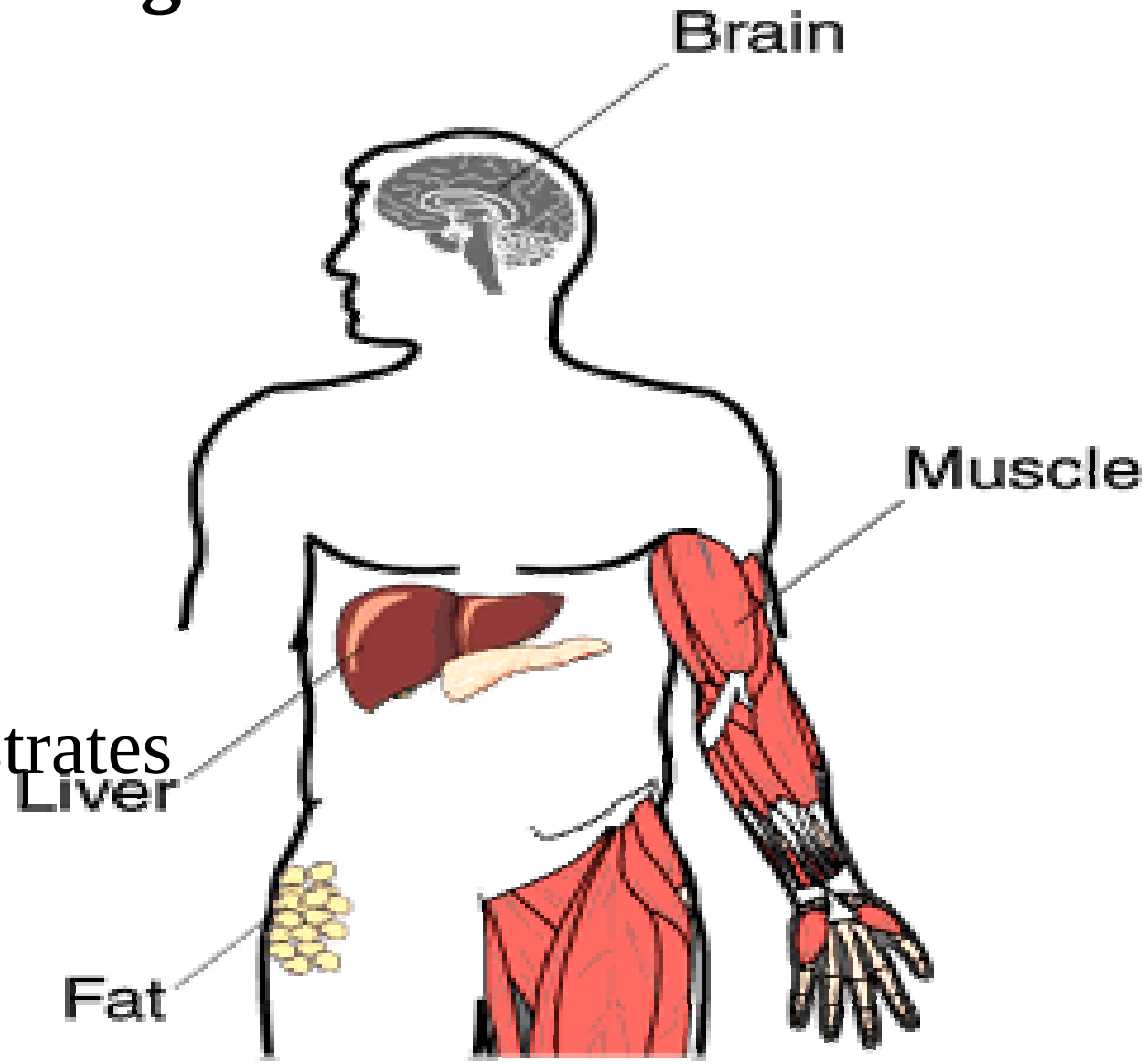
INSULIN SECRETORY DEFECTS IN AGING AND DIABETES

DIABETES AND METABOLISM SECTIONS

NIA/NIH, BALTIMORE, MD

How do tissues communicate about blood glucose levels?

- Hormones:
  - Insulin
  - Glucagon
- Nervous system
  - Ephinephrine
  - Cortisol
- Circulating substrates



Insulin

- Produced by the beta cells of the pancreas

Islet of
Langerhans cells
produce insulin

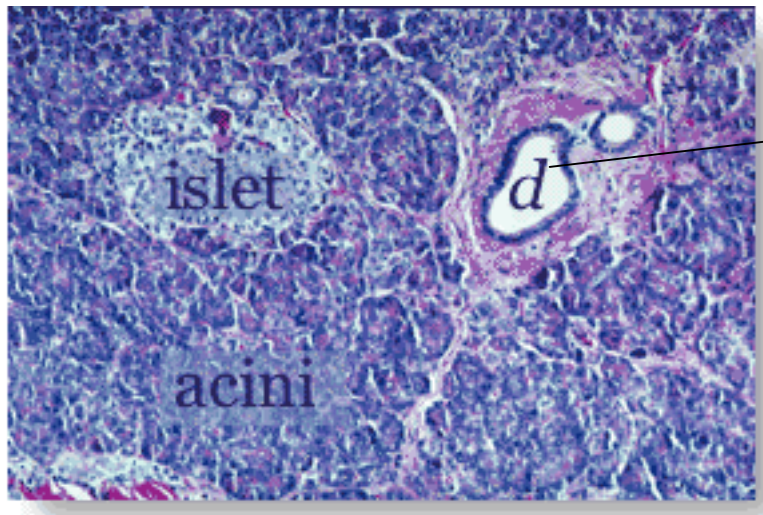


fig. 2-1

- **Anabolic** effects on metabolism
- Intravenous administration leads to immediate decrease in blood glucose
- Defects can lead to diabetes

Structure of Insulin

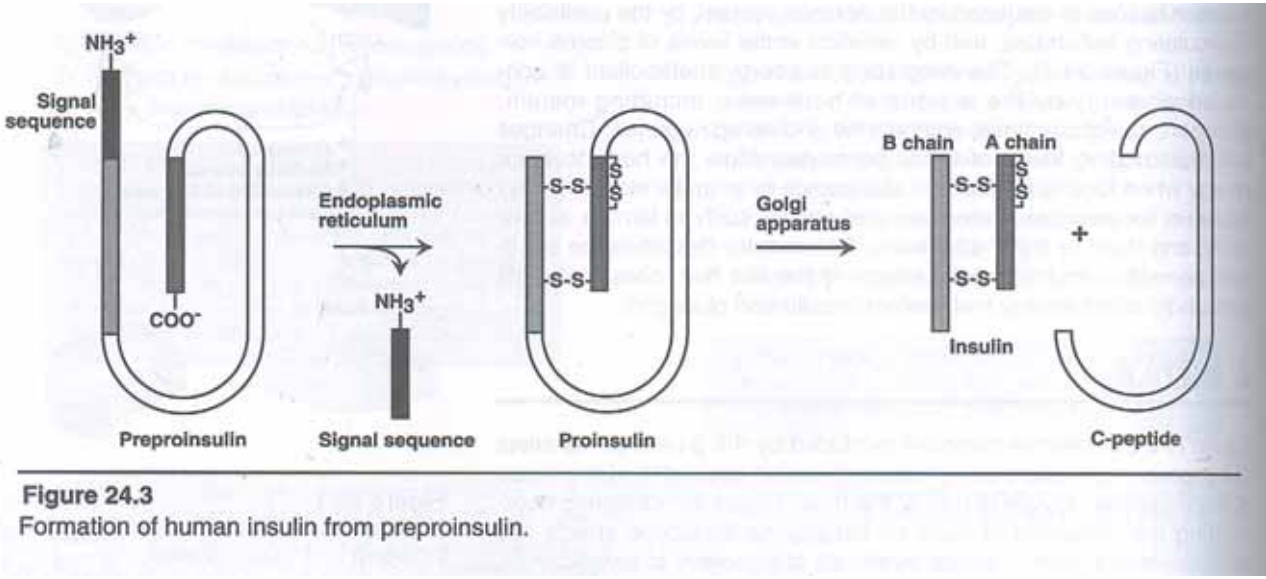
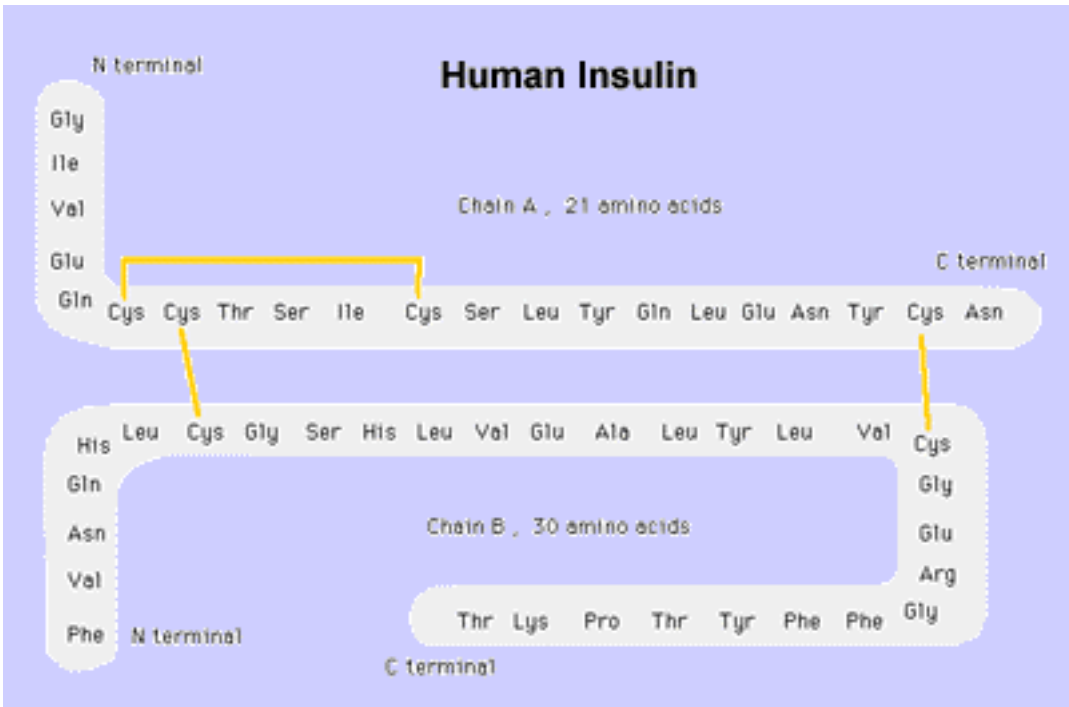


Figure 24.3
Formation of human insulin from preproinsulin.

