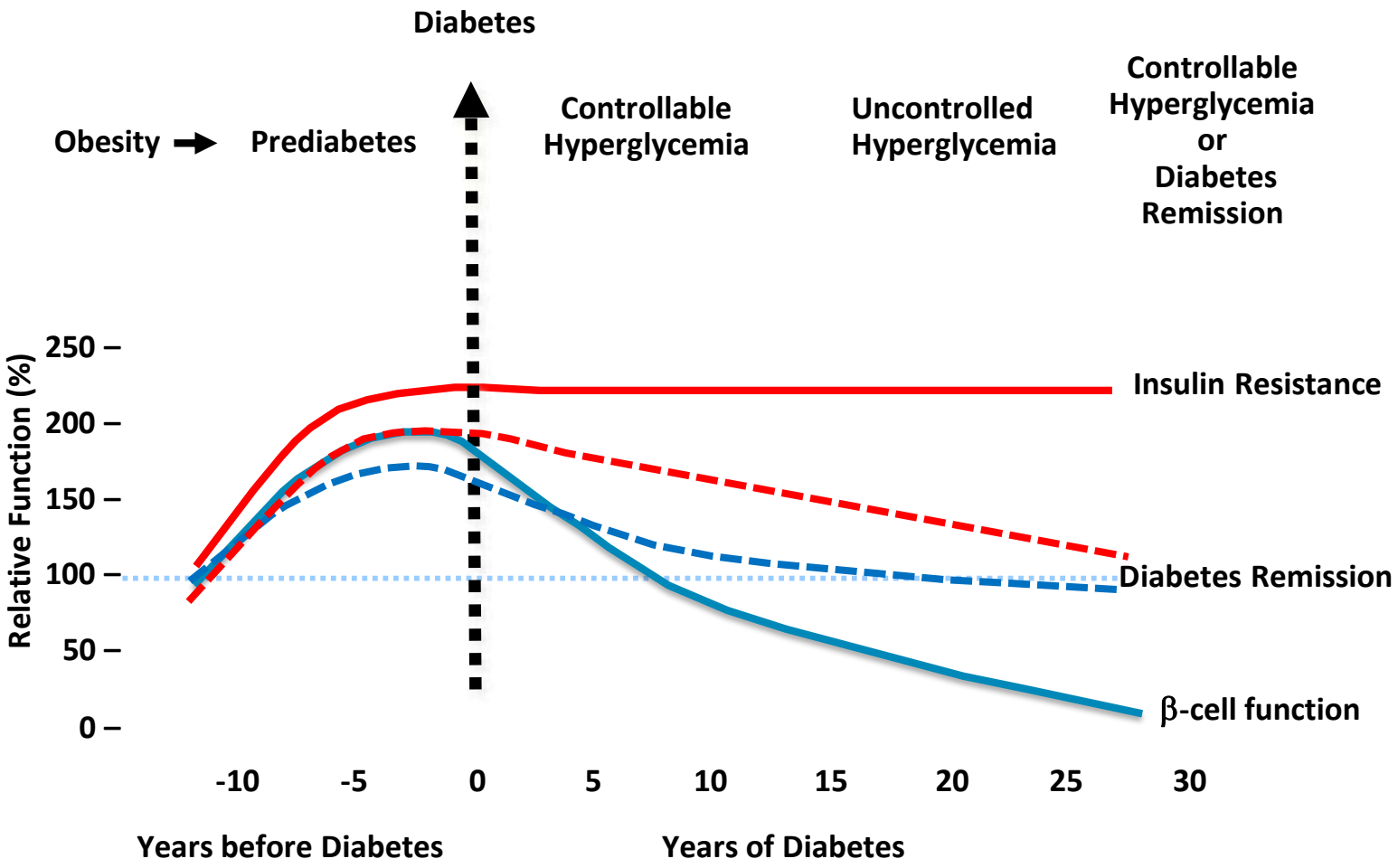
# Natural History of Diabetes



Donna at the end of Why WAIT in July 2009

**Donna at her Why WAIT start in April 2009**

63 yo with type 2 diabetes for 17 years
On 2 oral medications and >100 units of insulin
A1C 7.3%

**Donna at her last visit in July 2018**

Maintained 36 lbs (16 Kg) of weight loss
A1C 6%
0 medications
Diabetes remission for 6 years

# Family History of Diabetes

# Family History of Diabetes

- The single most powerful risk factor
- First degree relatives
- Homozygous or heterozygous
- Age adds a factor

Family History of Diabetes

Slight Weight Gain

Hyperinsulinemia

Accelerated Weight Gain

Insulin Resistance

Escape of Visceral Fat

Slower Weight Gain

Lipotoxicity

Hyperglycemia and Glucotoxicity

Full Picture of the Disease

# Slight Weight Gain

- Usually starts at age 20-30
- Only 2-4 Kg
- Carbohydrates related
- Central and upper half

**Overweight**

Family History of Diabetes
Slight Weight Gain
Hyperinsulinemia
Accelerated Weight Gain
Insulin Resistance
Escape of Visceral Fat
Slower Weight Gain
Lipotoxicity
Hyperglycemia and Glucotoxicity
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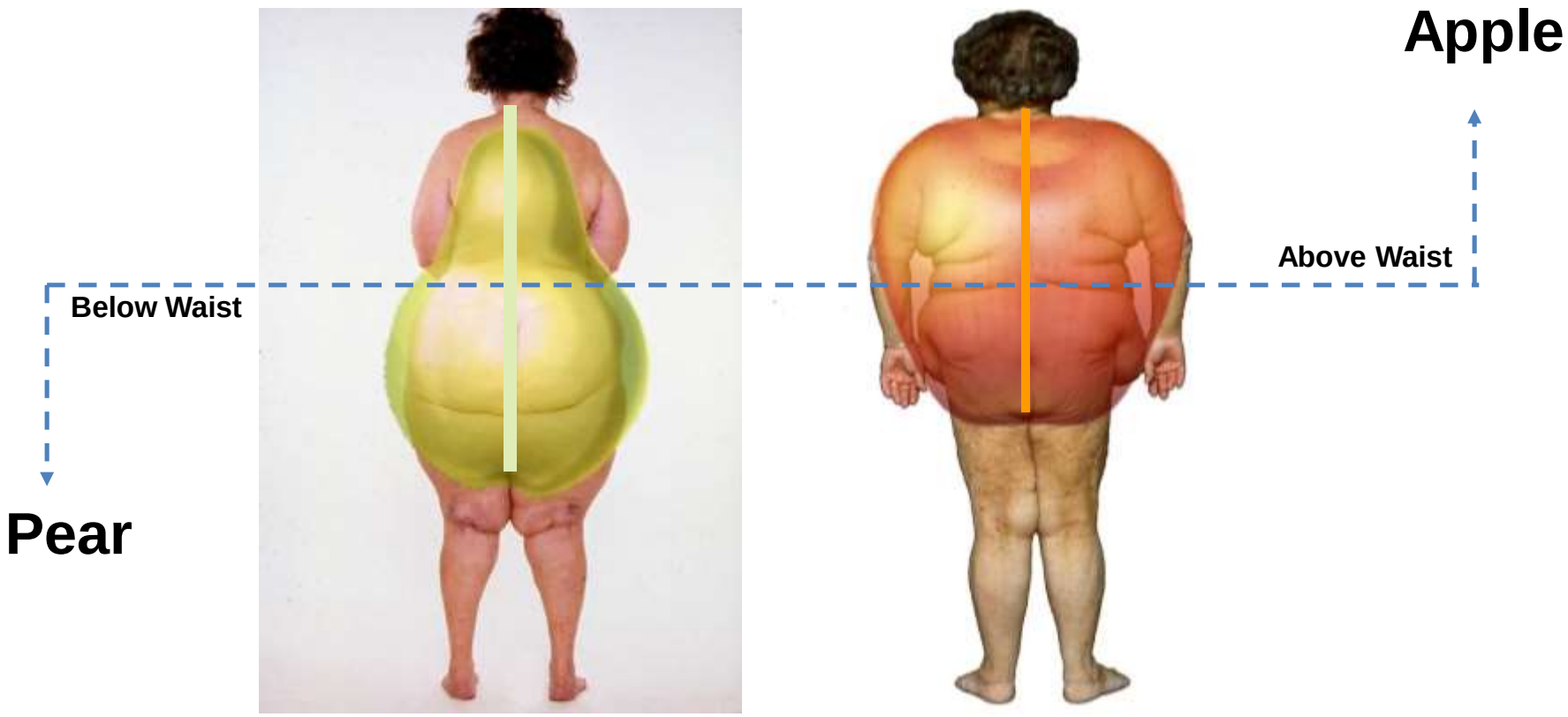
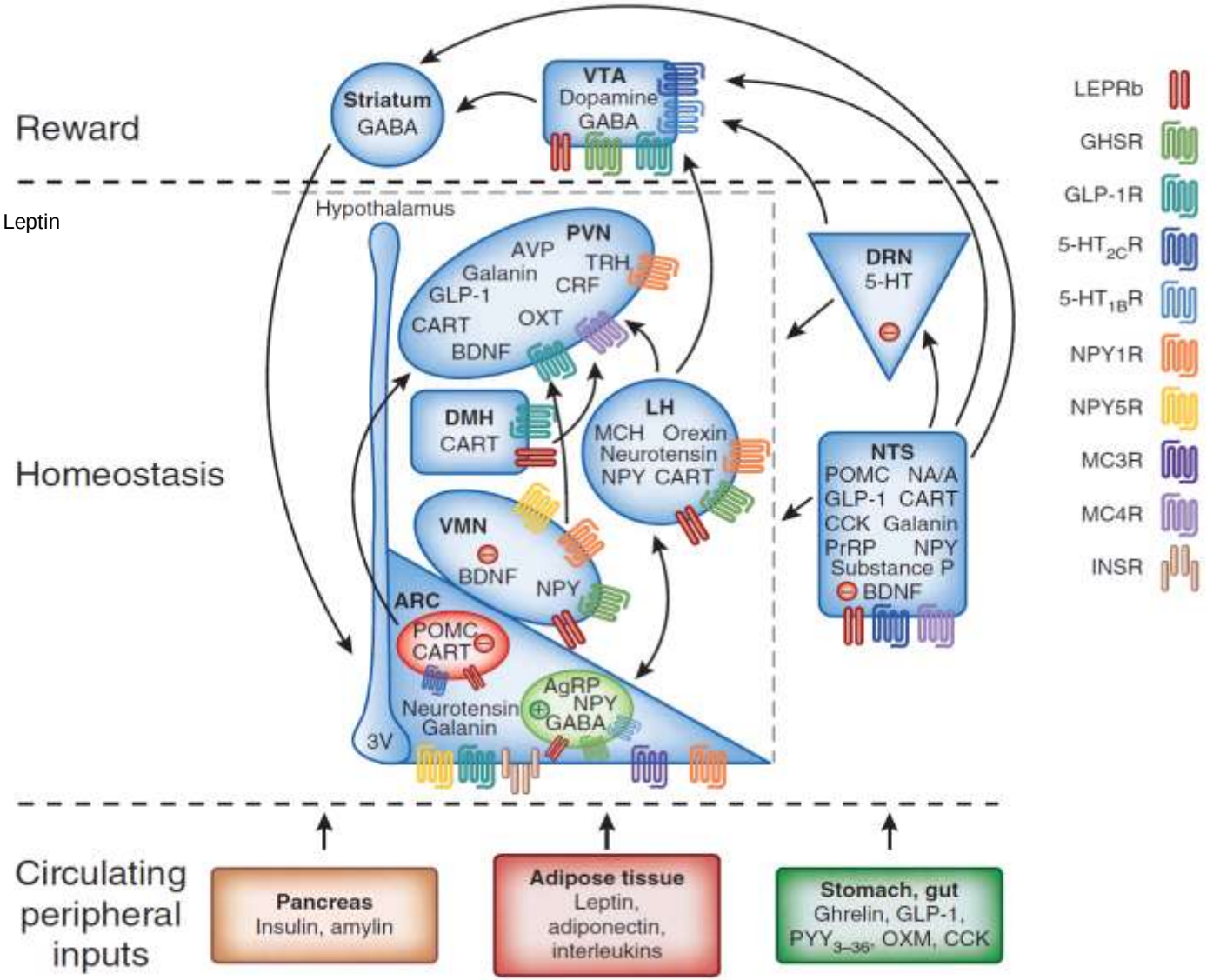
# Body Shape Defines the Risk