- 2 polypeptide chains linked by disulfide bonds
- Disulfide bonds also link A chain together
- Insulin forms hexamer for greater stability



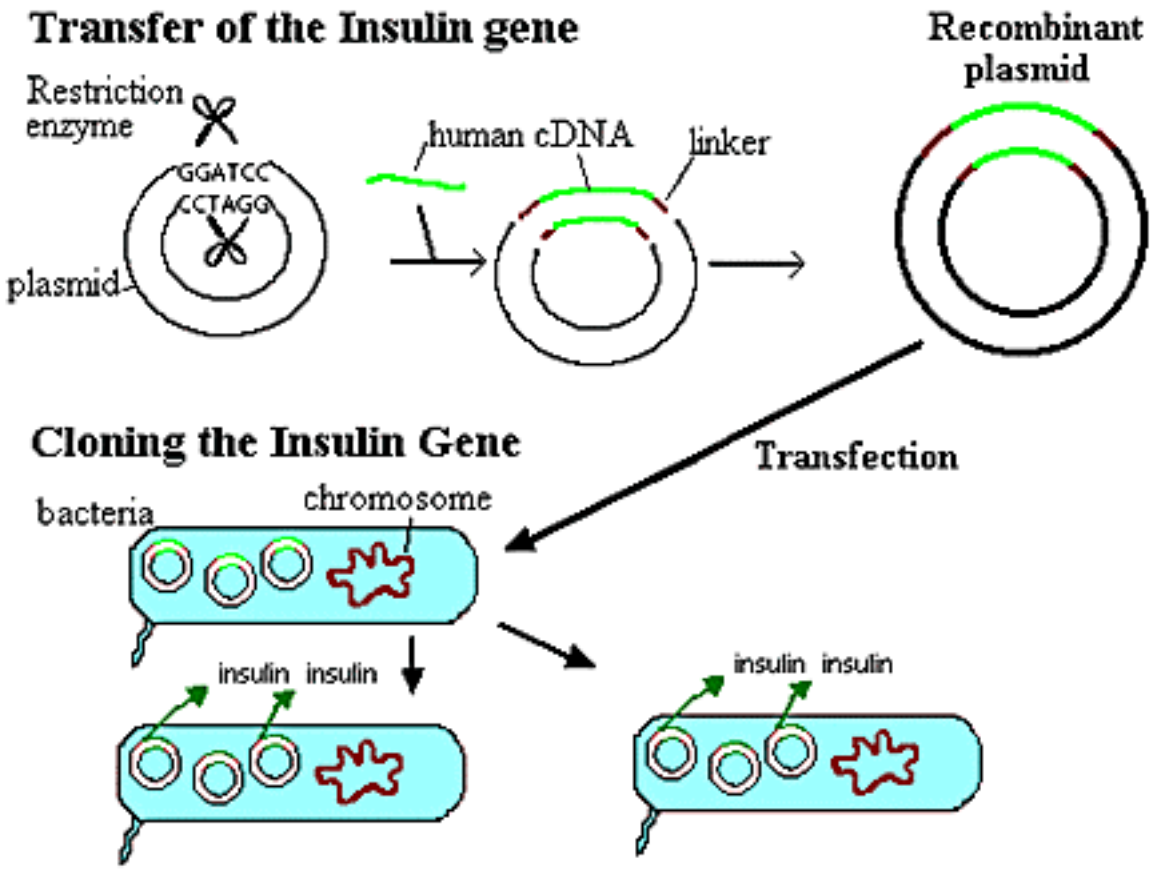
Production of insulin to treat diabetes

- Discovered in 1921 by Banting and Best
  - (won Nobel prize in 1923)

- Porcine insulin
  - Only differs from human by one amino acid (at the C-terminus)
  - Replacement of amino acid allows production of human insulin

- Recombinant DNA technology
  - 1985 began producing insulin in bacteria

Recombinant DNA technology to produce insulin



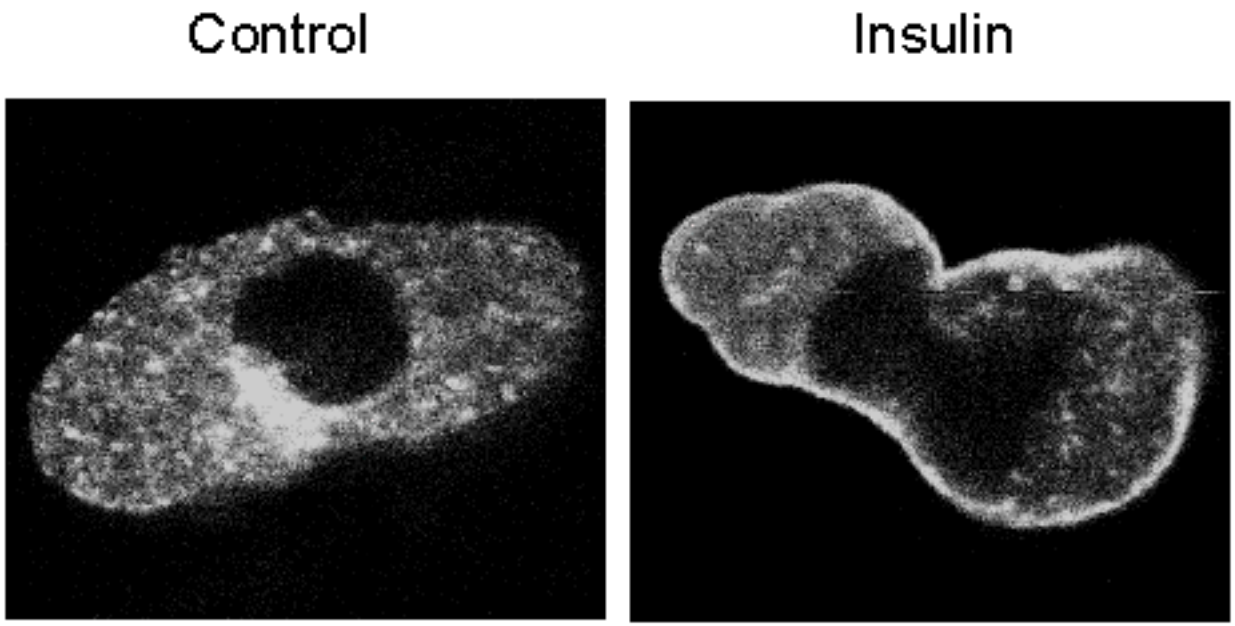
Transfer and cloning of the Insulin gene

Metabolic effects of insulin

- Carbohydrate
- Lipid
- Protein

Insulin induces glucose uptake

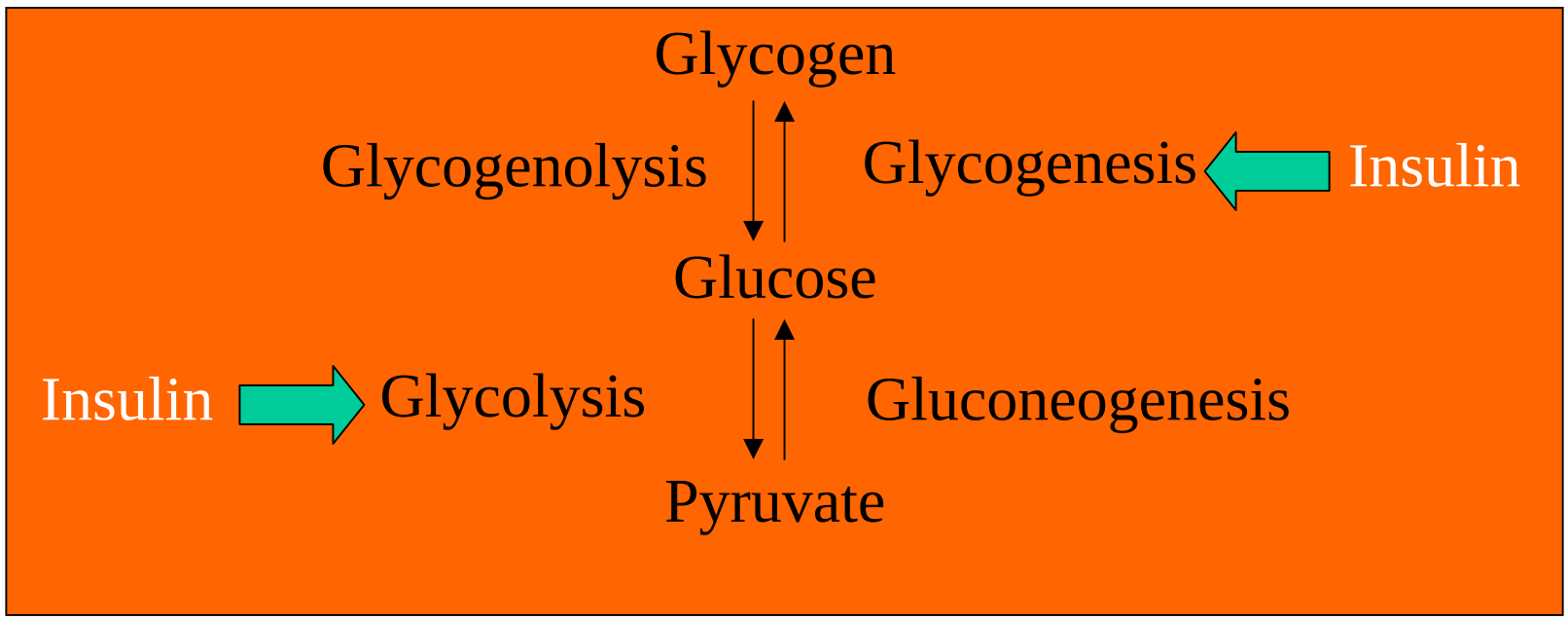
Increases glucose uptake through increased glucose transporters



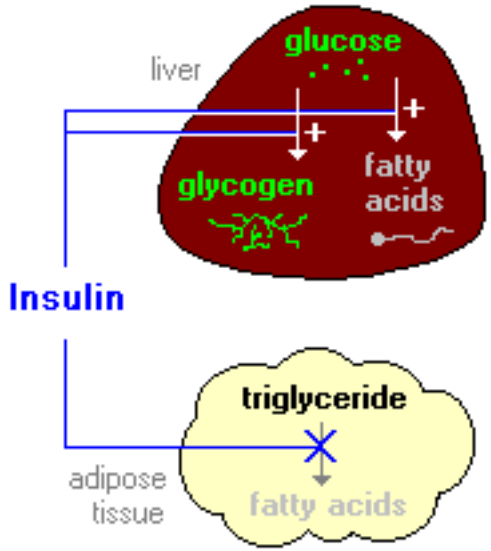
Glut4 protein in adipocytes

Carbohydrate metabolism and insulin

- Affects liver, muscle and adipose tissue
- Inhibits gluconeogenesis and glycogenolysis
- Increases glycogenesis and glycolysis



Lipid metabolism and insulin

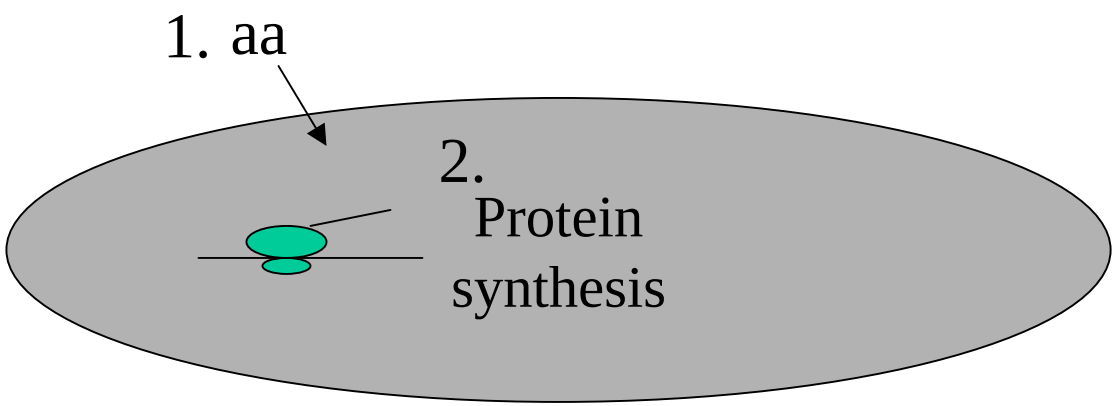


- Decrease in triacylglycerol degradation
  - Inhibits the action of hormone sensitive lipase