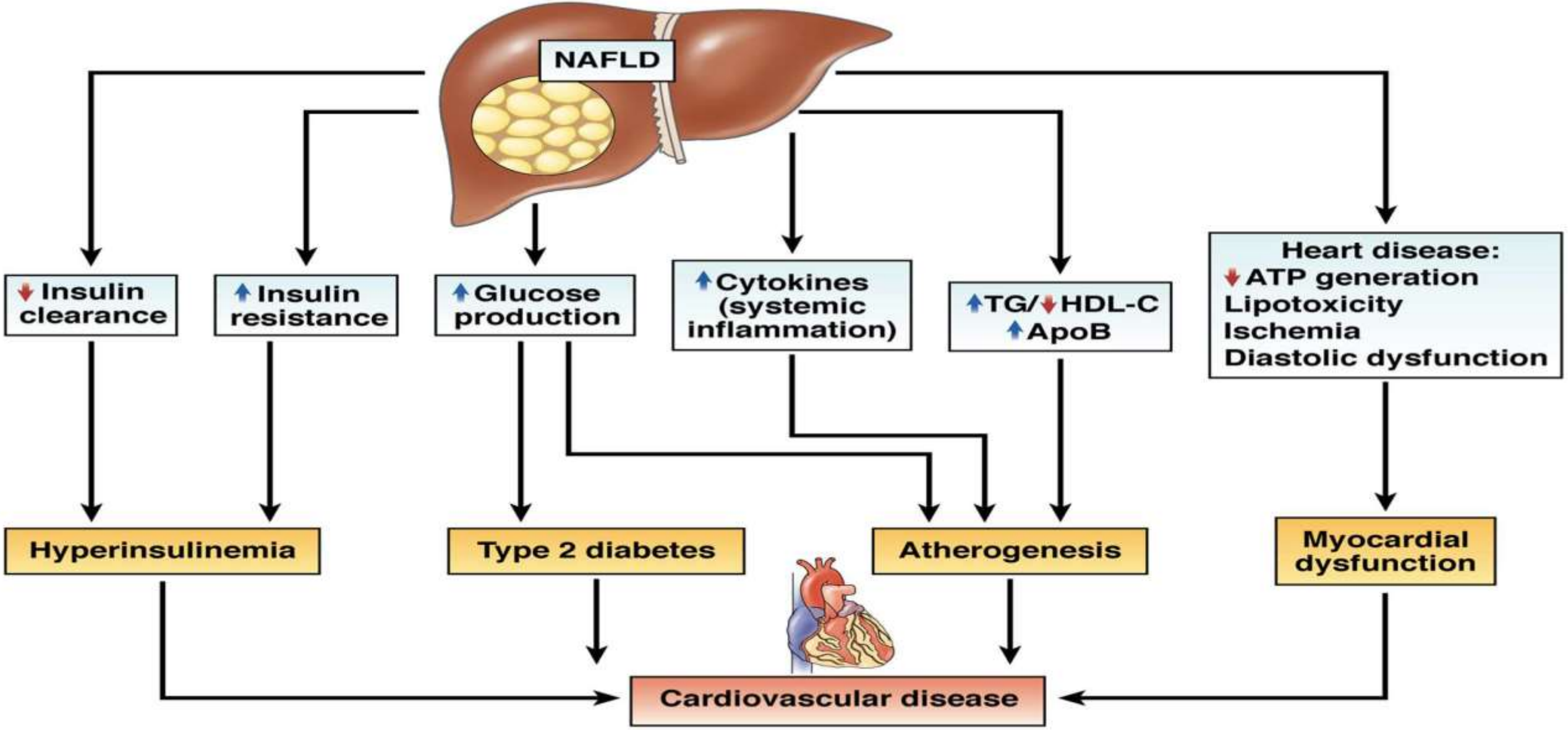
PVN= paraventricular nucleus
DMH= dorsomedial hypothalamus;
VMN= ventromedial nucleus;
LH= lateral hypothalamus;
ARC= arcuate nucleus;
VTA= ventral tegmental area;
DRN= dorsal raphe nucleus;
NTS= nucleus of the solitary tract.
3V= third ventricle.

1. LEPRb= Long 'signaling' Isoform of the Leptin
2. GHS= ghrelin
3. GLP-1= glucagon-like peptide 1
4. 5HT= Serotonin
5. NPY1= Neuropeptide Y1
6. NPY5= Neuropeptide Y5
7. MC3= melanocortin 3
8. MC4= melanocortin 4
9. INS= insulin
10. GABA= γ-Aminobutyric Acid
11. Dopamine
12. NA= noradrenaline
13. A= adrenaline
14. Leptin
15. Amylin
16. PYY3–36= peptide YY residues 3–36
17. Neurotensin
18. Galanin
19. Orexin
20. OXT= oxytocin
21. AVP= vasopressin
22. OXM= oxyntomodulin
23. CCK= cholecystokinin.
24. Substance P
25. CRF= corticotropin-releasing factor
26. TRH= thyrotropin-releasing hormone
27. PrRP= prolactin-releasing peptide
28. MCH= melanin-concentrating hormone
29. POMC= Pro-Opiomelanocortin
30. AgRP= Agouti-Related Protein
31. BDNF= Brain-derived Neurotrophic Factor
32. TrKB= Tropomyosin Receptor Kinase B
33. CART= cocaine- and amphetamine-regulated transcript
34. Ntrk2= Neurotrophic Tyrosin Kinase

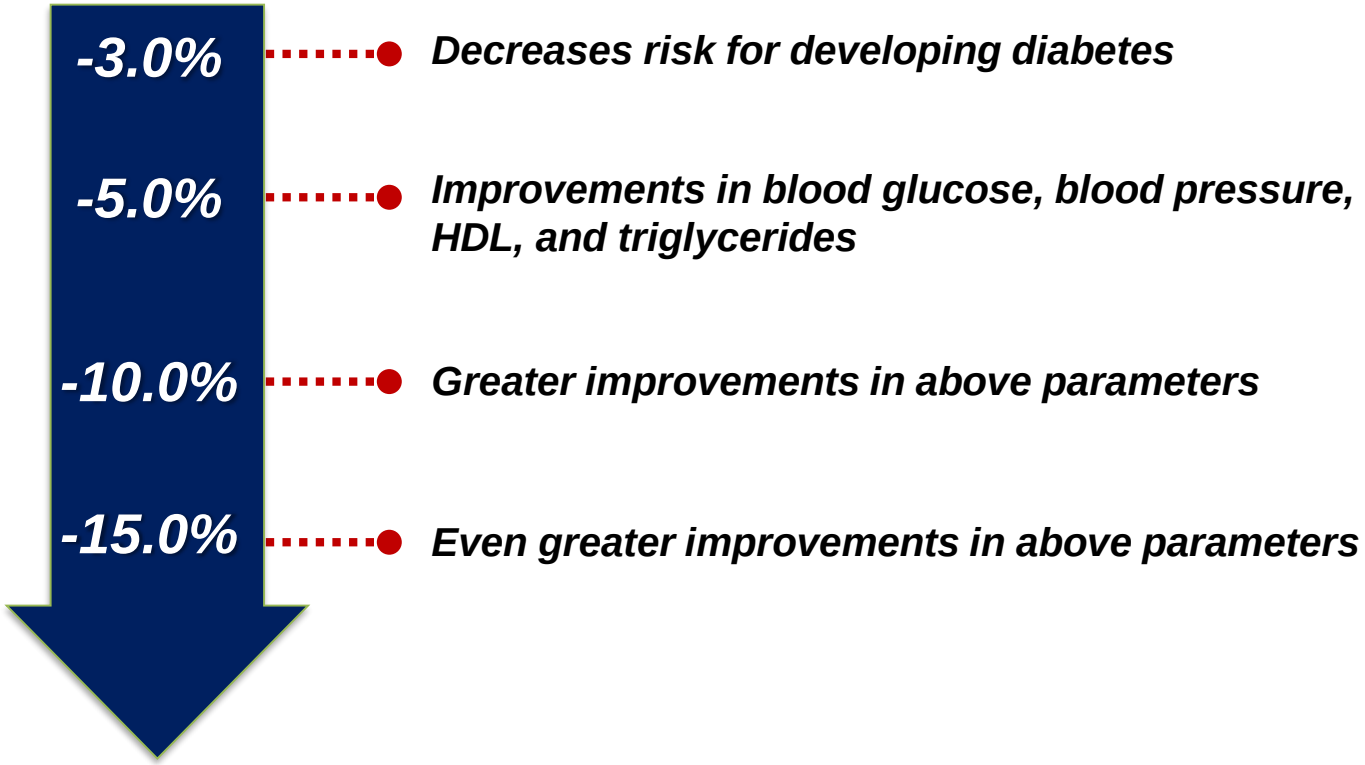


# Metabolic Consequences of NAFLD

Cusi. Gastroenterology. 2012;142:711.



# How Much Weight to Lose?



# Hyperinsulinemia

- Functioning pancreatic β-cells
- Hypertrophied pancreas
- High fasting insulin and C-peptide
- Insulin sensitive

**Overweight**
**Hyperinsulinemia**

Family History of Diabetes
Slight Weight Gain
Hyperinsulinemia
Accelerated Weight Gain
Insulin Resistance
Escape of Visceral Fat
Slower Weight Gain
Lipotoxicity
Hyperglycemia and Glucotoxicity
Full Picture of the Disease

# Accelerated Weight Gain

- Caused by the growth effect of insulin
- 5-10 Kg in less than 6 months
- Strong indicator of upcoming type 2 diabetes
- Normal insulin sensitivity, high insulin & c-peptide

**Obesity**
**Hyperinsulinemia**

Family History of Diabetes
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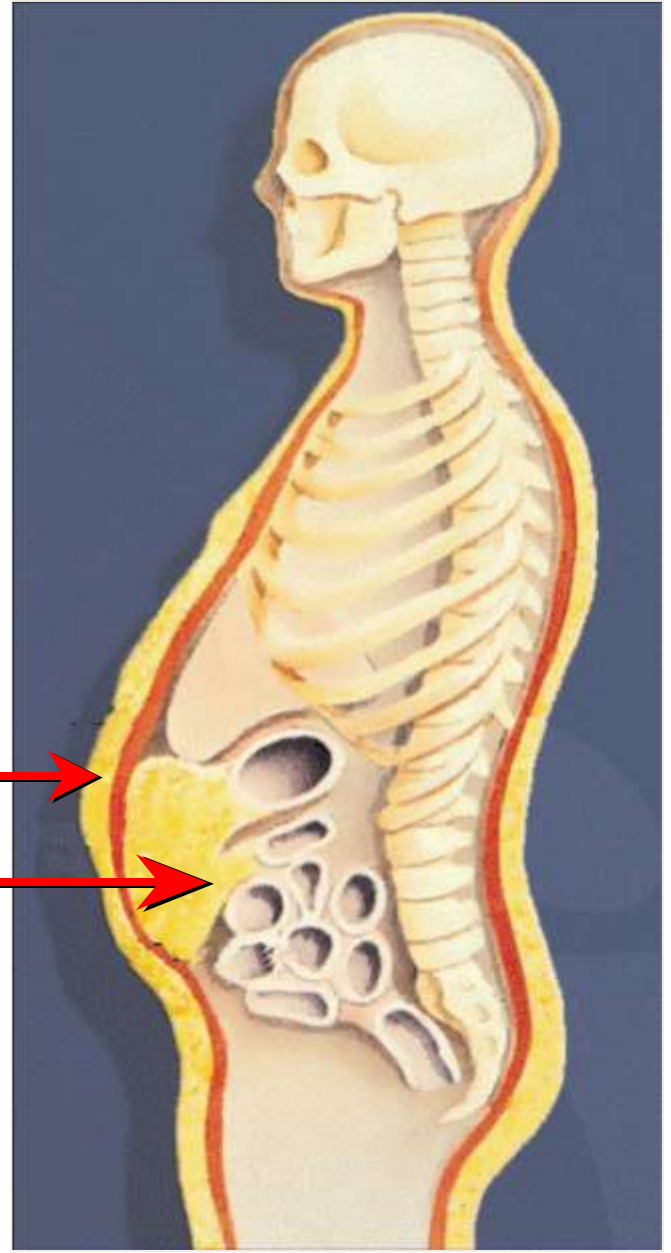
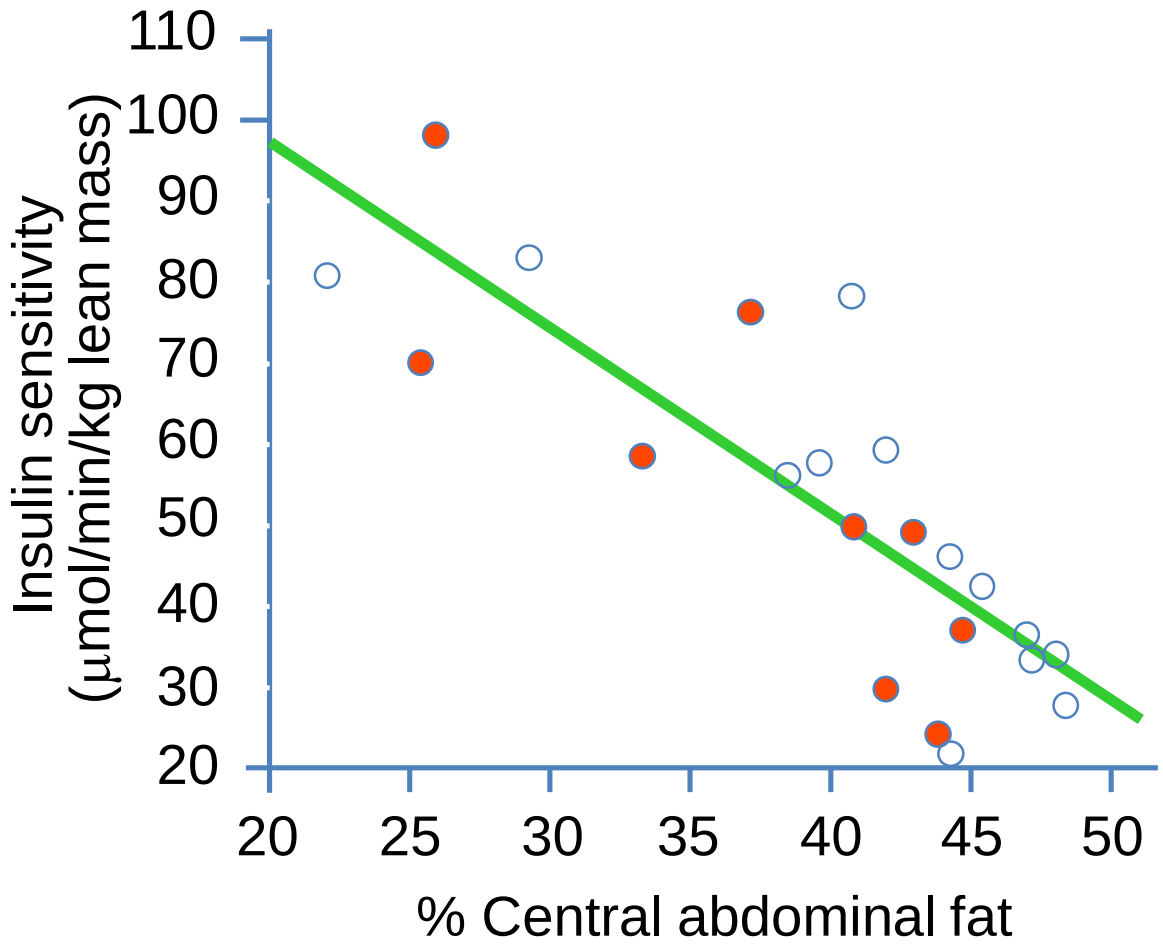
# Intra-abdominal Fat: The Critical Adipose Depot