- Increase in triacylglycerol synthesis
  - Increases glucose transport-providing glycerol3phosphate
  - Increases lipoprotein lipase in adipose tissu, providing FA

Protein metabolism and insulin

- Stimulation of entry of amino acids into cells and protein synthesis



The insulin receptor

- Insulin receptor: $\alpha_2\beta_2$
  - α extracellular, binds insulin
  - β transmembrane domains and tyrosine kinase
  - Autophosphorylation and phosphorylation of other proteins

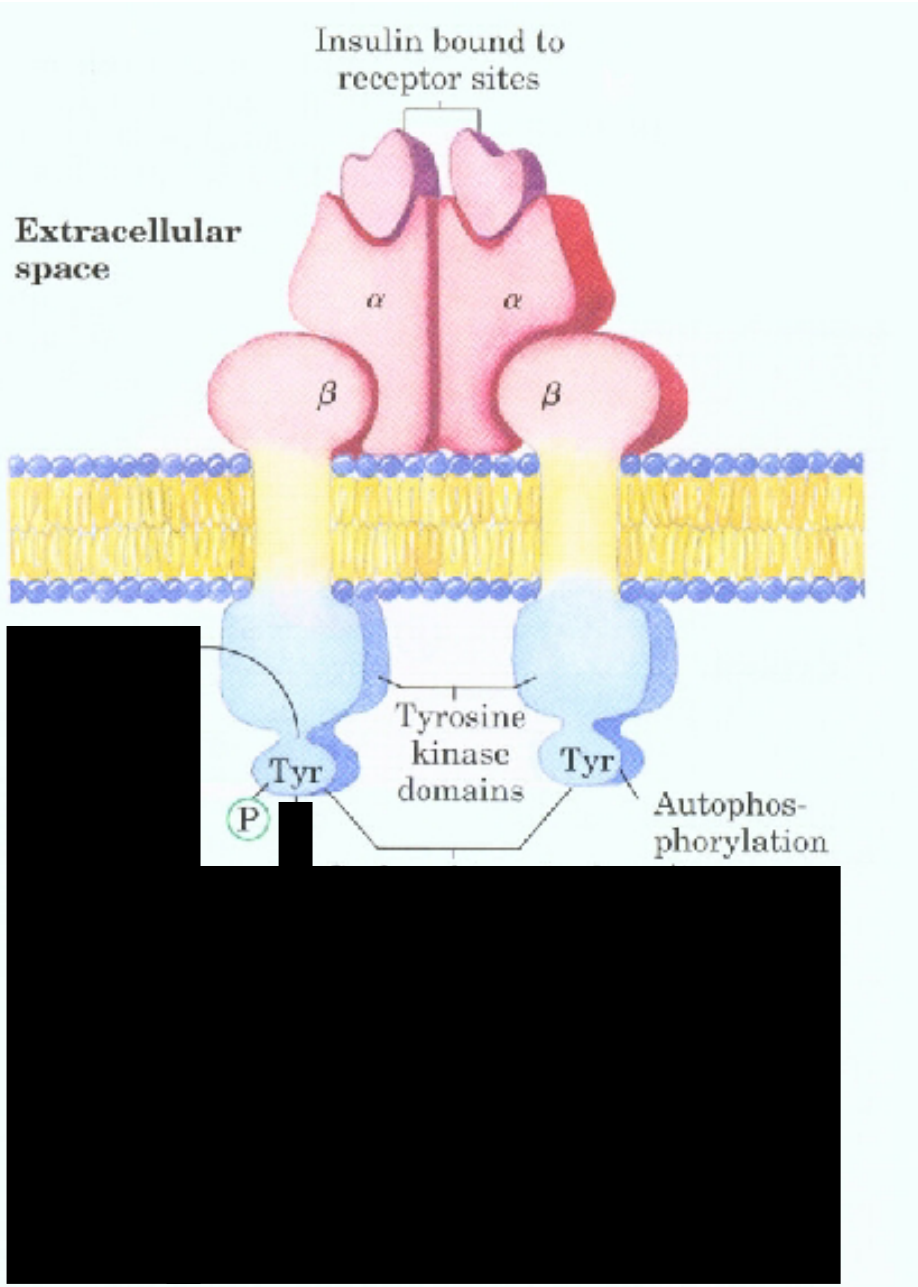
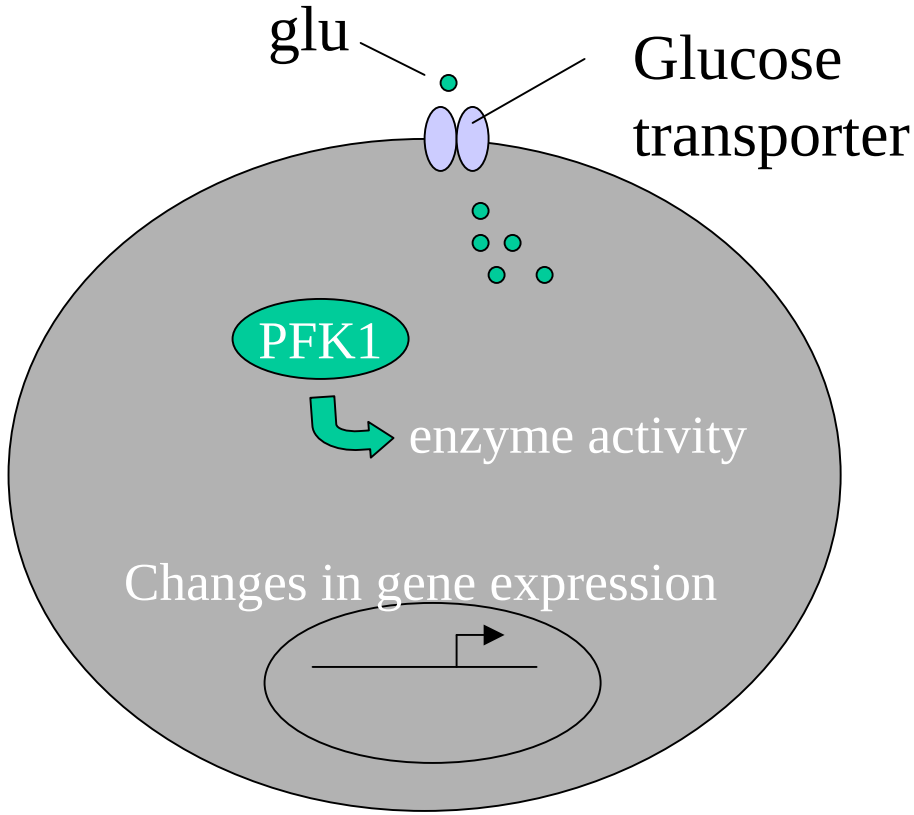


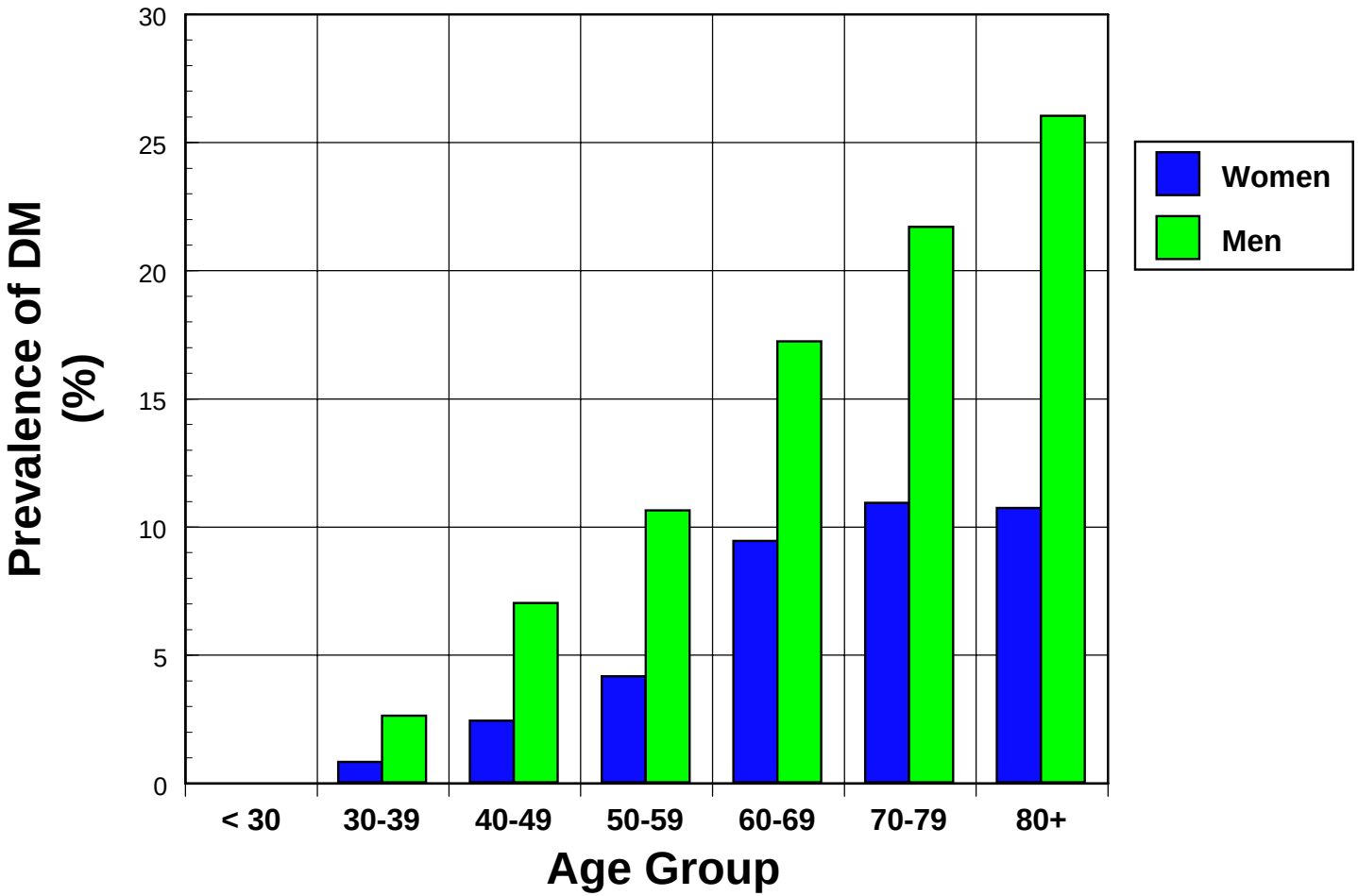
figure 13-6 Lehninger Principles Bchm 2000

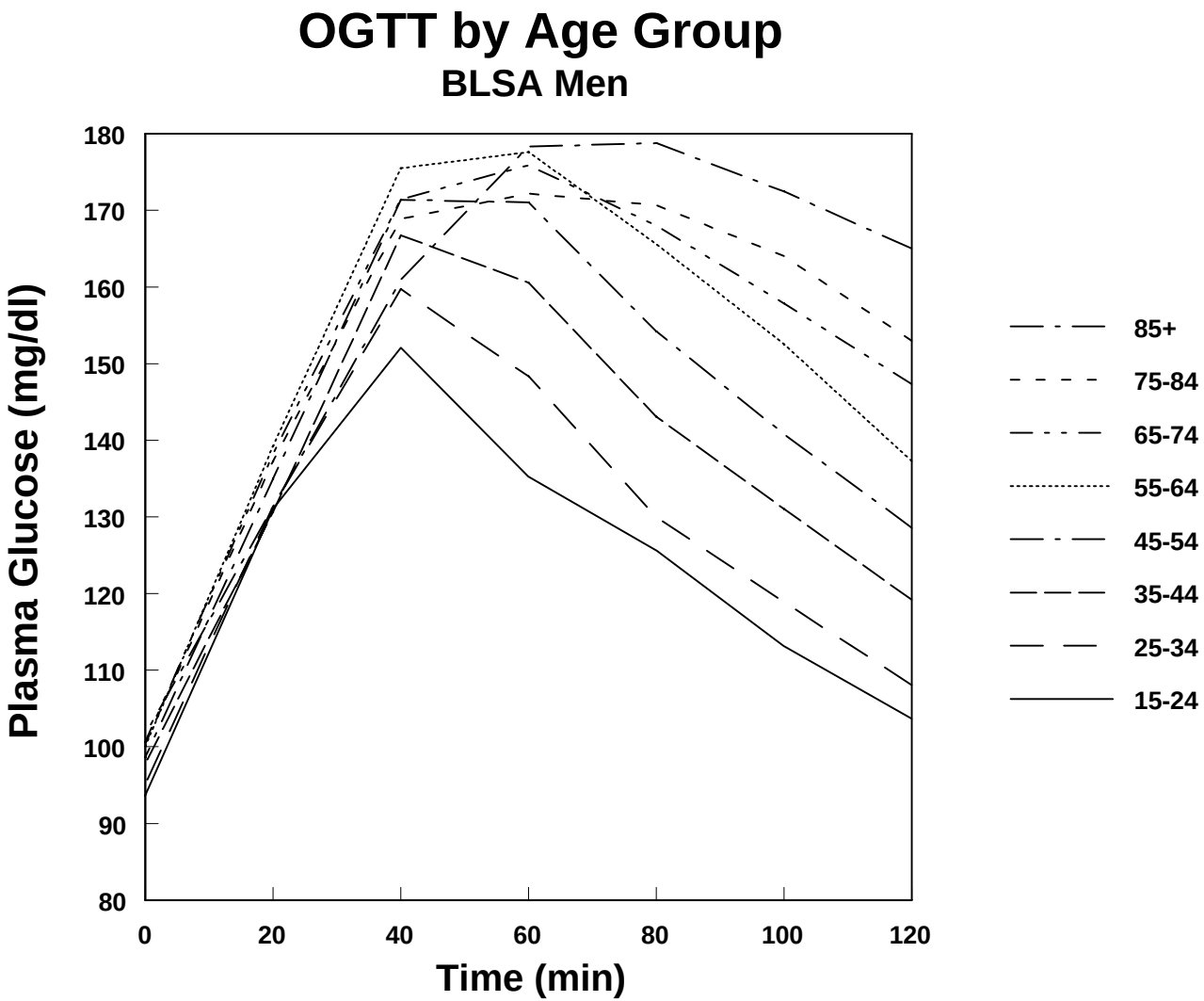
Time course for insulin action

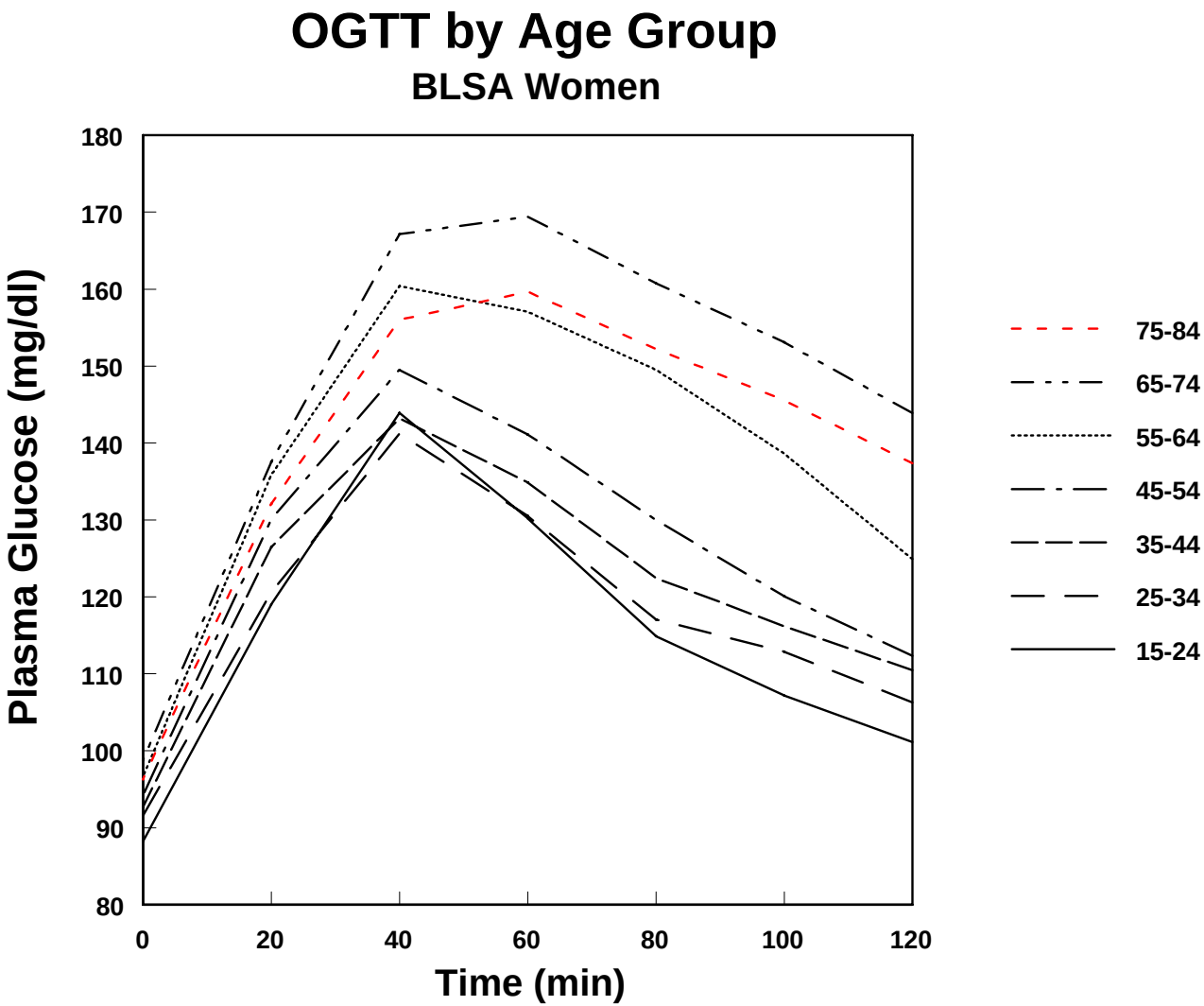
- Immediate increase in glucose uptake into cells (seconds)
- Changes in enzymatic activity (minutes)
- Increase in enzyme synthesis: glucokinase, PFK1, pyruvate kinaase (hours to days)
  - Changes in gene transcription



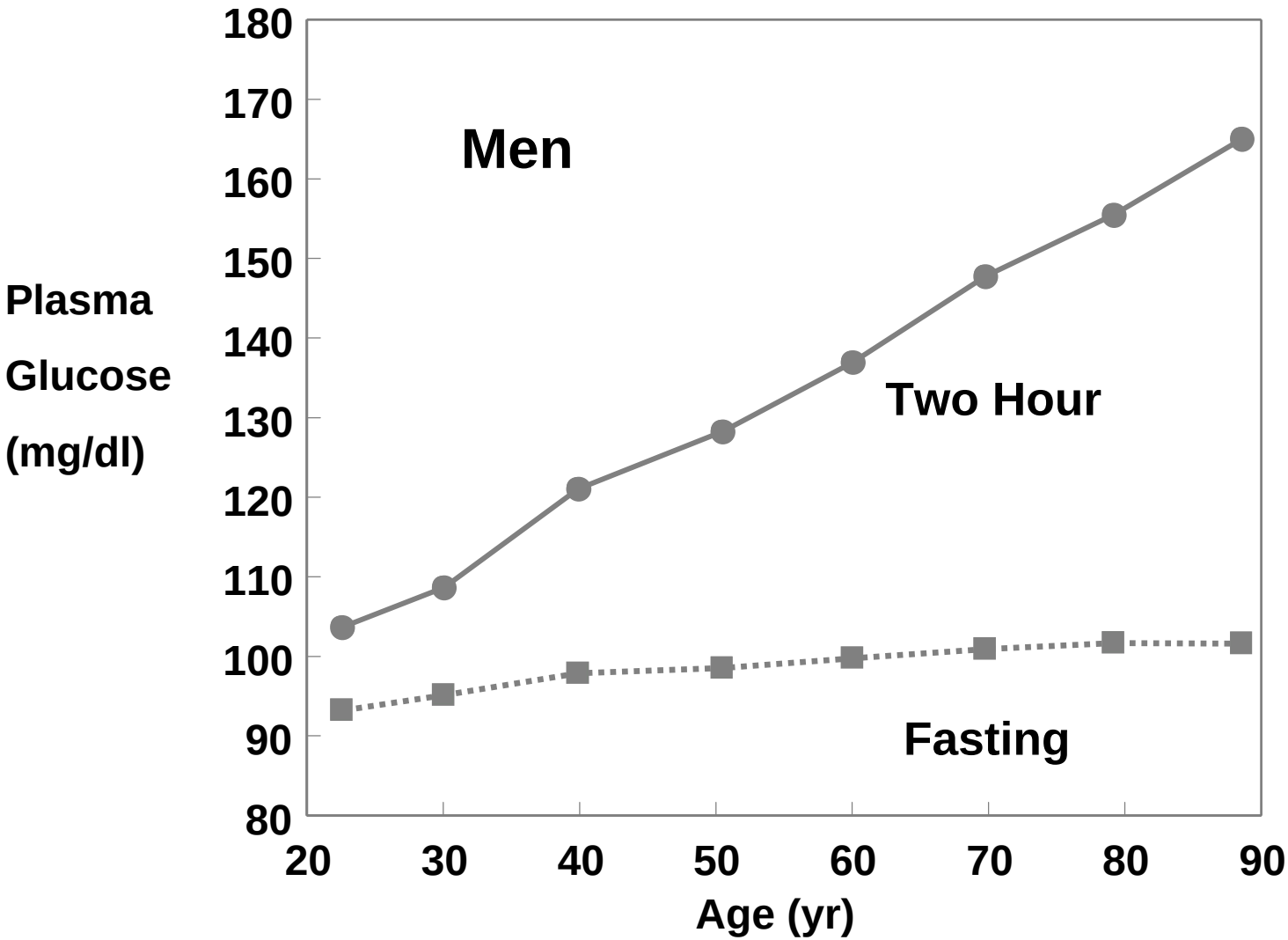
Prevalence of Diabetes Mellitus in the BLSA