# Insulin Sensitivity and Central Adiposity

**Variance in $S_I$ Accounted for by Regional Fat Mass**

| Region | $R^2$ Value |
|---|---|
| Central abdomen | 0.80 |
| Trunk | 0.60 |
| All nonabdominal | 0.44 |
| Arms | 0.30 |
| Legs | 0.10 |



# Insulin Resistance

- Liver, muscles and adipose tissue
- Increase waist circumference
- Still high fasting insulin & c-peptide

**Obesity**
**Hyperinsulinemia**
**Insulin resistance**

Family History of Diabetes
Slight Weight Gain
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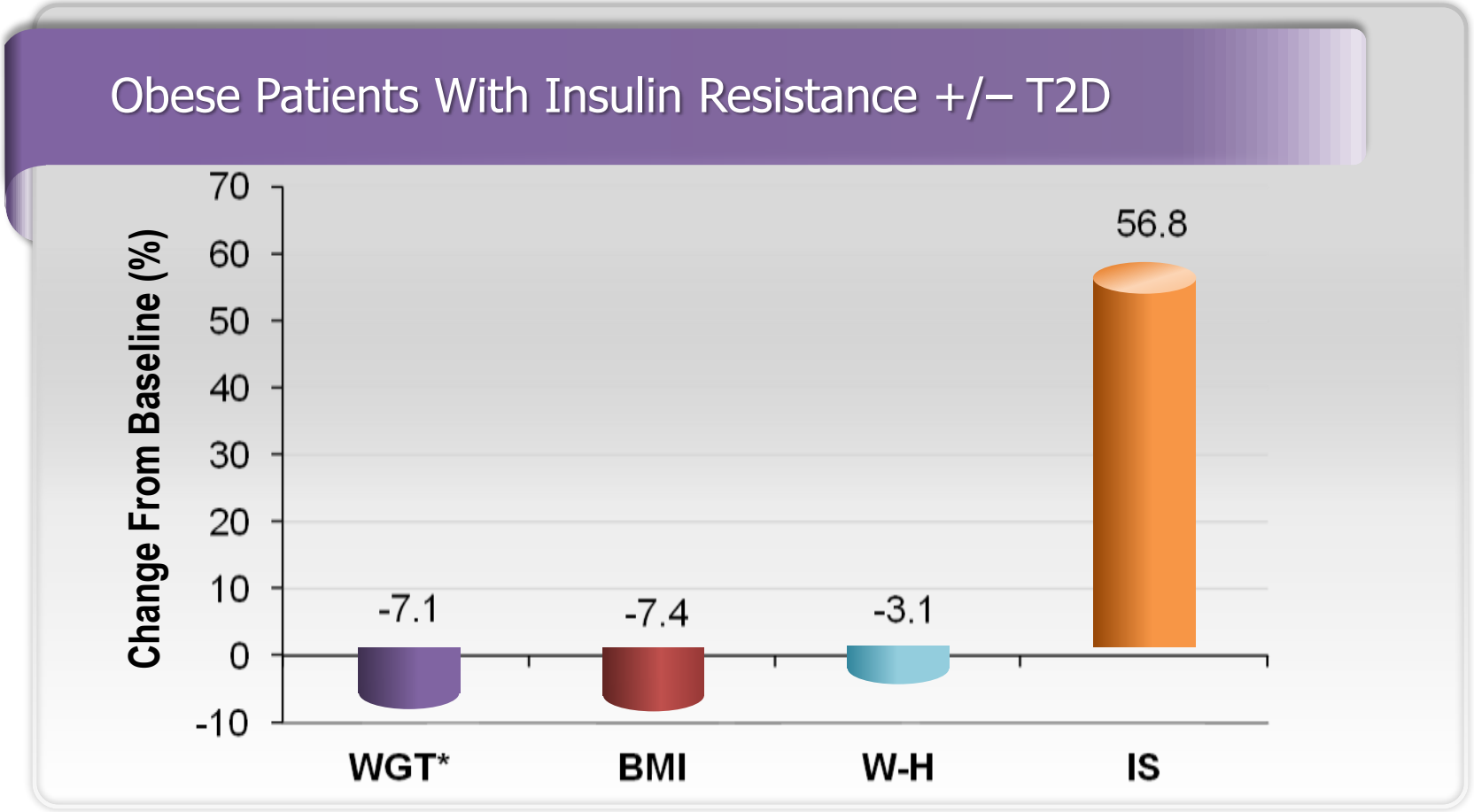
# Weight Loss Improves Insulin Sensitivity and May Prevent Diabetes or Reverse it




*$P$<0.001.

WGT, weight; BMI, body mass index; W-H, waist-to-hip ratio; IS, insulin sensitivity

# Escape of Visceral fat

- **Selective escape of visceral fat from insulin suppression of lipolysis**
- **Stoppage of lipogenesis in abdominal area and increase lipolysis of visceral fat**
- **High inflammation markers (TNF-a, IL-6, hsCRP, MCP-1, PAI-1)**

**Obesity**
**Hyperinsulinemia**
**Insulin resistance**
**Subclinical Inflammation**

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# Adipokines Theory

Genetic Factors

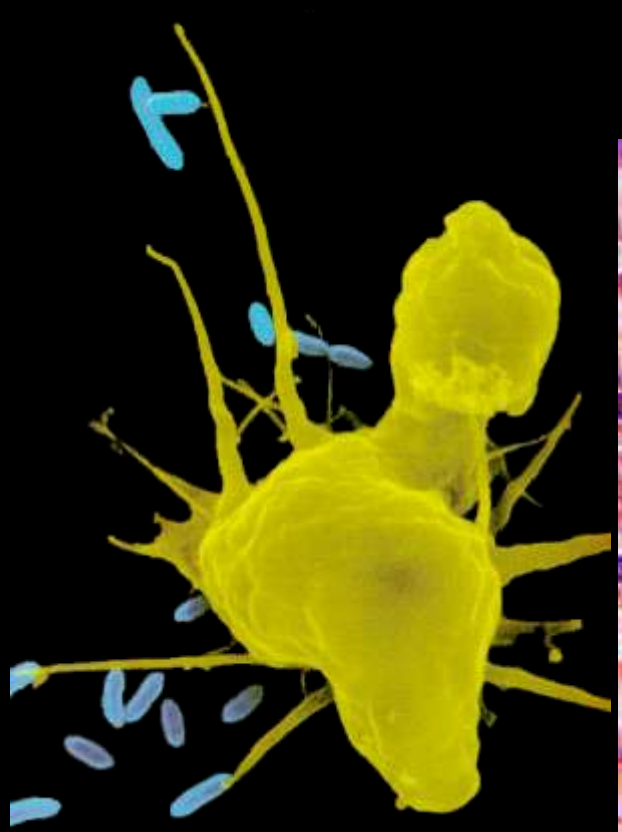
Environmental factors:
- ↓ Physical Activity
- ↑ Food Intake

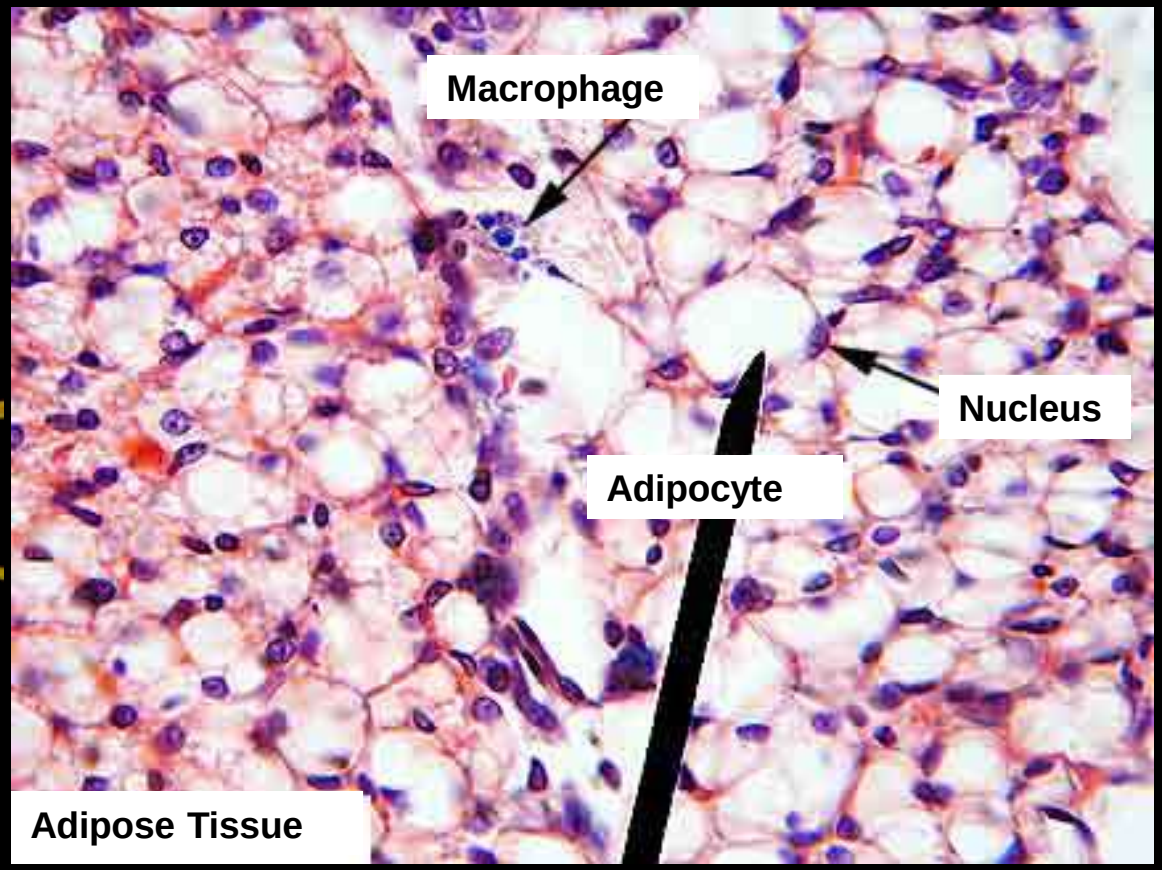

↑ FFA
↑ TNF-α
↑ IL-6
↑ PAI-1
↑ MCP-1
↑ Resistin
↓ Adiponectin

Insulin Resistance

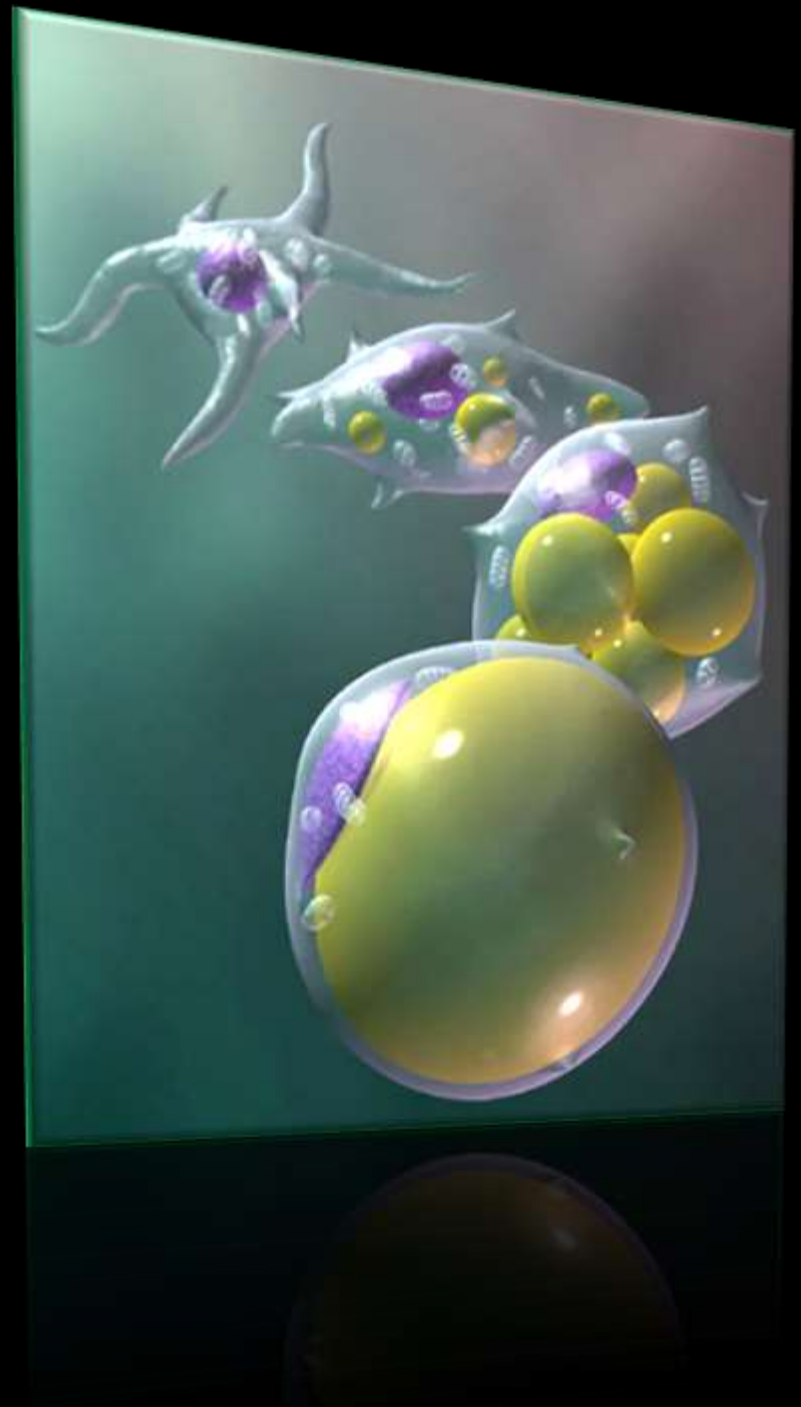
Endothelial Dysfunction

# Adipose Tissue Resident Macrophages





# Adipogenesis

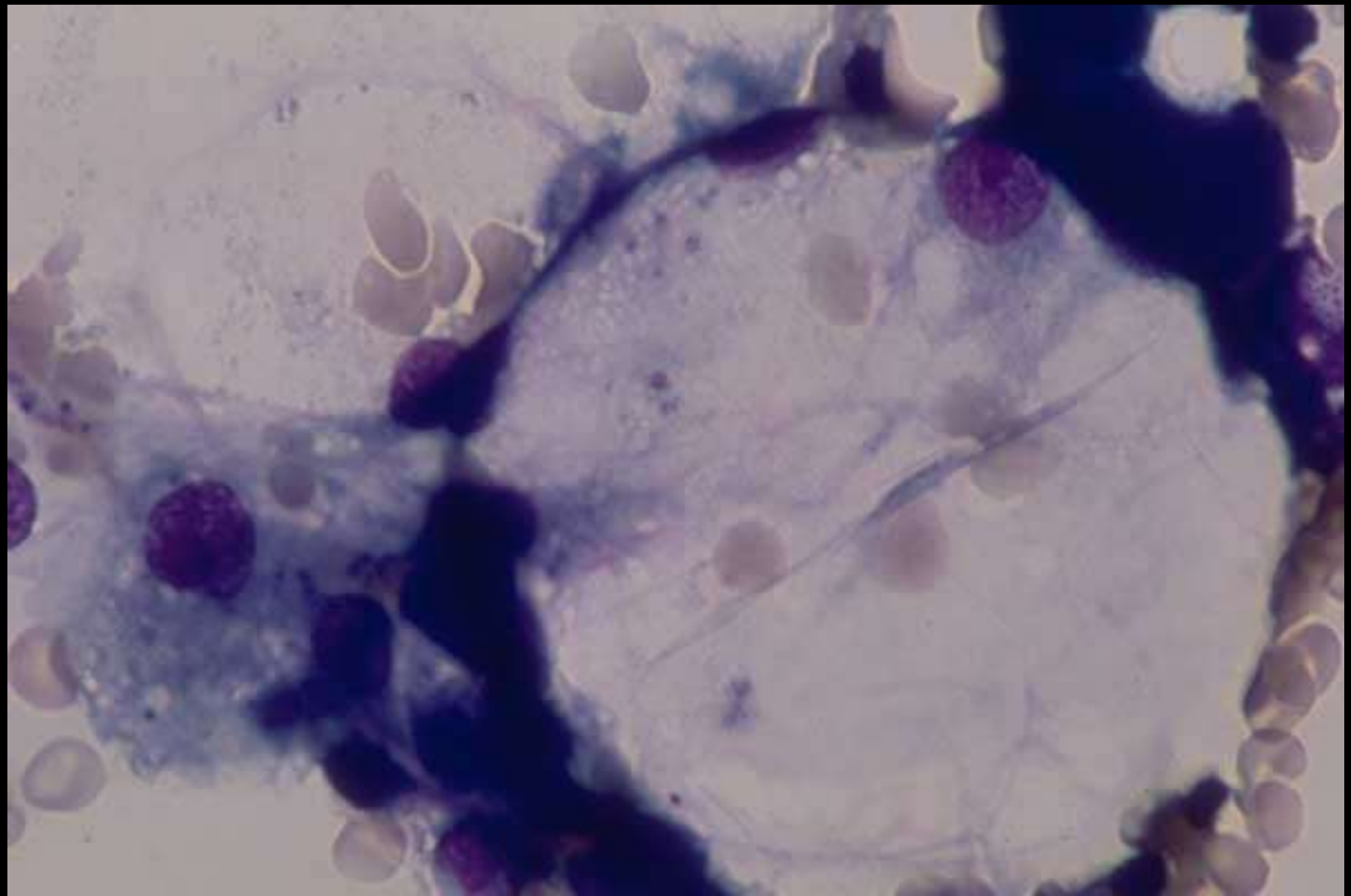


G. Carlson 2006

# Apoptosis

G. Carlson 2006

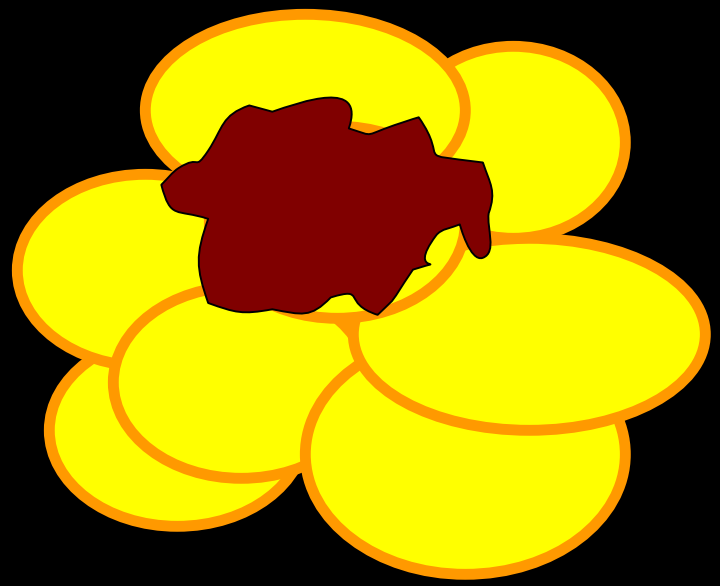
# Adipose Tissue Resident Macrophages



MCP-1

PAI-1

*Visceral Fat*

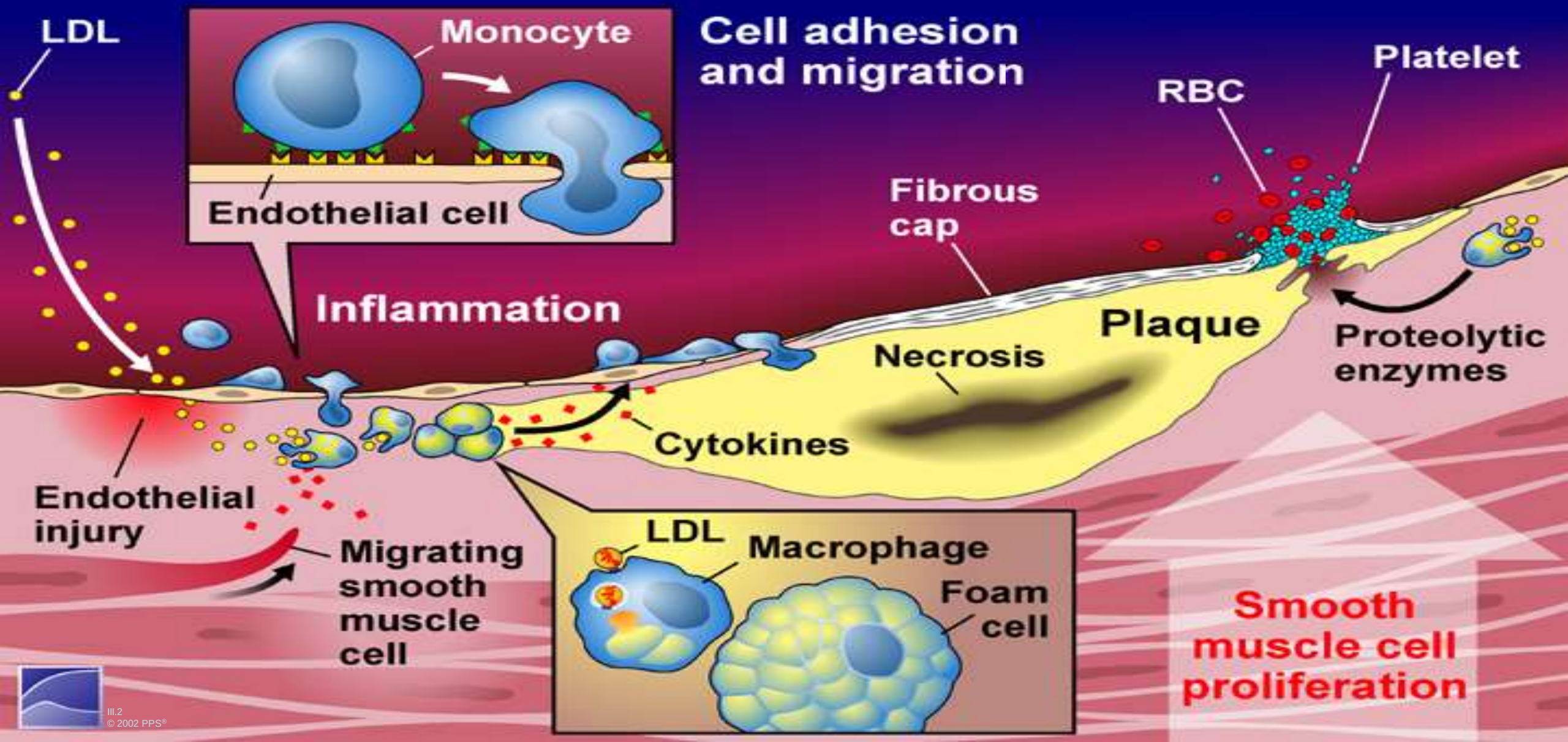


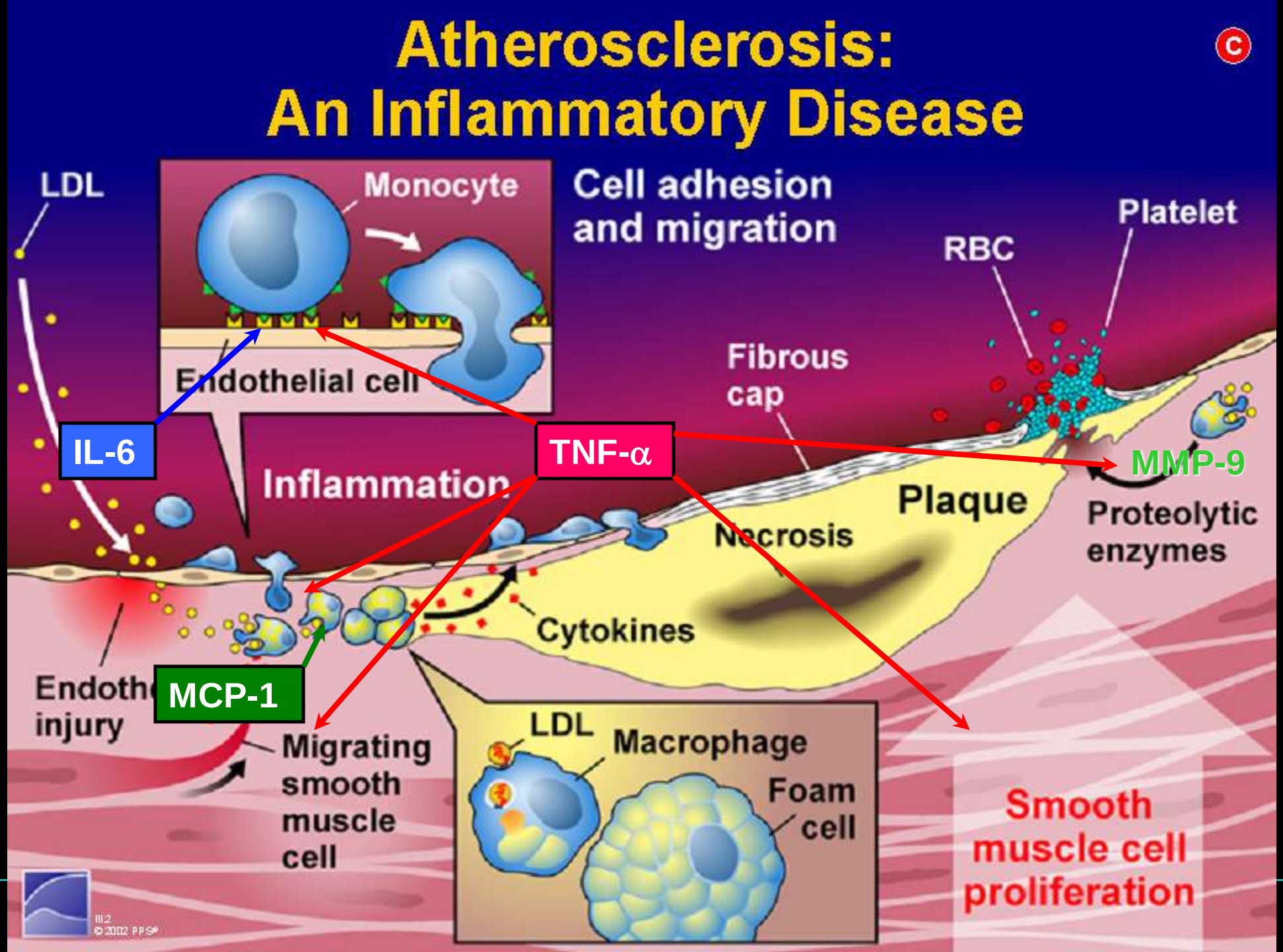
TNF-α

IL-6

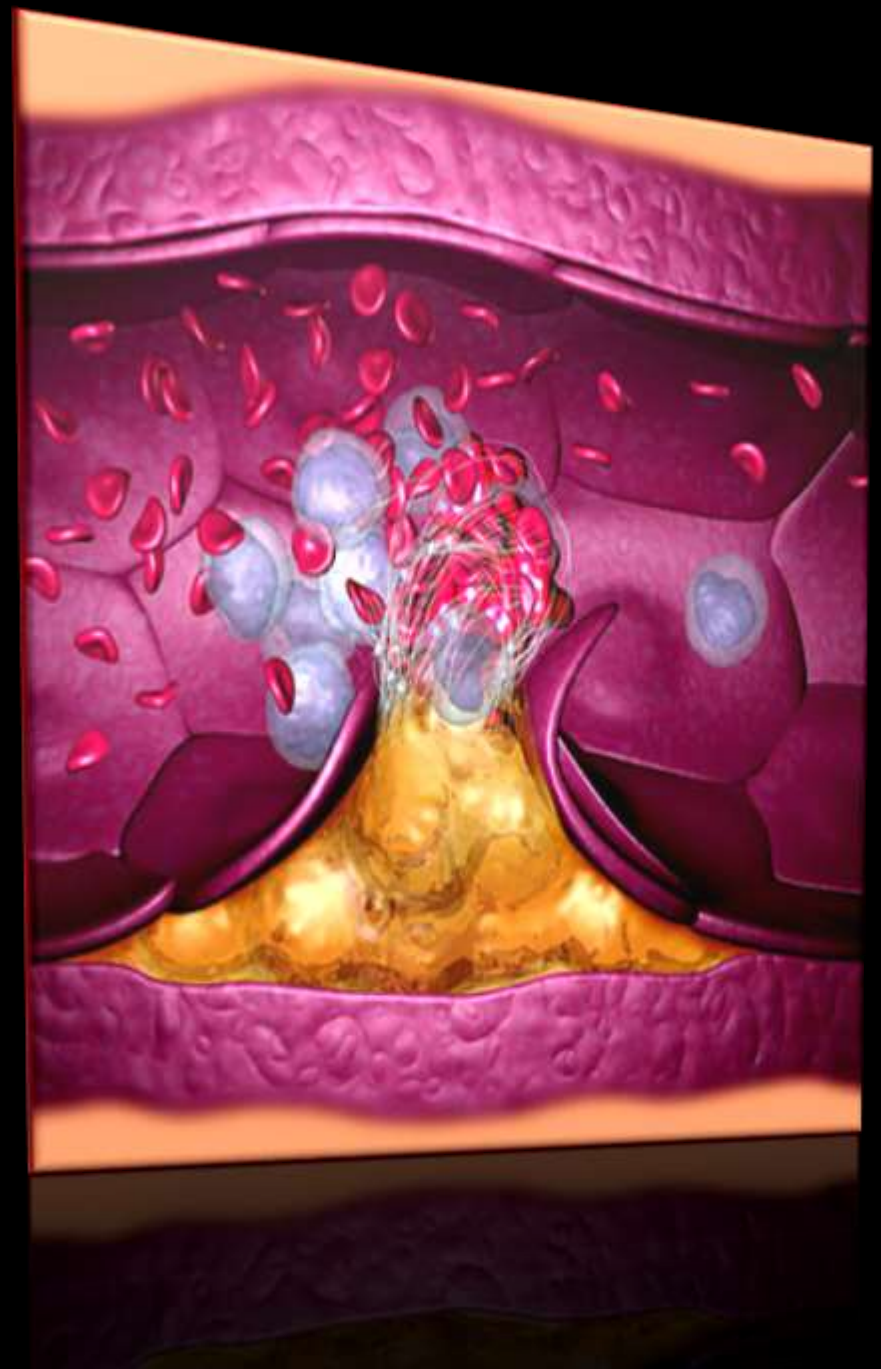
Hamdy O. Expert Rev Cardiovasc Ther 2005;3(2):231-241

# Atherosclerosis: An Inflammatory Disease




Atherosclerosis:
An Inflammatory Disease
LDL
Monocyte
Cell adhesion
and migration
Platelet
RBC
Endothelial cell
Fibrous
cap
IL-6
TNF-α
Inflammation
MMP-9
Plaque
Proteolytic
enzymes
Necrosis
Cytokines
Endoth
injury
MCP-1
Migrating
smooth
muscle
cell
LDL
Macrophage
Foam
cell
Smooth
muscle cell
proliferation

# Atherogenesis



G. Carlson 2006

# The Link Between Obesity, Diabetes and Cardiovascular Disease

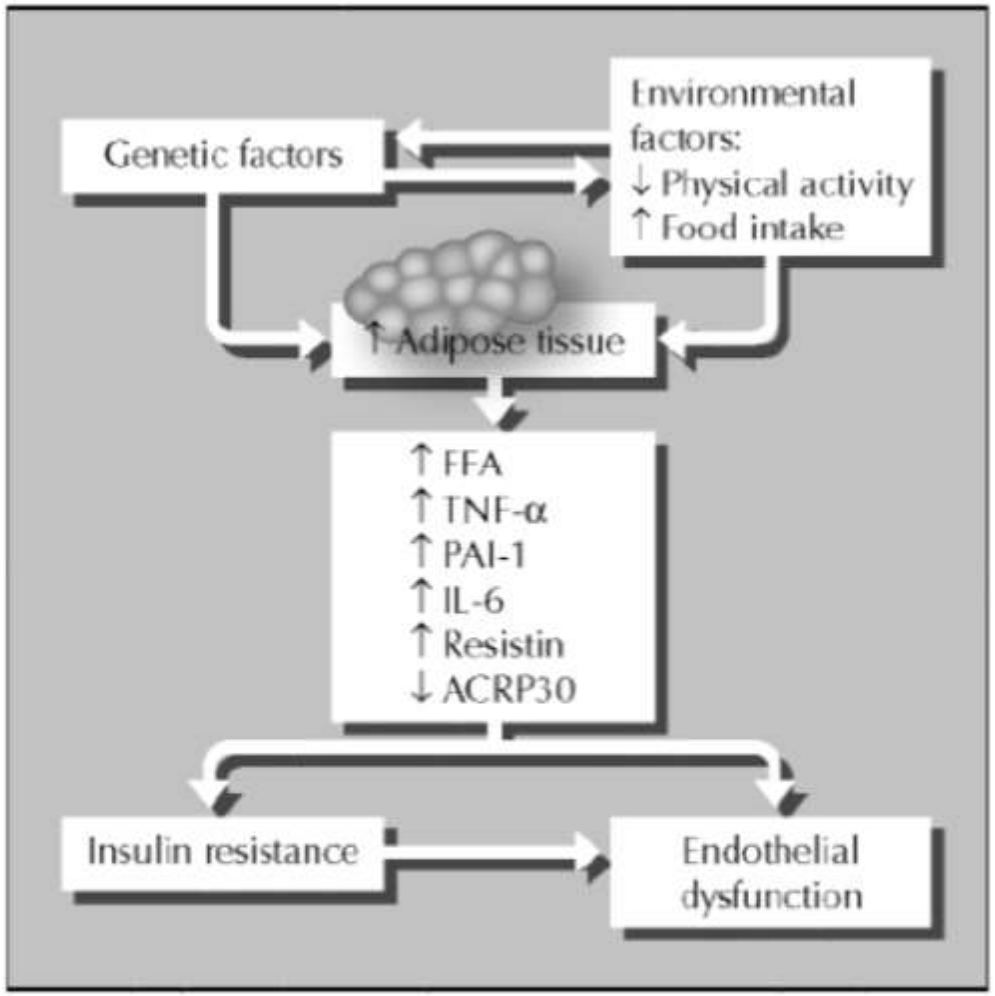



**Figure 1.** The links between adipose tissue mass and both insulin resistance and endothelial dysfunction. ACRP30—adipocyte complement-related protein; FFA—free fatty acid; IL-6—interleukin-6; PAI-1—plasminogen activator inhibitor-1; TNF-α—tumor necrosis factor-α.

Aldhahi W & Hamdy O. Curr Diab Rep. 2003;3(4):293-8

# Slower Weight Gain

- Deceleration of weight gain in central area due to lipolysis
- Continuation of peripheral weight gain

Family History of Diabetes
Slight Weight Gain
Hyperinsulinemia
Accelerated Weight Gain
Insulin Resistance
Escape of Visceral Fat
**Slower Weight Gain**
Lipotoxicity
Hyperglycemia and Glucotoxicity
Full Picture of the Disease

**Obesity**
**Hyperinsulinemia**
**Insulin resistance**
**Subclinical Inflammation**

# Lipotoxicity

- High influx of FFA into the portal circulation
- High level of serum FFA
- Fatty infiltration of liver and pancreas
- β-cell dysfunction

**Obesity**
**Normal or low fasting insulin**
**Insulin resistance**
**Subclinical Inflammation**
**High serum FFA**

Family History of Diabetes
Slight Weight Gain
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Accelerated Weight Gain
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Slower Weight Gain
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Hyperglycemia and Glucotoxicity
Full Picture of the Disease

# Hyperglycemia and Glucotoxicity

- High fasting and PP plasma glucose due to β-cell dysfunction