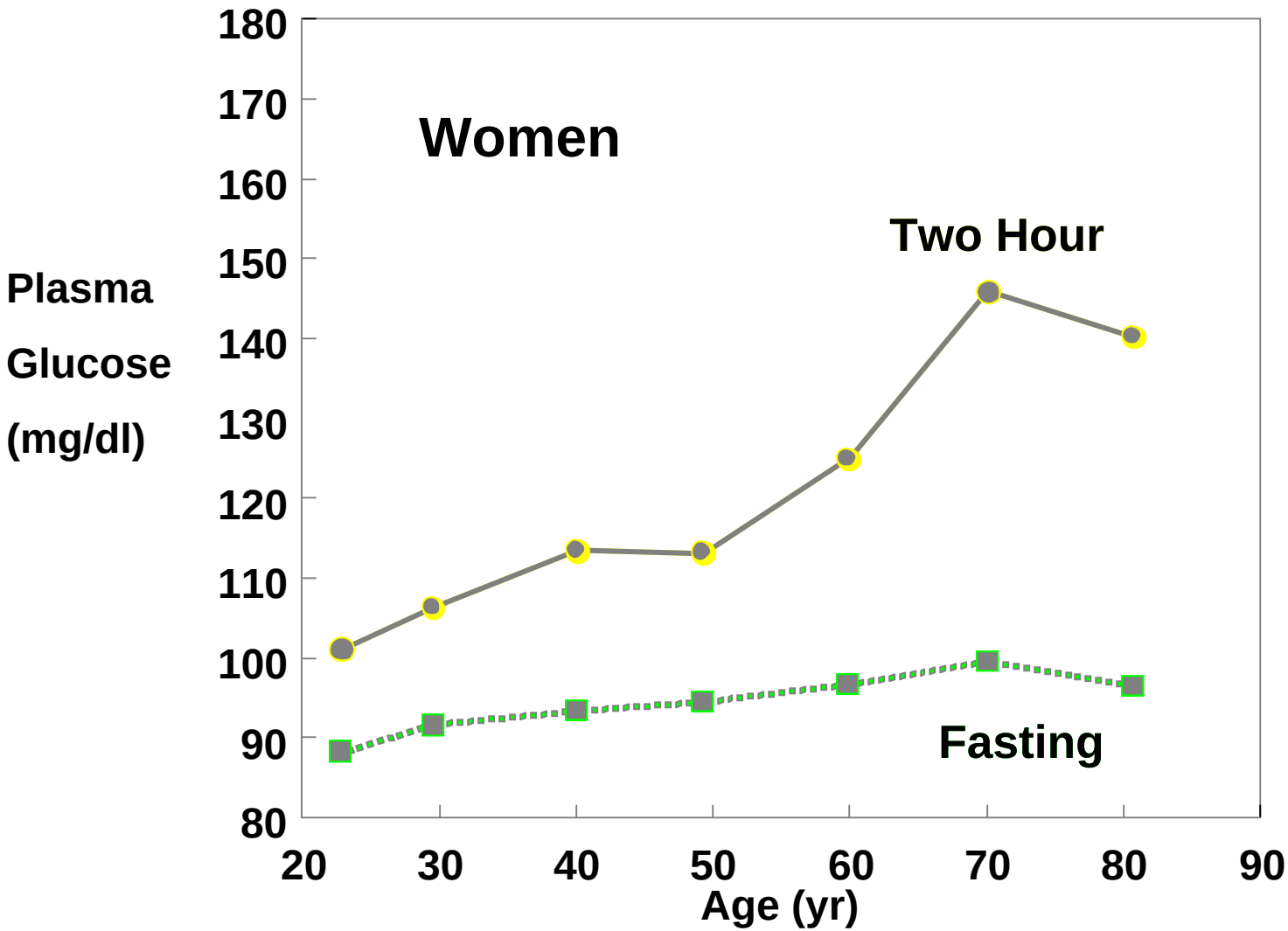

OGTT by Age Group
BLSA Men
Plasma Glucose (mg/dl)
180
170
160
150
140
130
120
110
100
90
80
0
20
40
60
80
100
120
Time (min)
85+
75-84
65-74
55-64
45-54
35-44
25-34
15-24

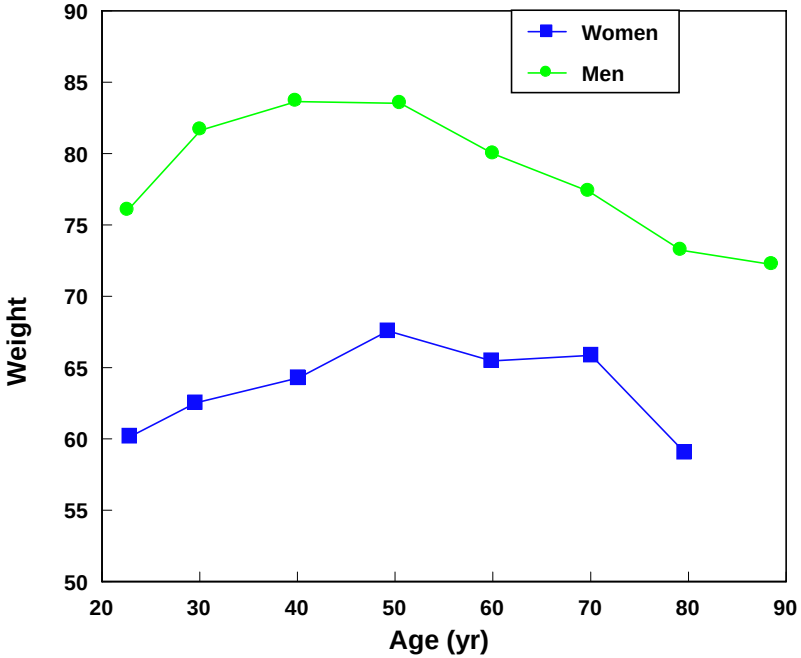

OGTT by Age Group
BLSA Women
Plasma Glucose (mg/dl)
180
170
160
150
140
130
120
110
100
90
80
0
20
40
60
80
100
120
Time (min)
75-84
65-74
55-64
45-54
35-44
25-34
15-24

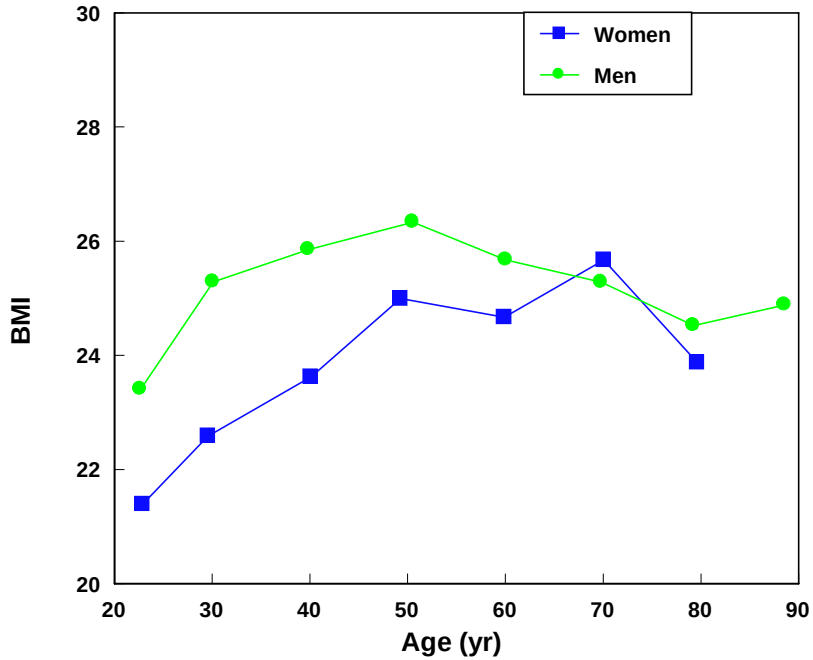
Effect of Age on Fasting and Two Hour Plasma Glucose Level BLSA

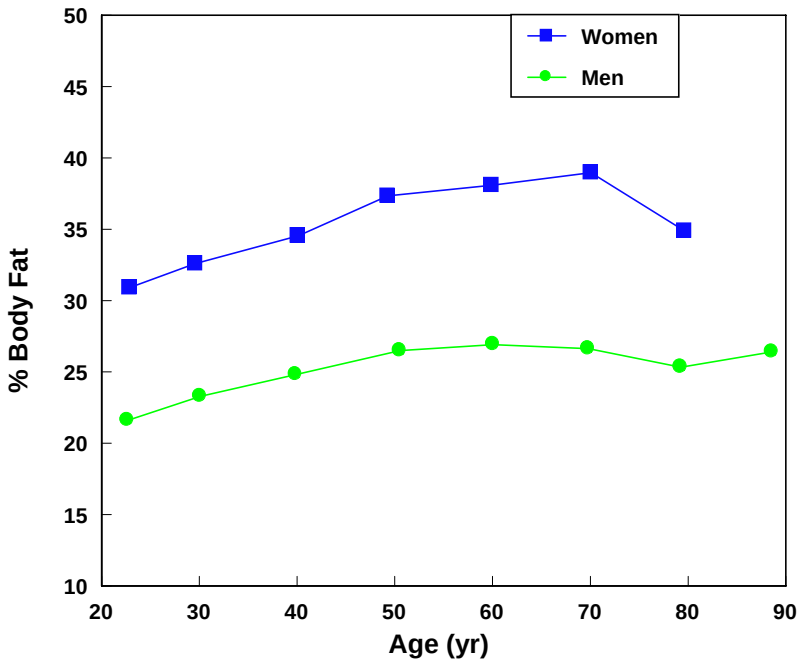


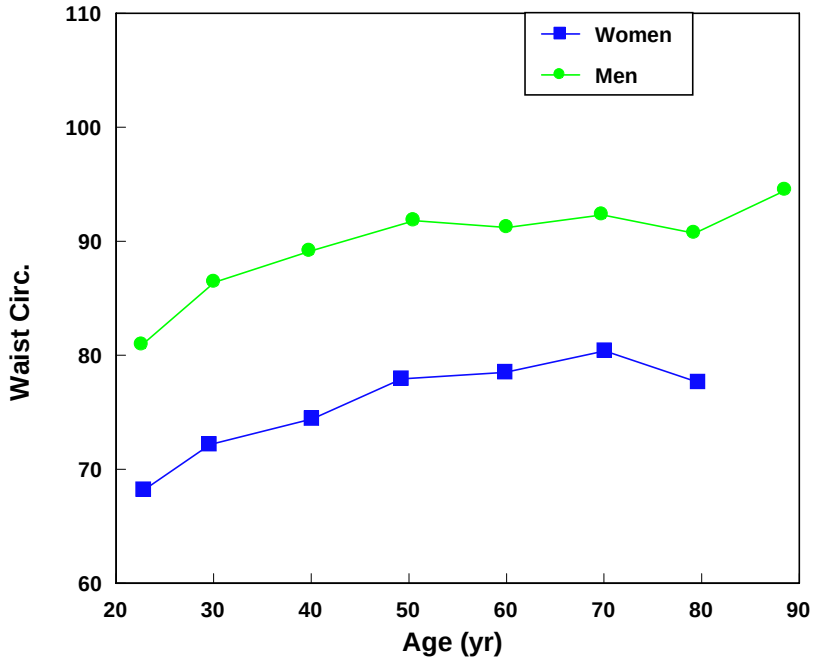
Effect of Age on Fasting and Two Hour Plasma Glucose Level BLSA