- Glucotoxicity occurs if diagnosis is missed with further β-cells dysfunction

Obesity
Normal or low fasting insulin
Insulin resistance
Subclinical Inflammation
High serum FFA
Hyperglycemia

Family History of Diabetes
Slight Weight Gain
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Accelerated Weight Gain
Insulin Resistance
Escape of Visceral Fat
Slower Weight Gain
Lipotoxicity
Hyperglycemia and Glucotoxicity
Full Picture of the Disease

# Full Picture of the disease

- Aggressive intervention is needed before further damage of β-cells by gluco- and lipotoxicity
- Insulin may be needed for short-term use in severe cases

**Obesity**
**Normal or low fasting insulin**
**Insulin resistance**
**Subclinical Inflammation**
**High serum FFA**
**Hyperglycemia**

Family History of Diabetes
Slight Weight Gain
Hyperinsulinemia
Accelerated Weight Gain
Insulin Resistance
Escape of Visceral Fat
Slower Weight Gain
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# Practical Tips

- Patient may stay at each stage for a variable period of time giving more chance for intervention
- better understanding of the clinical and biochemical indicators
- Recognition of each stage may lead to precise intervention and indicates accurate prognosis

Family History of Diabetes
Slight Weight Gain
Hyperinsulinemia
Accelerated Weight Gain
Insulin Resistance
Escape of Visceral Fat
Slower Weight Gain
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Hyperglycemia and Glucotoxicity
Full Picture of the Disease

# Intervention and Reversibility

| | |
|---|---|
| Avoid Weight Gain → | Family History of Diabetes |
| Aim for weight loss → | Slight Weight Gain |
| Prevention if diagnosed → | Hyperinsulinemia |
| Optimal time for prevention → | Accelerated Weight Gain |
| Precise prevention time if diagnosed → | Insulin Resistance |
| Difficult to diagnose clinically → | Escape of Visceral Fat |
| Clinical indicator by careful history → | Slower Weight Gain |
| Dangerous Situation → | Lipotoxicity |
| May need aggressive therapy → | Hyperglycemia and Glucotoxicity |
| Reversable within 5 years → | Full Picture of the Disease |

# Proven Effective Ways to Manage T2DM at Different Stages

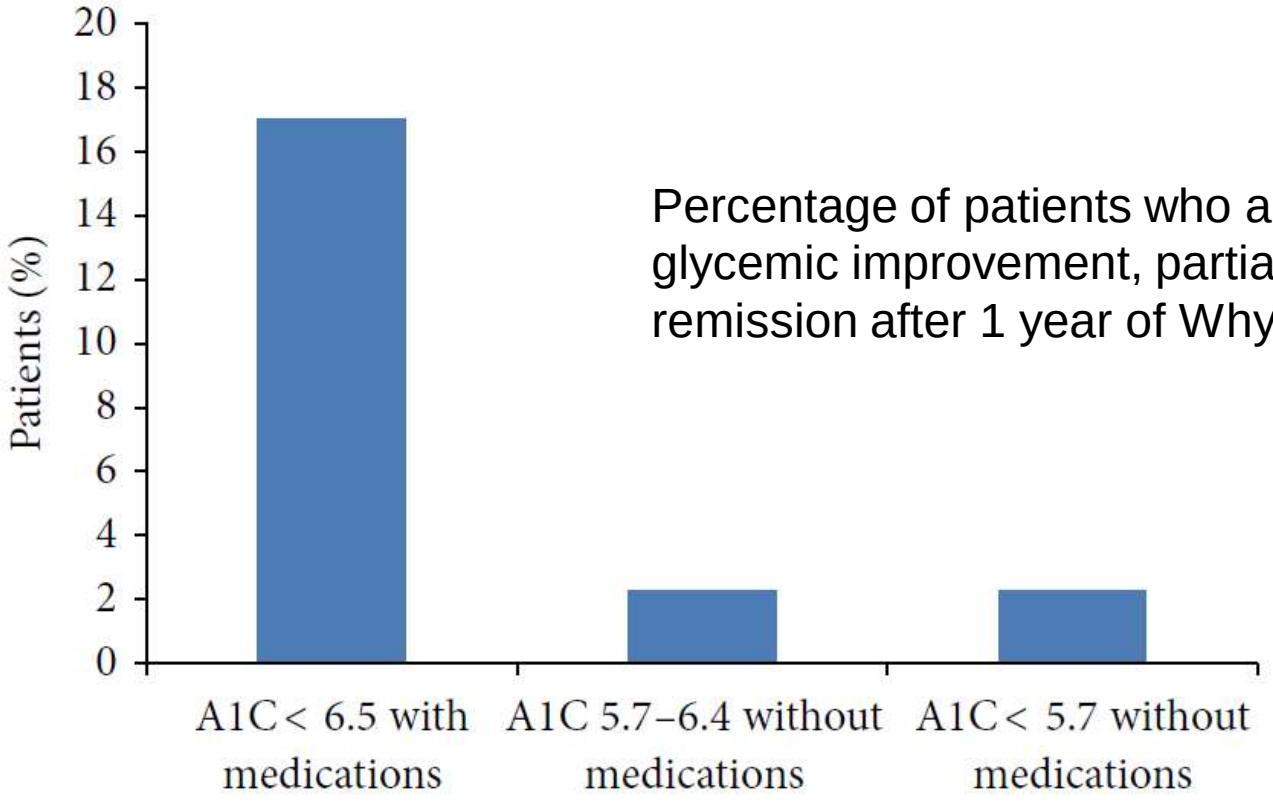
| | |
|---|---|
| | Family History of Diabetes |
| | Slight Weight Gain |
| | Hyperinsulinemia |
| Medical or Surgical Weight Loss → | Accelerated Weight Gain |
| Metformin → | Insulin Resistance |
| | Escape of Visceral Fat |
| | Slower Weight Gain |
| Insulin, TZDs, SUs → | Lipotoxicity |
| Periods of fasting, SGLT-2 I → | Hyperglycemia and Glucotoxicity |
| GLP-1 analogs → | Full Picture of the Disease |

*Research Article*

# Diabetes Remission after Nonsurgical Intensive Lifestyle Intervention in Obese Patients with Type 2 Diabetes

**Adham Mottalib, Mahmoud Sakr, Mohamed Shehabeldin, and Osama Hamdy**

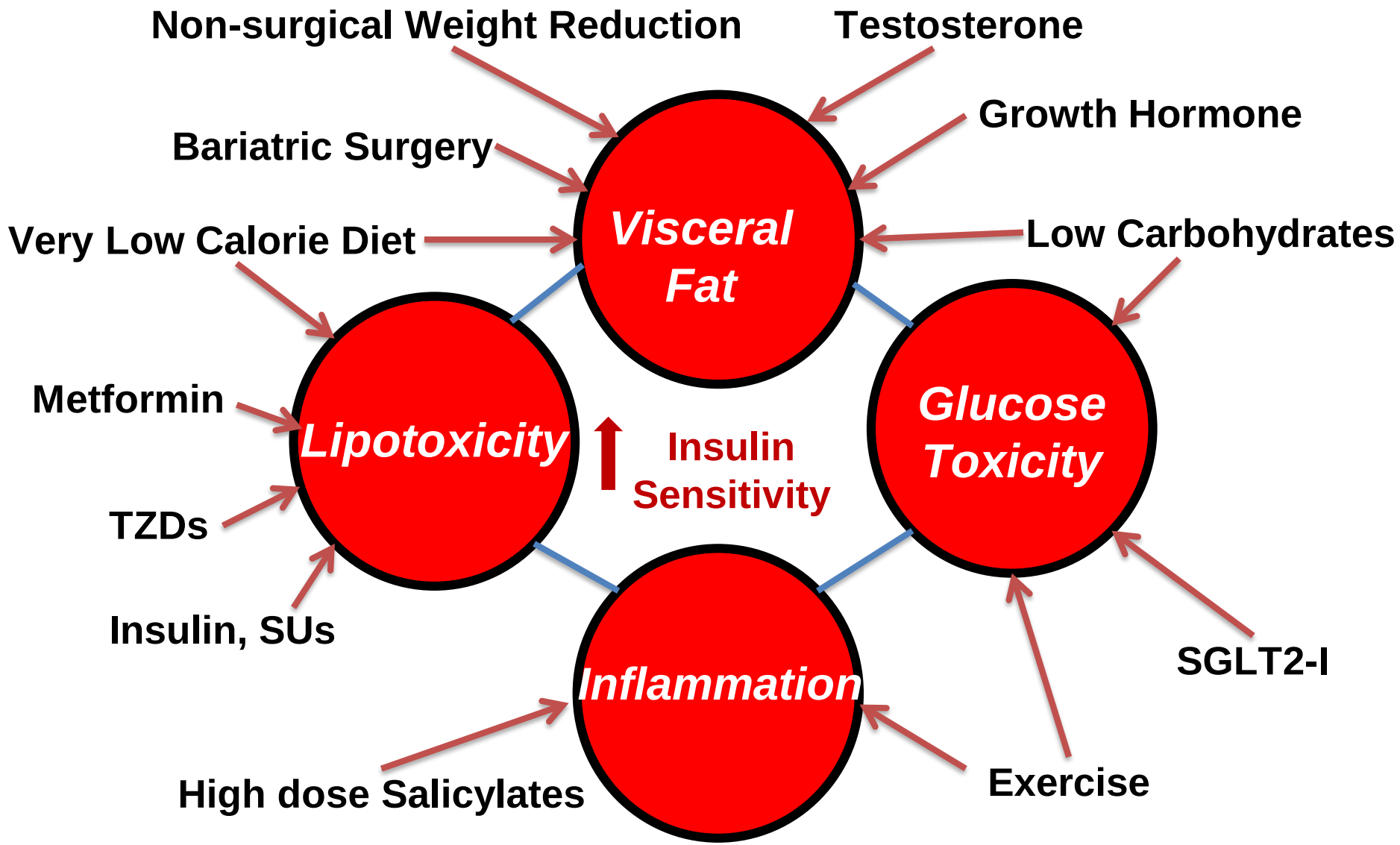
*Joslin Diabetes Center, One Joslin Place, Boston, MA 02215, USA*




Percentage of patients who achieved major glycemic improvement, partial or complete remission after 1 year of Why WAIT program

Mottalib A, Hamdy O et al. J Diabetes Res. 2015;2015:468704

# Targeting Insulin Resistance



Hepatology

BMJ Open Gastroenterology

# Prevalence of and risk factors for non-alcoholic fatty liver disease (NAFLD) and fibrosis among young adults in Egypt

Shaheen Tomah ,[1,2] Osama Hamdy,[1,2] Megahed M Abuelmagd,[3] Attia H Hassan,[4] Naim Alkhouri,[5] Marwa R Al-Badri,[1,2] Hannah Gardner,[1] Ahmed H Eldib,[1,2] Elsayed A Eid[4]

BMJ Open Gastroenterol: first published as 10.1136/b

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgast-2021-000780).

Data from this work were presented at the American Diabetes Association's 79th Scientific Sessions, June 2019, San Francisco, CA, USA.

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## ABSTRACT

**Objective** Limited literature has examined the epidemiology of non-alcoholic fatty liver disease (NAFLD) and fibrosis among young adults in Egypt, a country with one of the highest obesity rates globally. We assessed the prevalence of steatosis and fibrosis among college students in Egypt.

**Design** In this cross-sectional study, we recruited students unaware of having fatty liver via a call-for-participation at a private university in the Dakahlia governorate of Egypt. Primary outcomes were the prevalence of steatosis as determined by the controlled attenuation parameter component of transient elastography and fibrosis as determined by the liver stiffness measurement component of transient elastography. Secondary outcomes were clinical parameters and socioeconomic factors associated with the presence and severity of steatosis and fibrosis.

**Results** Of 132 participants evaluated for the study, 120 (91%) were included (median (IQR) age, 20 (19–21) years; 65 (54.2%) female). A total of 38 participants (31.6%) had steatosis, among whom 22 (57.9%) had S3 (severe) steatosis. There was a higher risk for steatosis in persons with overweight (adjusted OR 9.67, 95% CI (2.94 to 31.7, p<0.0001) and obesity (adjusted OR 13.87, 95% CI 4.41 to 43.6, p<0.0001) compared with lean persons. Moreover, higher level of parental education was associated with progressing steatosis stages (S1–S3). Six (5%) participants had transient elastography values equivalent to F2–F3 fibrosis (four with F2 fibrosis (≥7.9 kPa), and two with F3 fibrosis (≥8.8 kPa)).

**Conclusion** In this cohort of college students in Egypt, around 1 in 3 had steatosis, and 1 in 20 had moderate-to-advanced fibrosis, an established risk factor for hepatic and extrahepatic morbidity and mortality. These data underscore the urgency to address the silent epidemic of NAFLD among young adults in the Middle East-North Africa region.

## Summary box

### What is already known about this subject?

- Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in the world.
- Egypt has one of the highest obesity rates globally.
- There are limited data on the prevalence of NAFLD among young adults in Egypt.

### What are the new findings?

- In this cohort of asymptomatic Egyptian young adults, about 1 in 3 had steatosis, and 1 in 20 had moderate-to-advanced fibrosis.
- Overweight, obesity and increased adiposity were the strongest predictors of having steatosis and its severity.
- Parental attainment of a college-level education was associated with increasing steatosis stages.

### How might it impact on clinical practice in the foreseeable future?

- There is an urgency to address the silent epidemic of NAFLD among young adults in Egypt, which could represent a significant burden to healthcare systems in this country.
- Increasing awareness of NAFLD and its complications and promoting lifestyle modification with diet and exercise among young adults in Egypt are warranted.

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease with an estimated global prevalence of 25% of adults.[1] NAFLD is a spectrum that comprises two main histological phenotypes with varying prognoses: NAFL or simple steatosis and non-alcoholic steatohepatitis (NASH). The latter is an advanced inflammatory form of NAFLD that confers higher risk of fibrosis, end-stage liver disease and cardiovascular disease mortality.[2 3] In western societies, NASH prevalence among adults is estimated to be around 3%–4%, with as high as 40% of the cases progressing to advanced liver fibrosis.[1 4] NAFLD progression is closely related to insulin resistance, obesity and type

***Project Title:*** Prevalence and Progression of Obesity, Pre-diabetes, and Diabetes Among College Students over Four Years

Our proposed model may close the gap in our understanding of the development and progression of several chronic non-communicable diseases in Egypt. The developed score may allow us to widely screen young Egyptian adults and create specialized prevention plans for obesity, T2D and hypertension.

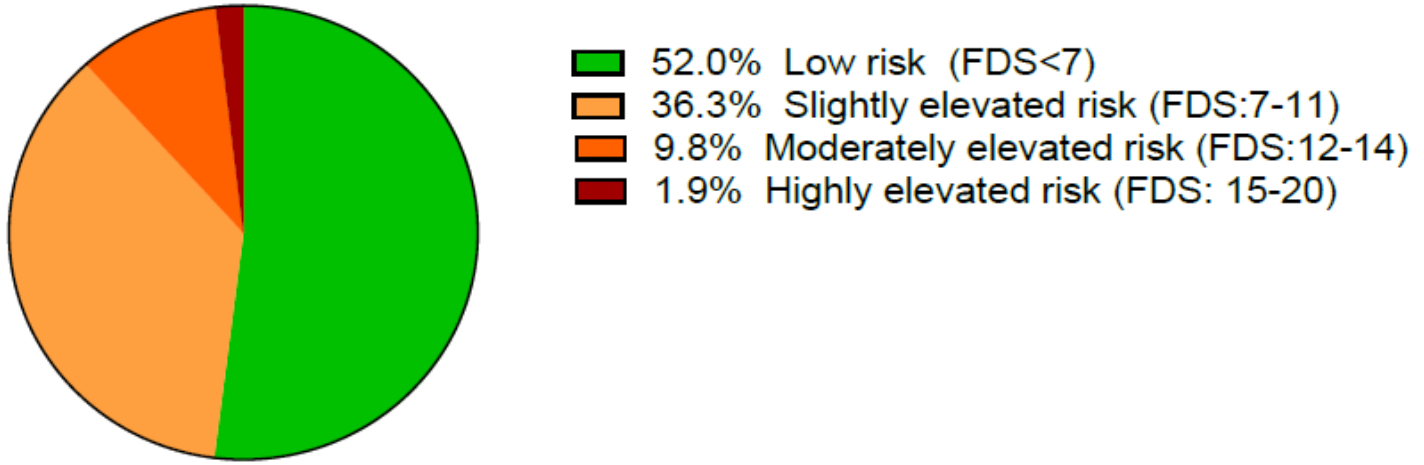
The project will be conducted in collaboration between Joslin Diabetes Center and several medical schools in Egypt.

Delta University for Science and Technology
جامعة الدلتا للعلوم والتكنولوجيا

Joslin Diabetes Center

كلية الطب - جامعة المنصورة
MANSOURA UNIVERSITY FACULTY OF MEDICINE

## Figure 2: Stratification of the study cohort according Finnish Diabetes Risk Score (FDS)




**n=377**

**Data Set-A**

**Low risk (LR):FDS<7**
**Greater risk (GR): FDS≥7 (slightly, moderately, and highly elevated risk)**

# CONCLUSIONS

- Increased T2D risk is notable among Egyptian college students, especially among females and over-weight individuals
- Social stress and fast-food con-sumption should be considered as important risk factors and may be recommended in future develop-ment of T2D risk model in Egypt

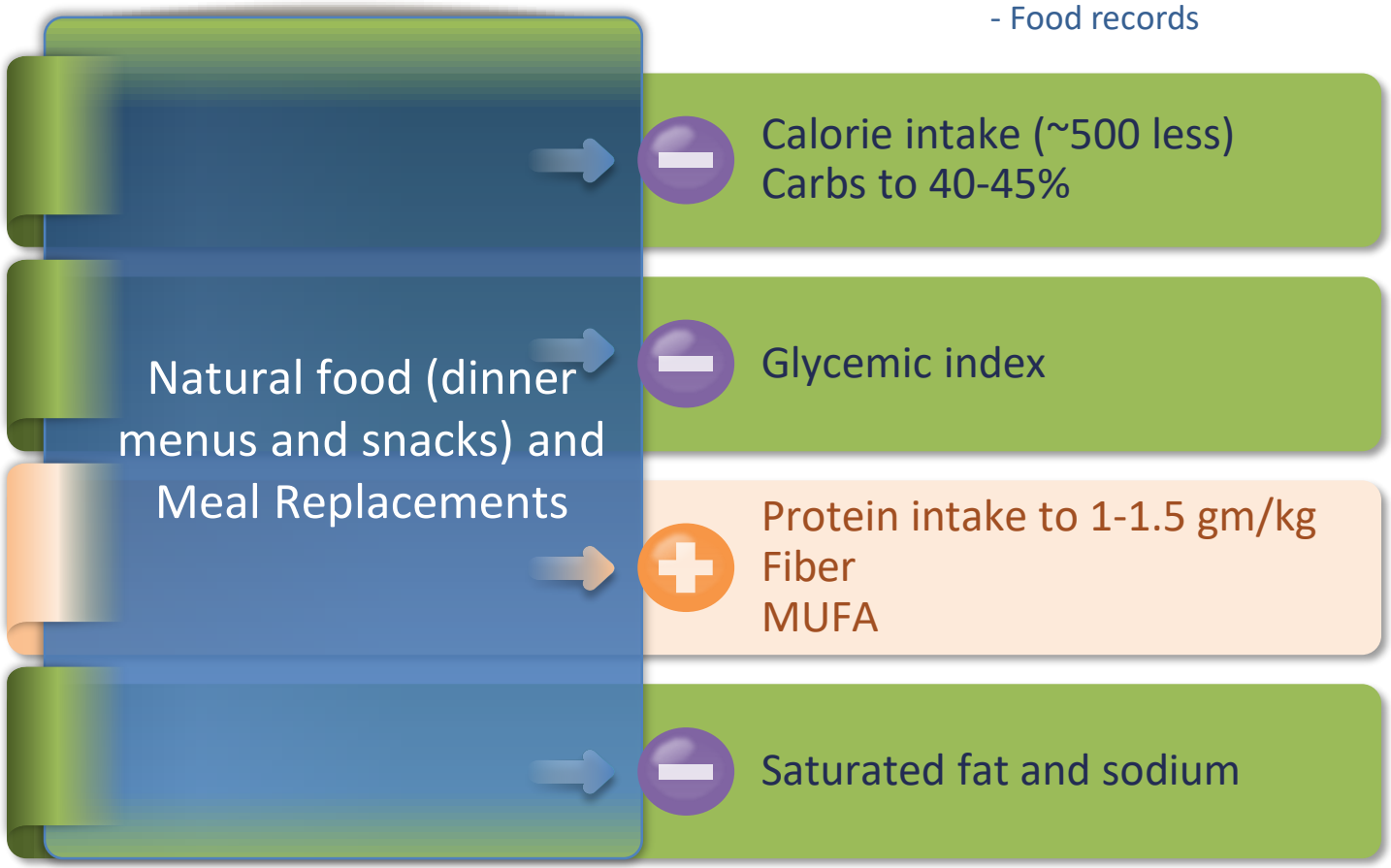
- Having 48% of college students at greater T2D risk is alarming. This warrants urgent need for an earlier-age screening program and imple-mentation of an efficient diabetes prevention program with specific aims of reducing body weight, re-ducing consumption of fast food and easing social stress