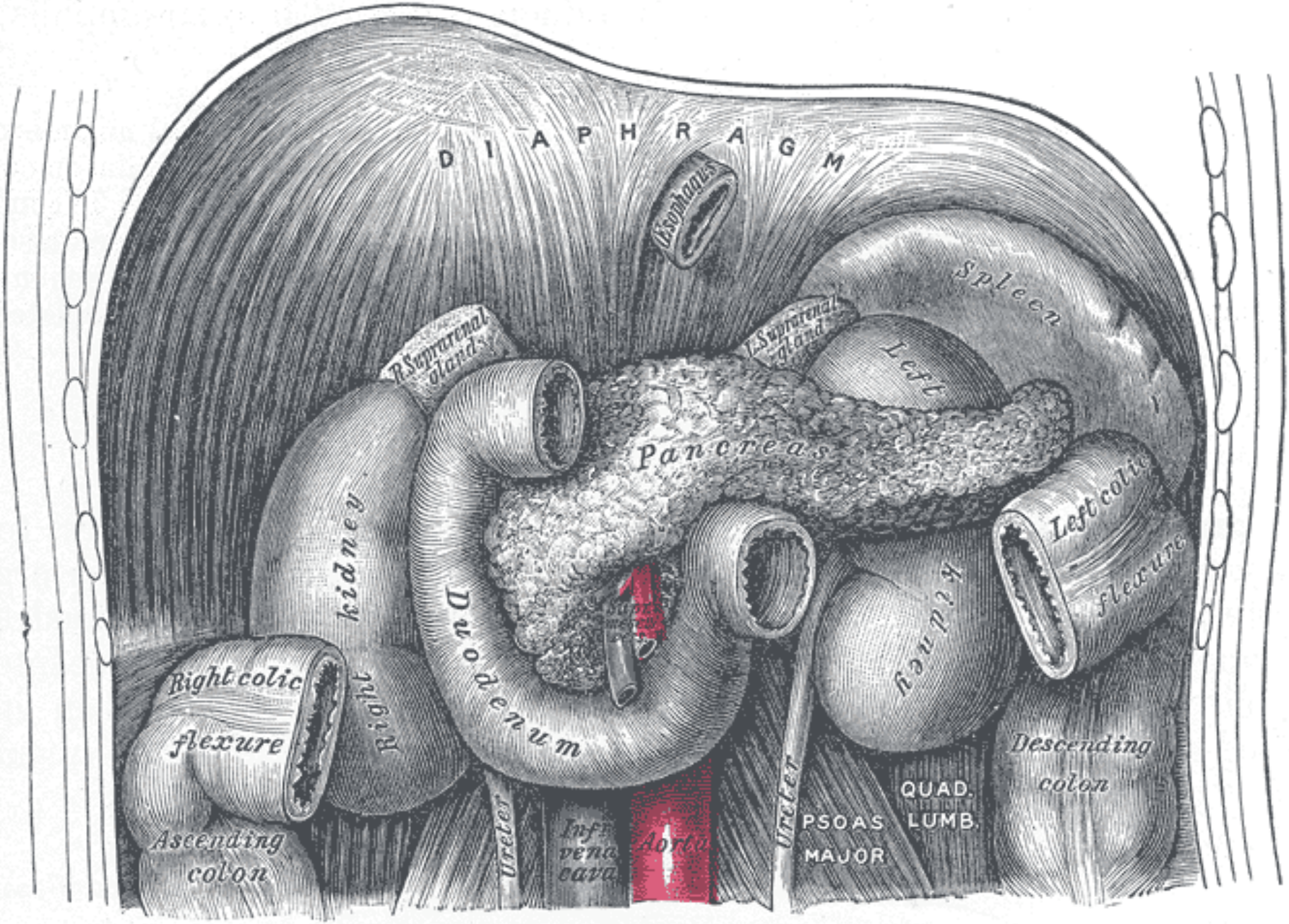


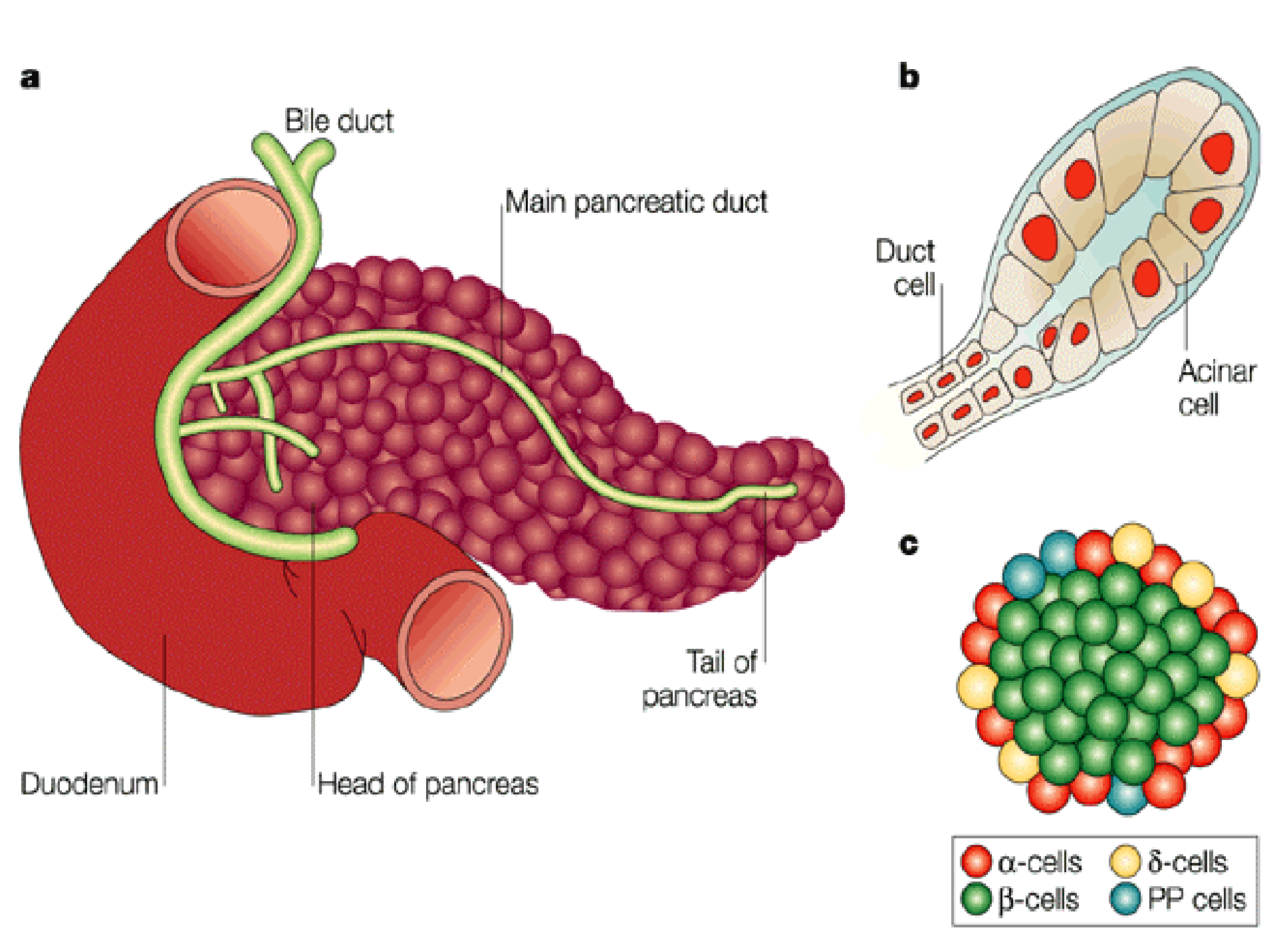

Weight
Age (yr)
Women
Men
90
85
80
75
70
65
60
55
50
20
30
40
50
60
70
80
90

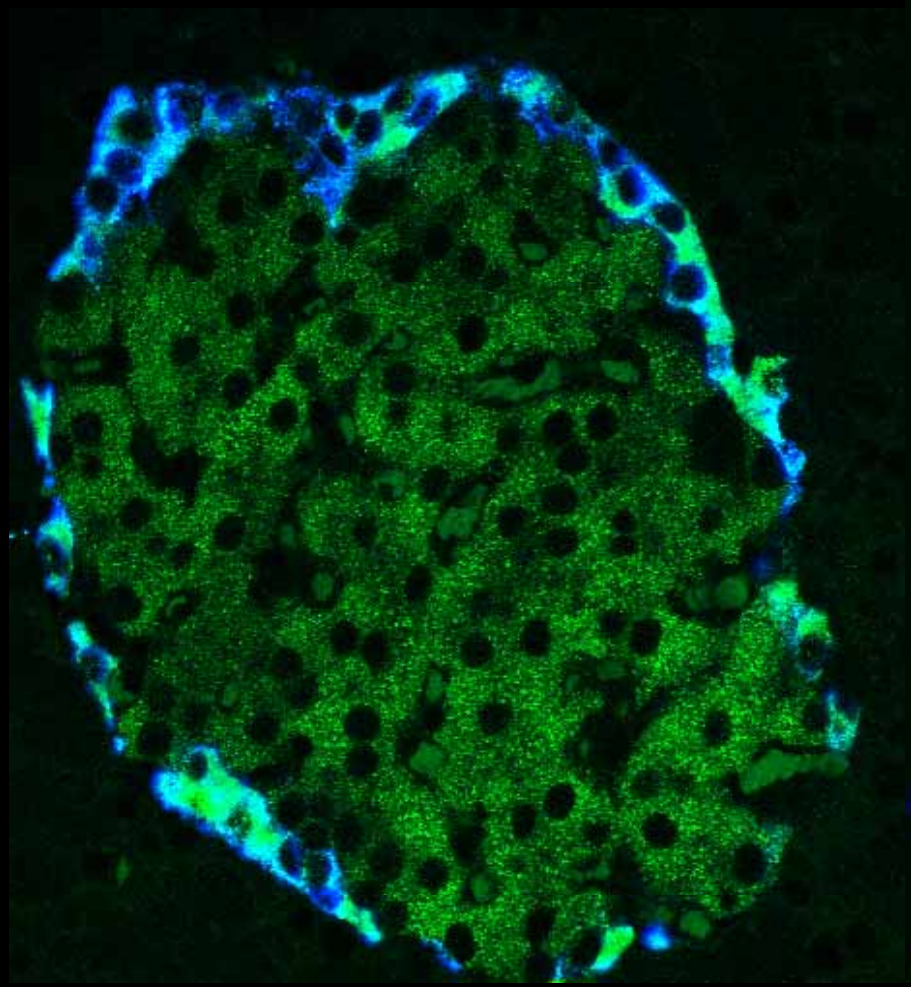

BMI
Age (yr)
Women
Men
30
28
26
24
22
20
20
30
40
50
60
70
80
90

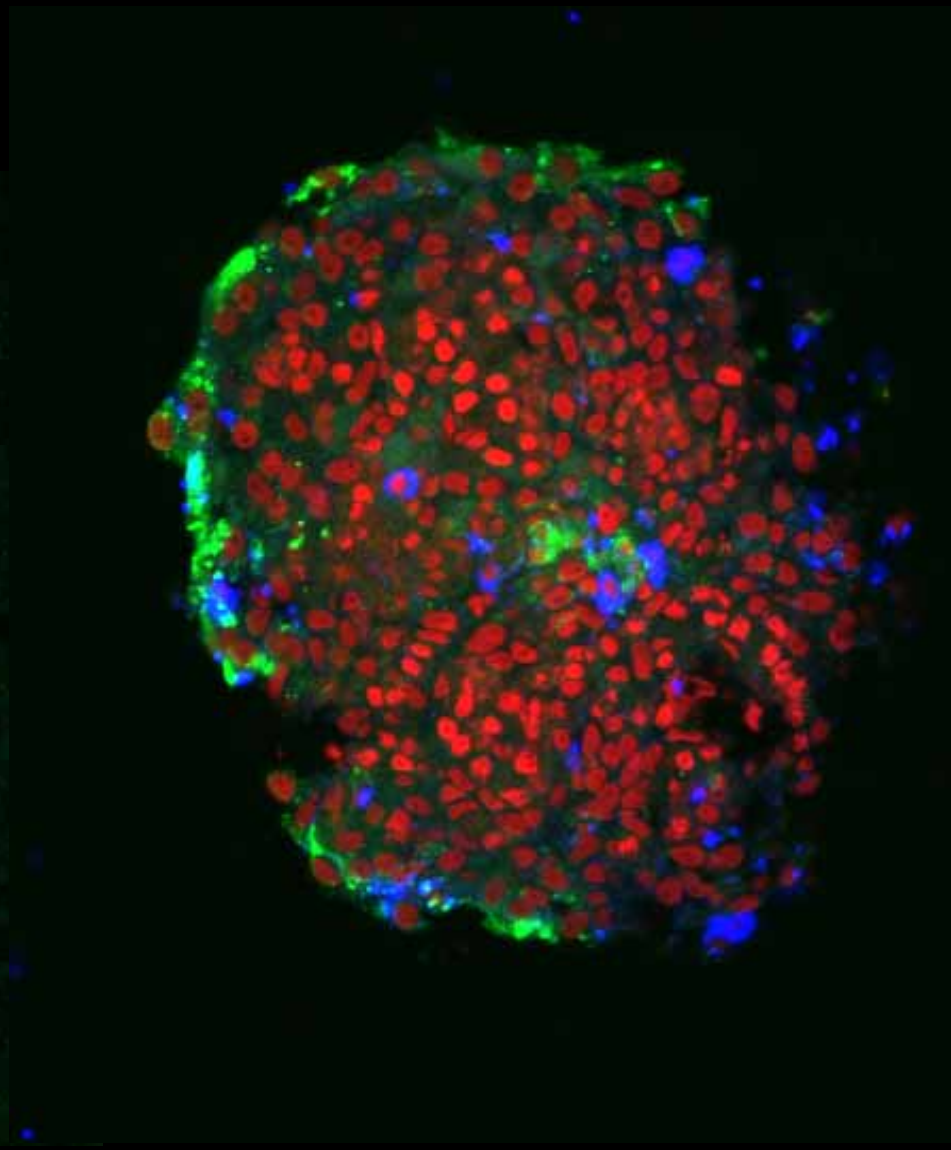

% Body Fat
Age (yr)
Women
Men
50
45
40
35
30
25
20
15
10
20
30
40
50
60
70
80
90


Waist Circ.
Age (yr)
Women
Men
110
100
90
80
70
60
20
30
40
50
60
70
80
90

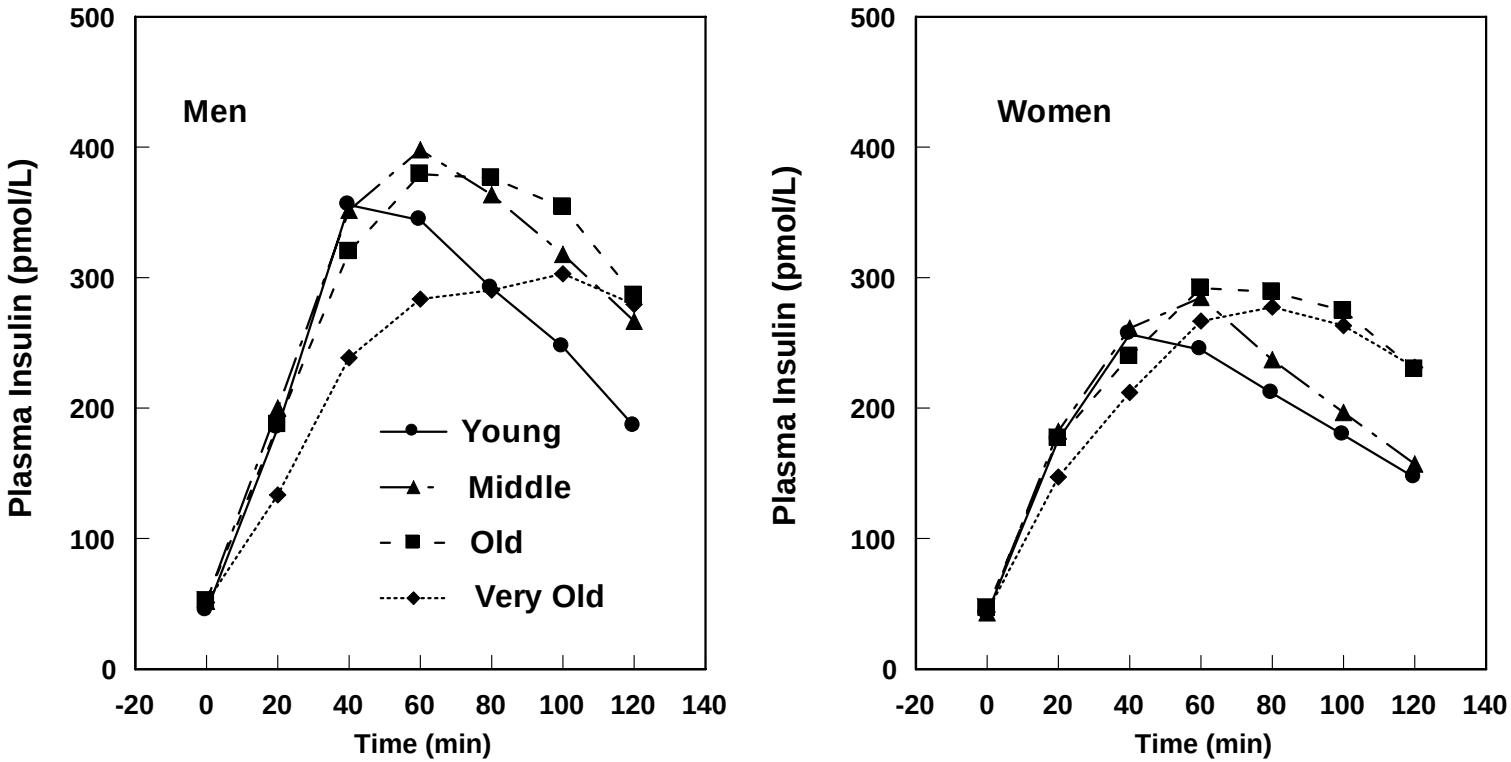

DIAPHRAGM
Œsophagus
Spleen
R. Suprarenal gland
L. Suprarenal gland
Left kidney
Pancreas
Left colic flexure
Right kidney
Duodenum
Right colic flexure
Descending colon
Ascending colon
Ureter
Inf. vena cava
Aorta
Ureter
PSOAS MAJOR
QUAD. LUMB.

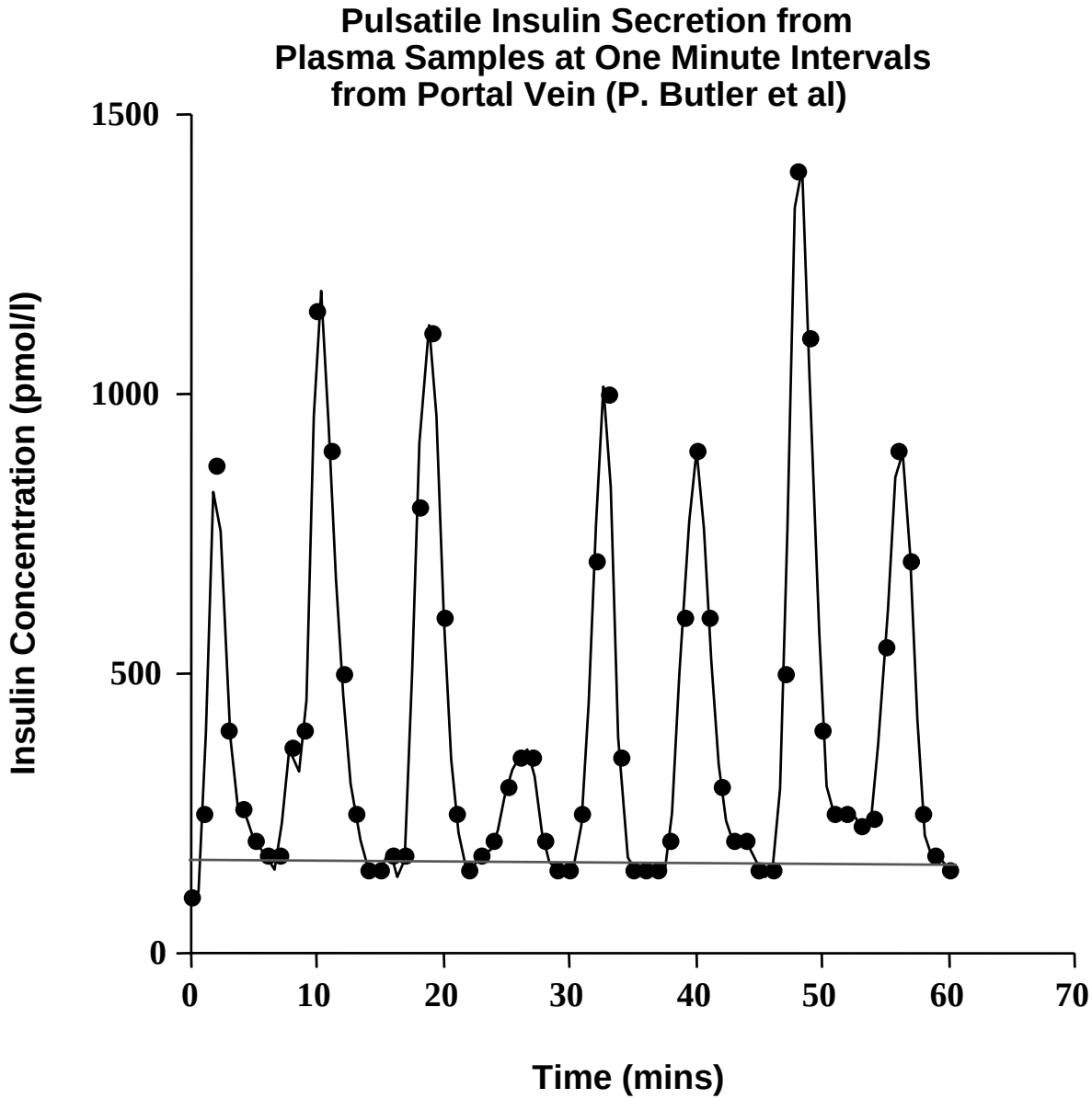

a
Bile duct
Main pancreatic duct
Tail of pancreas
Duodenum
Head of pancreas
b
Duct cell
Acinar cell
c
α-cells
δ-cells
β-cells
PP cells