# Thank You

| | Classical Model | Alternative Model |
|---|---|---|
| Primary Target | HbA1c | Body Weight |
| Medications | Increase Over Time | Possible Reduction |
| Cost | Higher on Long-term | Lower on Long-term |
| Body Weight | Increases Over Time | Decreases or Maintain |
| HbA1c | May Achieve Goal | Achieve Same or Better Goal |
| CAD Risk | Reduction | Significant Reduction |
| Quality of life | Decreases Over Time | Improves |

# 1- Structured dietary intervention & modified macronutrient composition

- Relatively higher protein, LGI & higher fibers
  - Provide structure menus
  - Calorie replacements
  - Food records

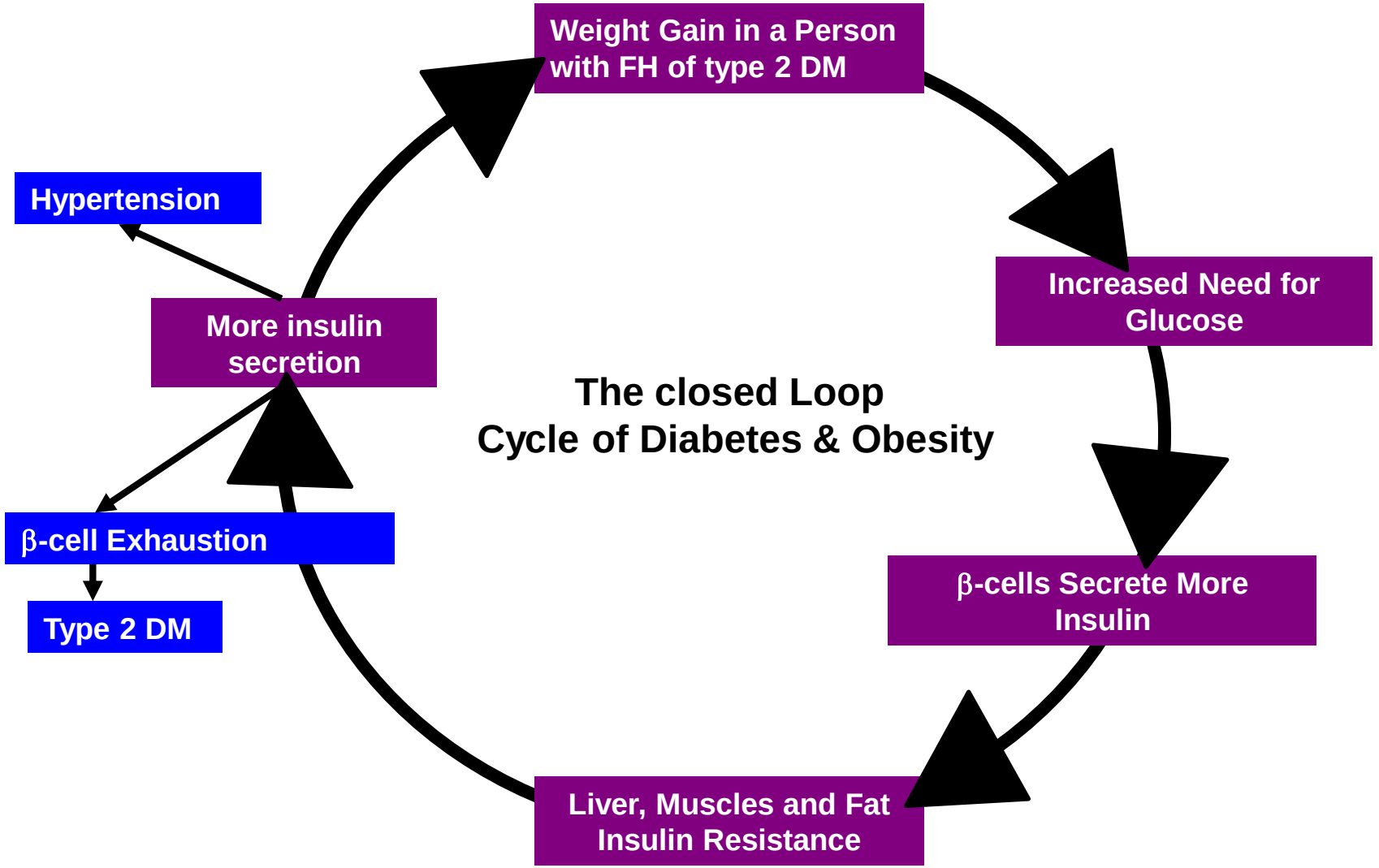


Periods of fasting to reduce glucose toxicity
Insulin to increase FA flux to adipose tissue
Metformin to improve hepatic insulin resistance
Pioglitazone to reverse lipolysis and increase lipogenesis
Weight loss medical or surgical
SGLT-2I to reduce glucose toxicity
GLP-1 analog to stimulate pancreatic function and improve weight loss

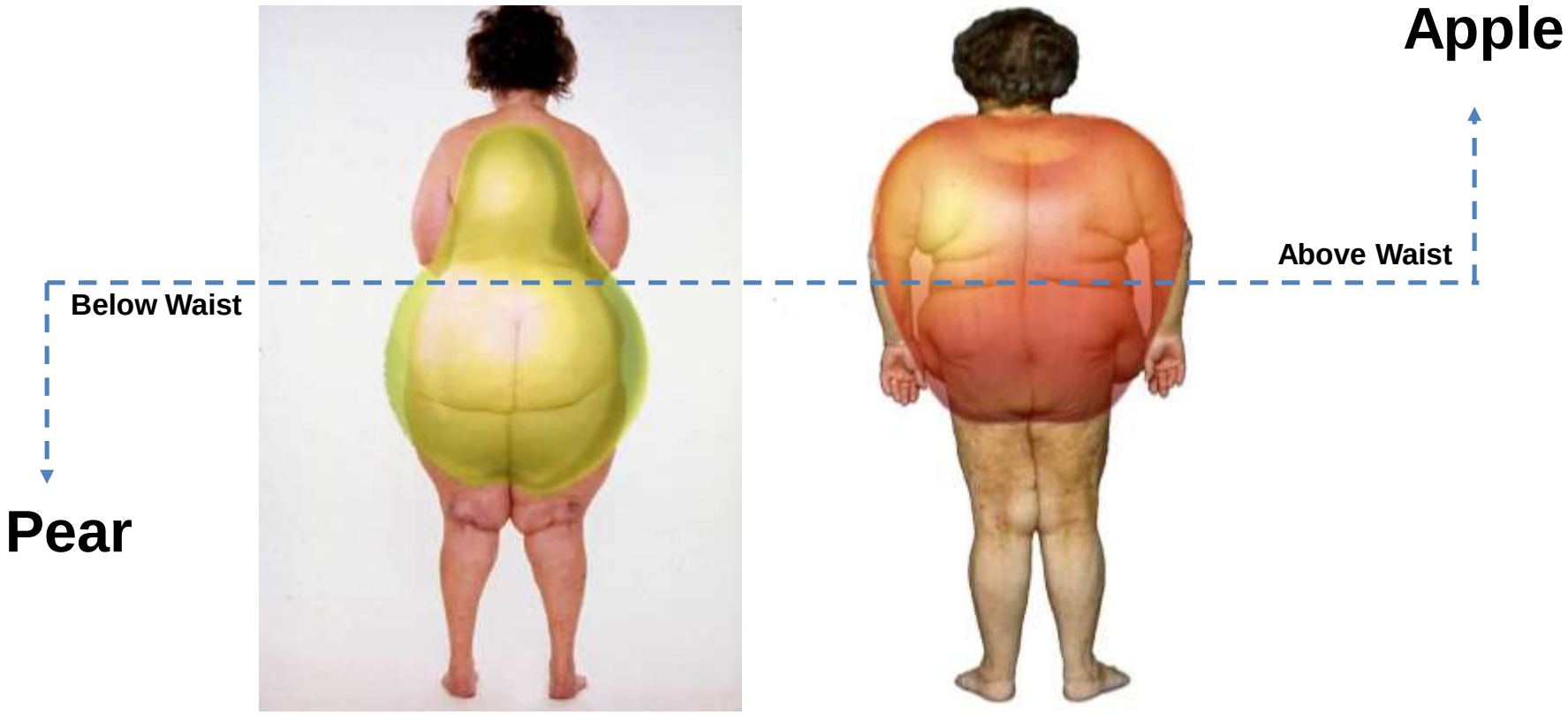
Improvement of insulin resistance may improve beta-cell function and potentially reverse diabetes if conducted early.

Indicator of optimal time is 1- accelerated weight loss period and 2- sudden increase in insulin secretion 3- early in diabetes within initial 5 years

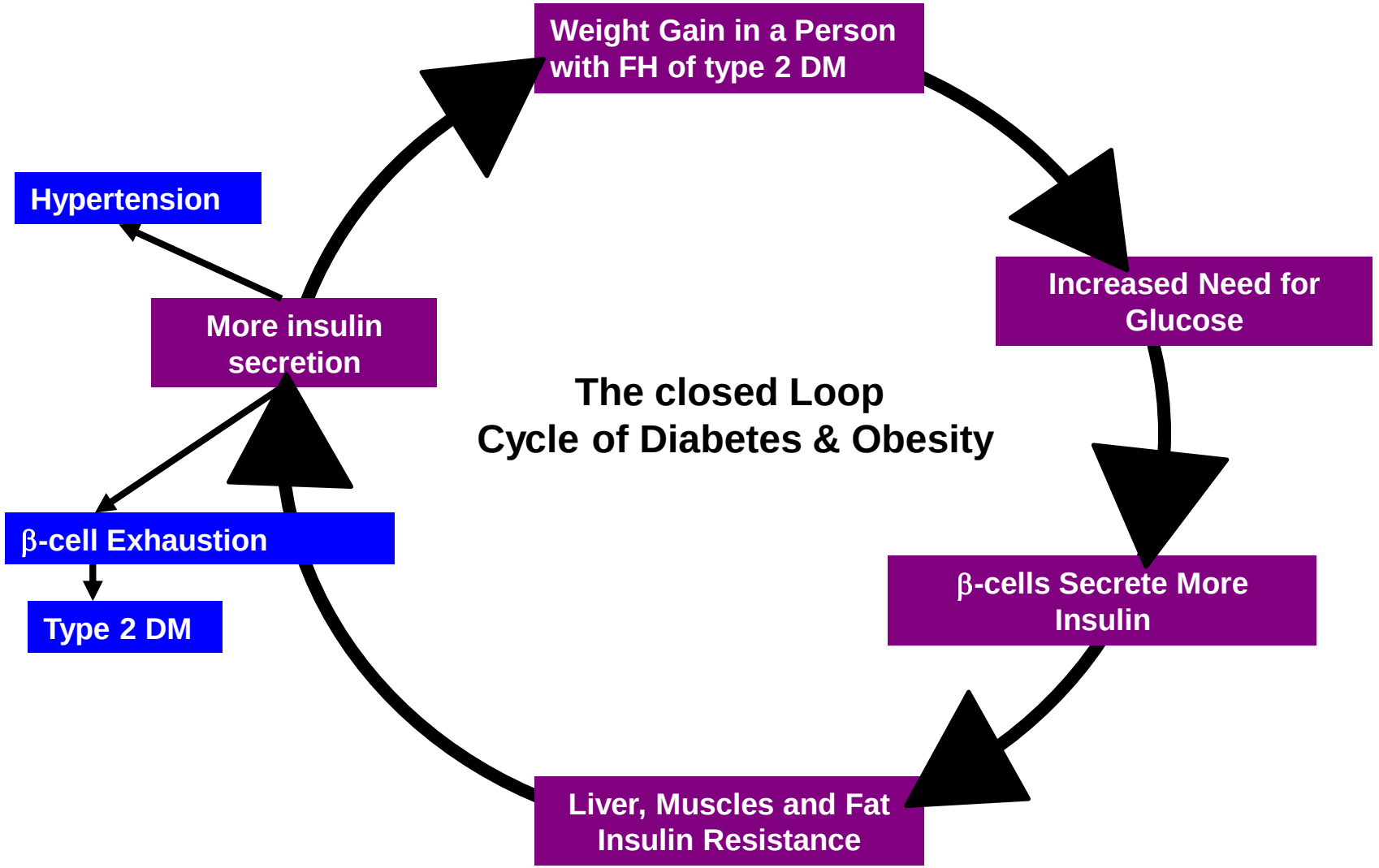
Sent from my iPhone


Weight Gain in a Person with FH of type 2 DM
Increased Need for Glucose
β-cells Secrete More Insulin
Liver, Muscles and Fat Insulin Resistance
β-cell Exhaustion
Type 2 DM
Hypertension
More insulin secretion
The closed Loop
Cycle of Diabetes & Obesity

# Body Shape Defines the Risk



**What is the link Between Obesity and Type 2 Diabetes?**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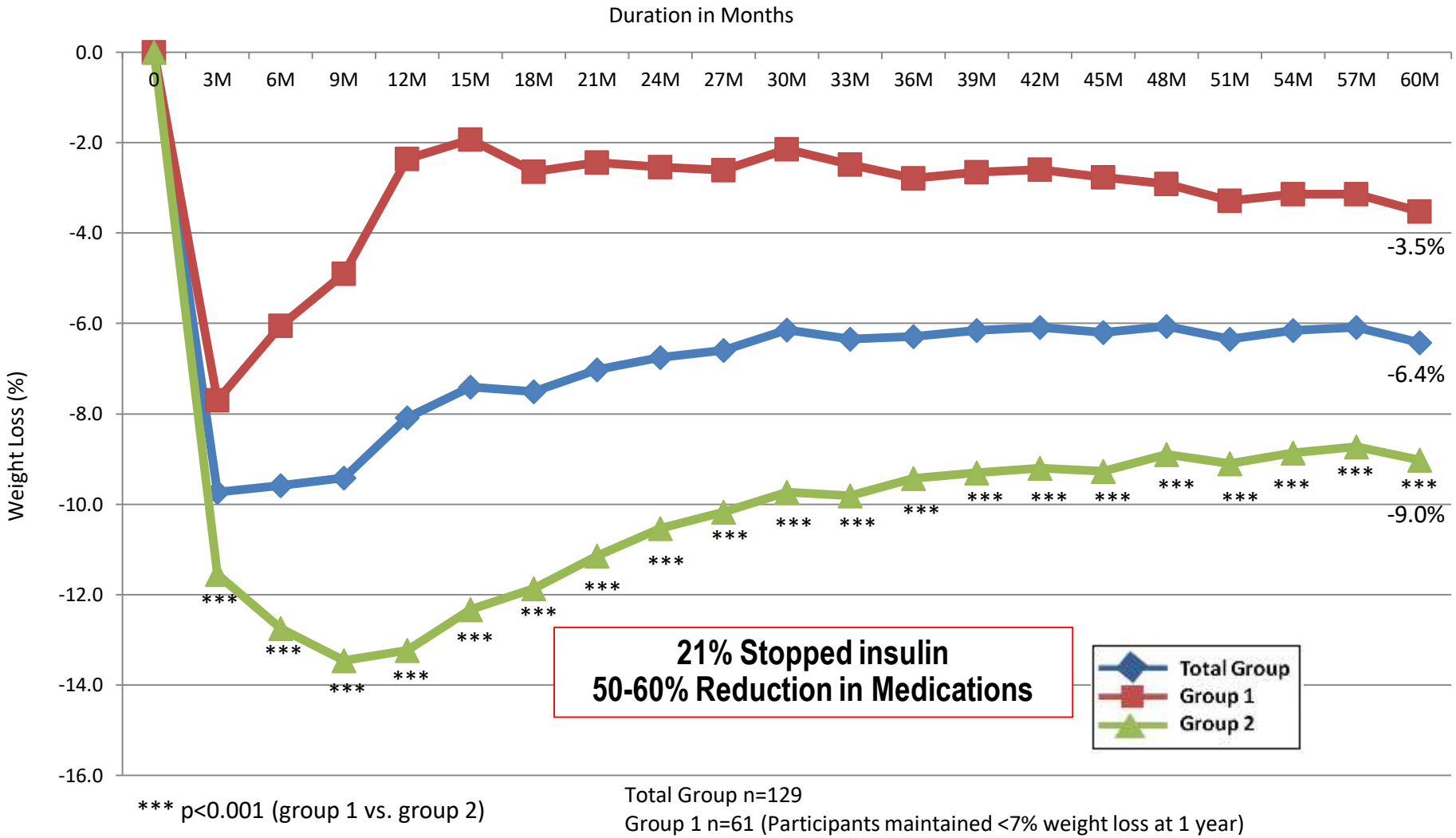
**Type 2 Diabetes:** is it Just an Insulin Resistance disease?

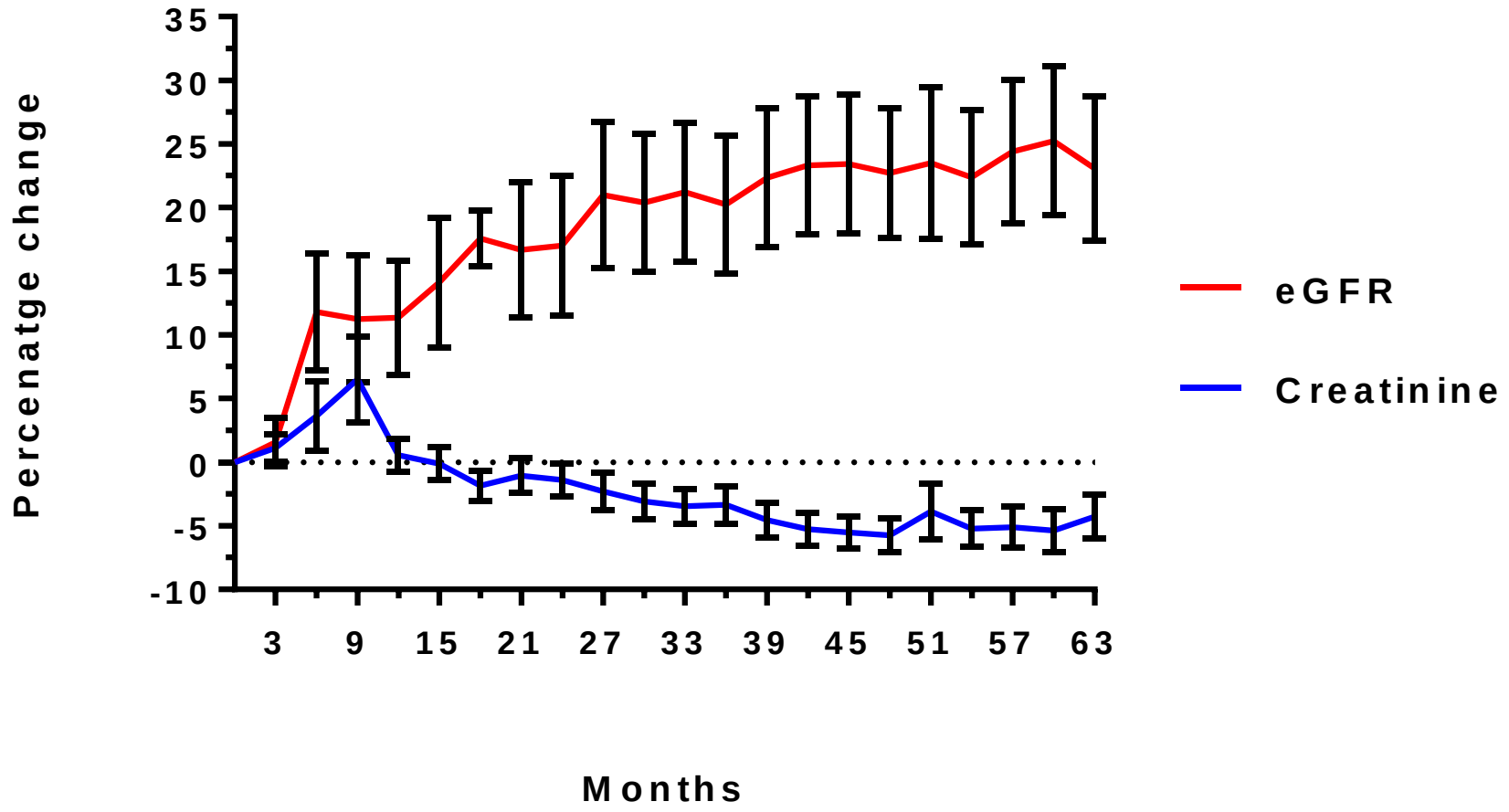
# Percentage Weight Reduction in Patients with Diabetes in the Real-World Clinical Practice over 5 years (Joslin Why WAIT Program)



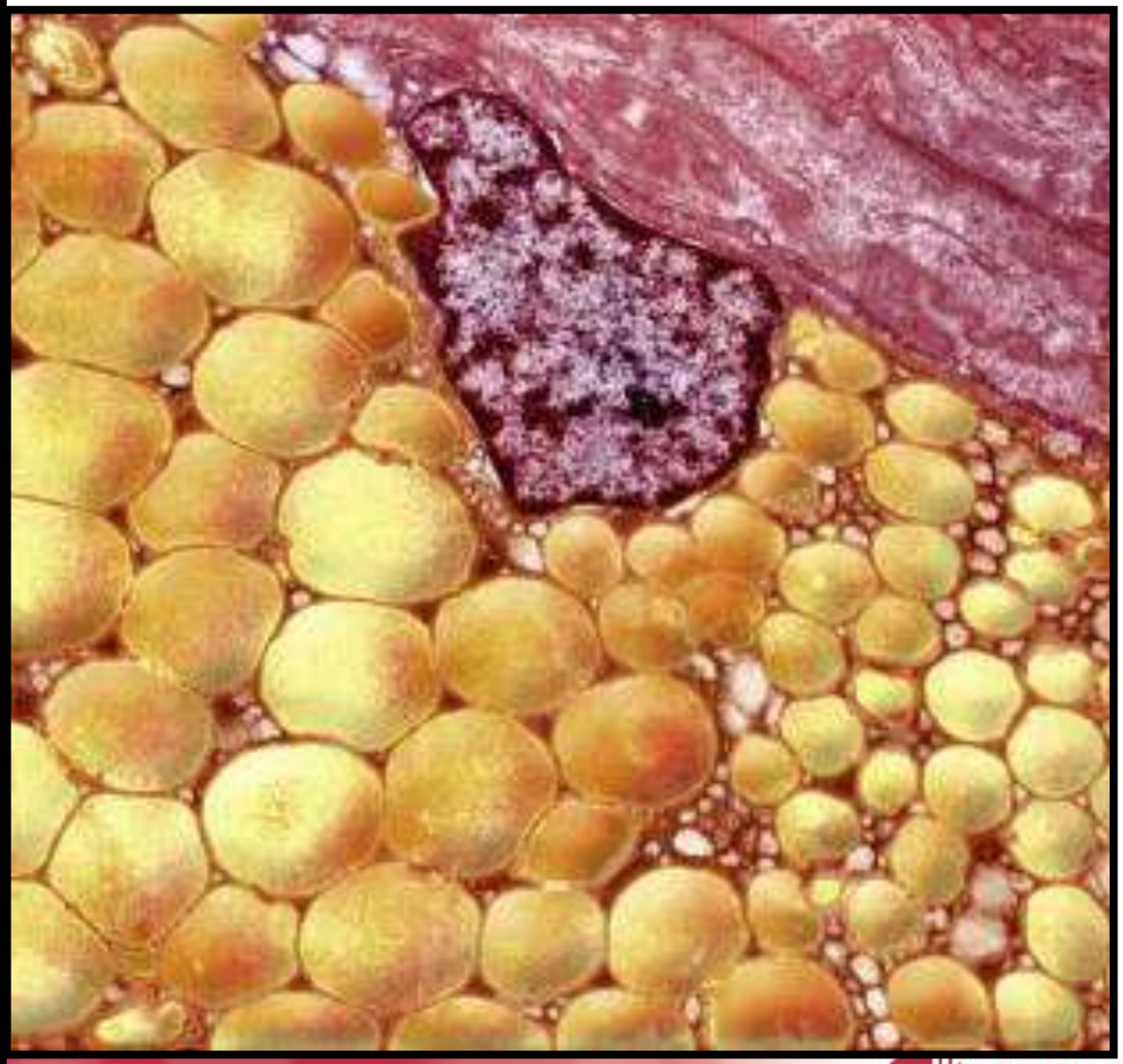

*** p<0.001 (group 1 vs. group 2)

Total Group n=129
Group 1 n=61 (Participants maintained <7% weight loss at 1 year)
Group 2 n=68 (Participants maintained ≥ 7% weight loss at 1 year)

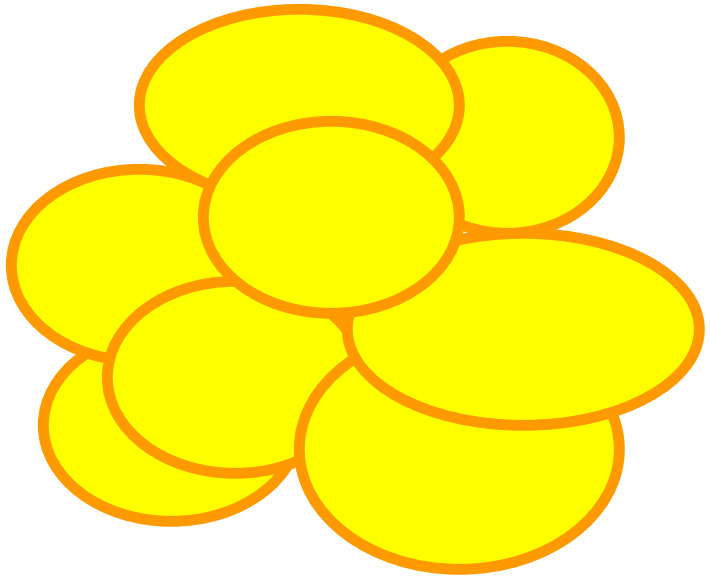
## Percenatge change of eGFR and Creatinine over 63 months



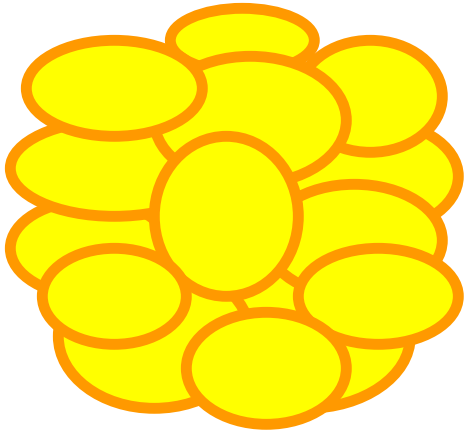
# Size of Fat Cell



## *Dysfunctional Fat (Visceral Fat)*



## *Functional Fat*



↓ Cytokines → ↑ IS

↑ Adiponectin → ↑ IS

↑ Fatty A Oxidation → ↓ TG



Hamdy O. Expert Rev Cardiovasc Ther 2005;3(2):231-238

# Adipokines Theory

Genetic Factors

Environmental factors:
- ↓ Physical Activity
- ↑ Food Intake


↑ FFA
↑ TNF-α
↑ IL-6
↑ PAI-1
↑ MCP-1
↑ Resistin
↓ Adiponectin

Insulin Resistance

Endothelial Dysfunction