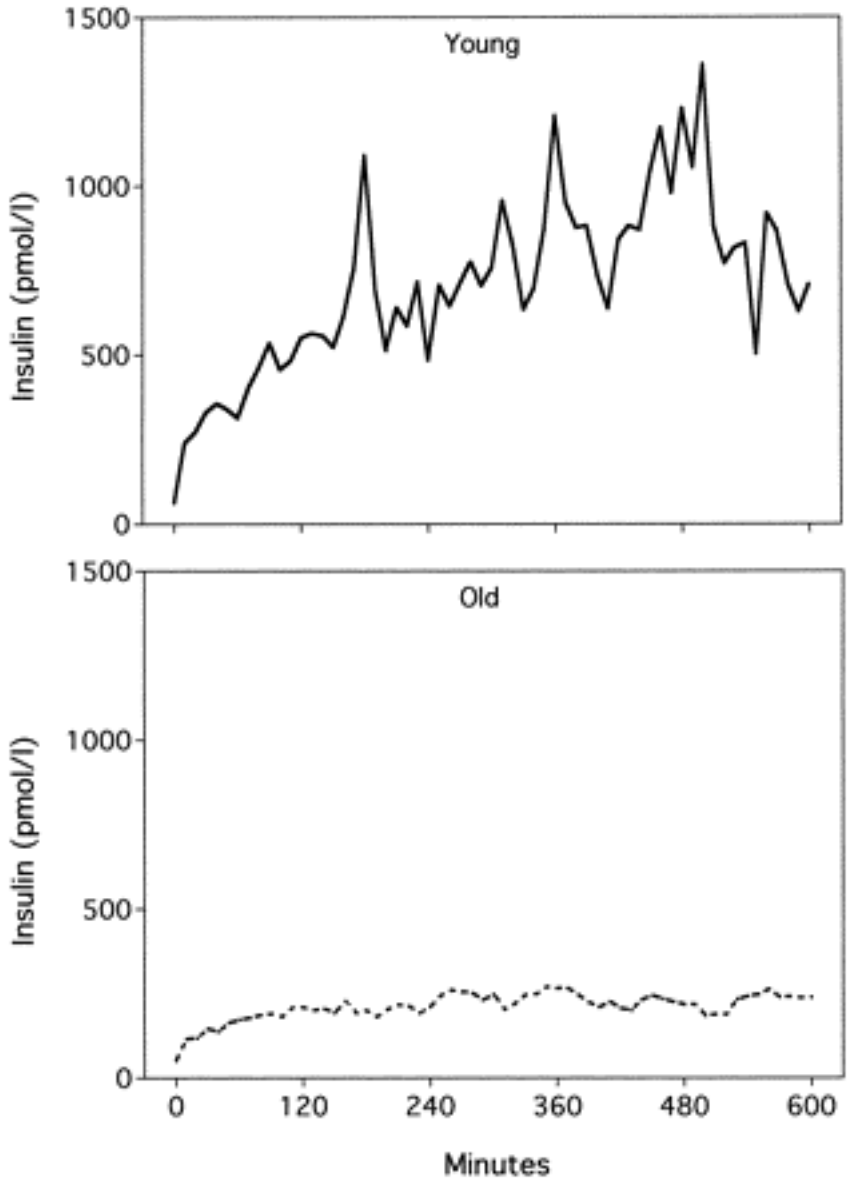


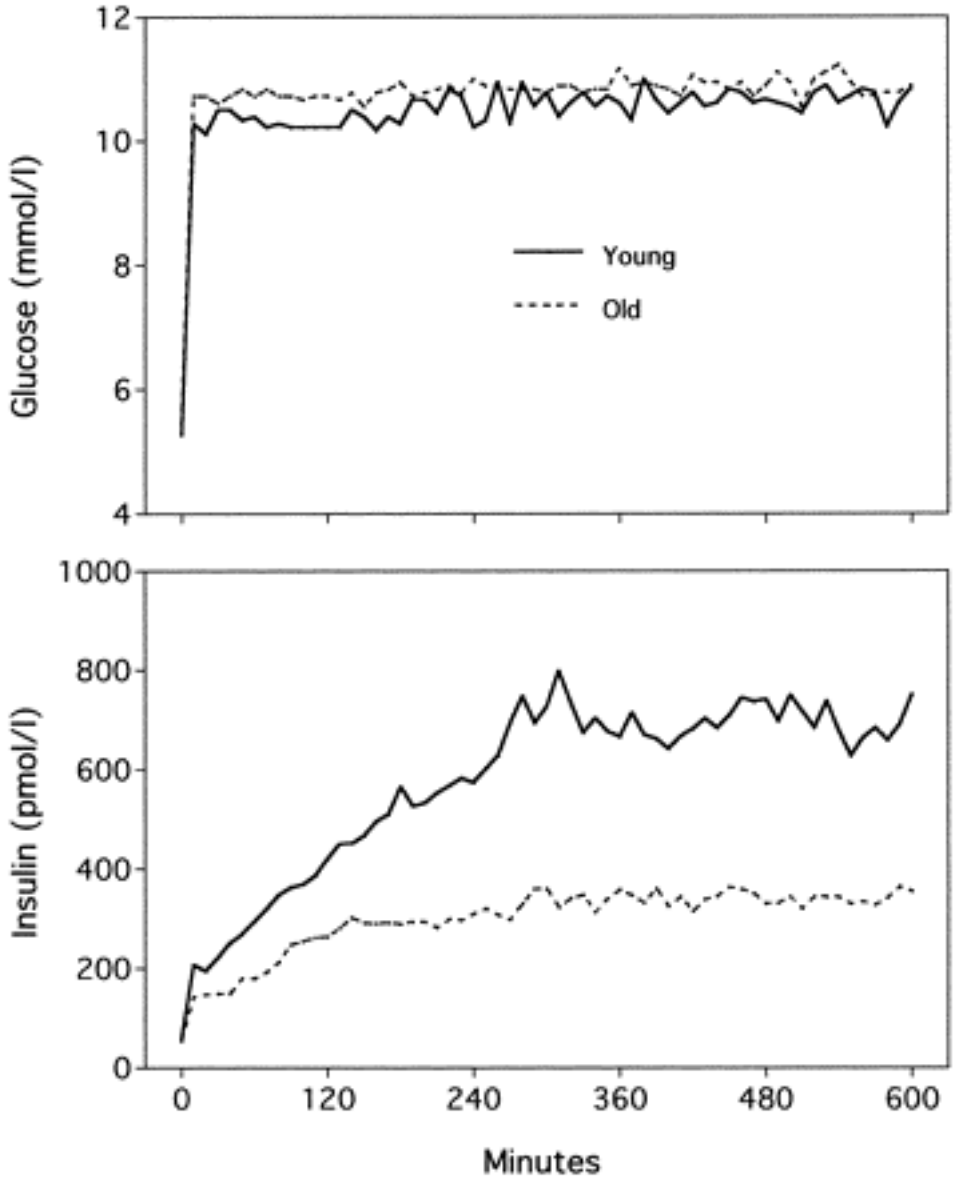
Plasma Insulin for OGTT by Age Groups

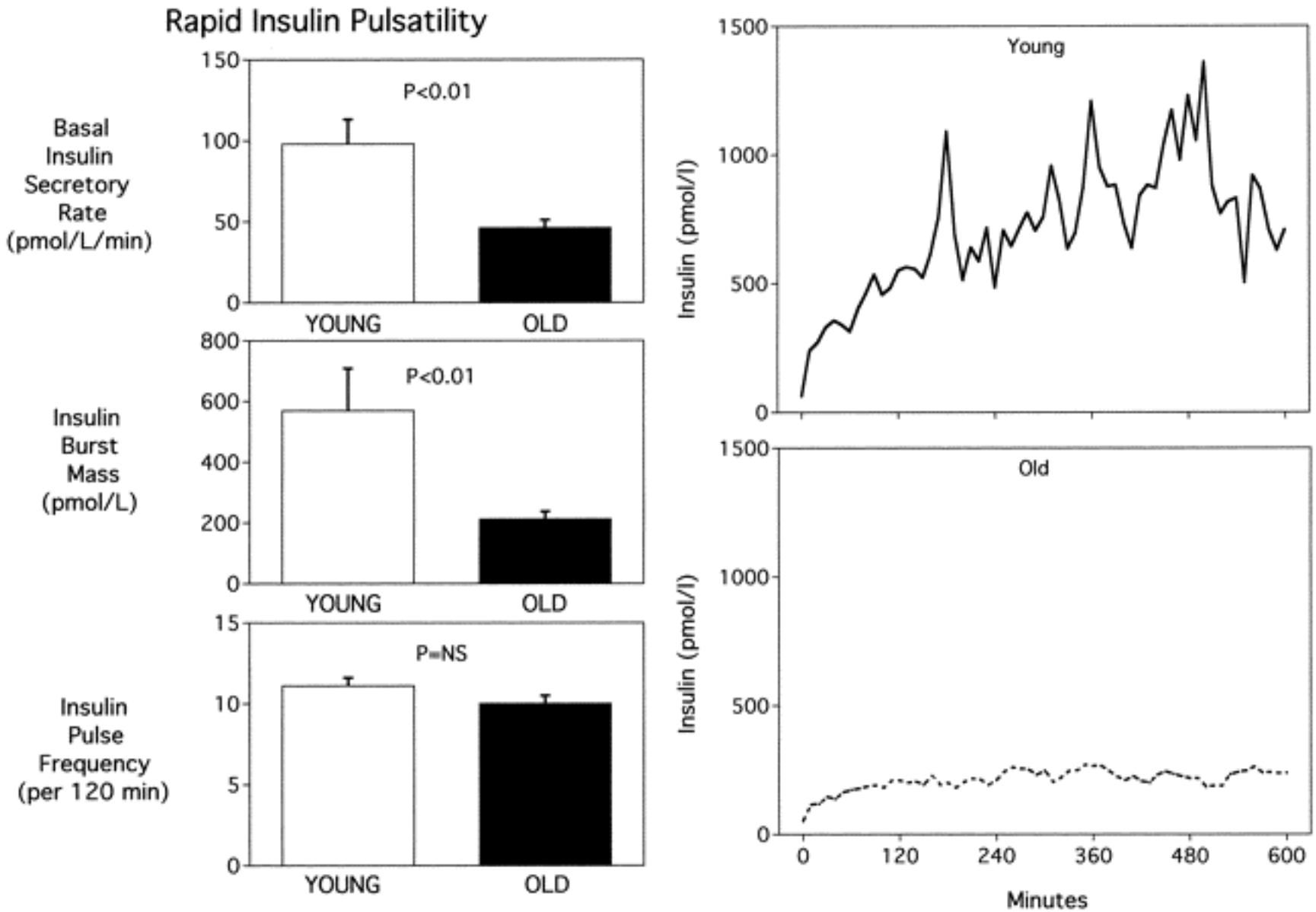


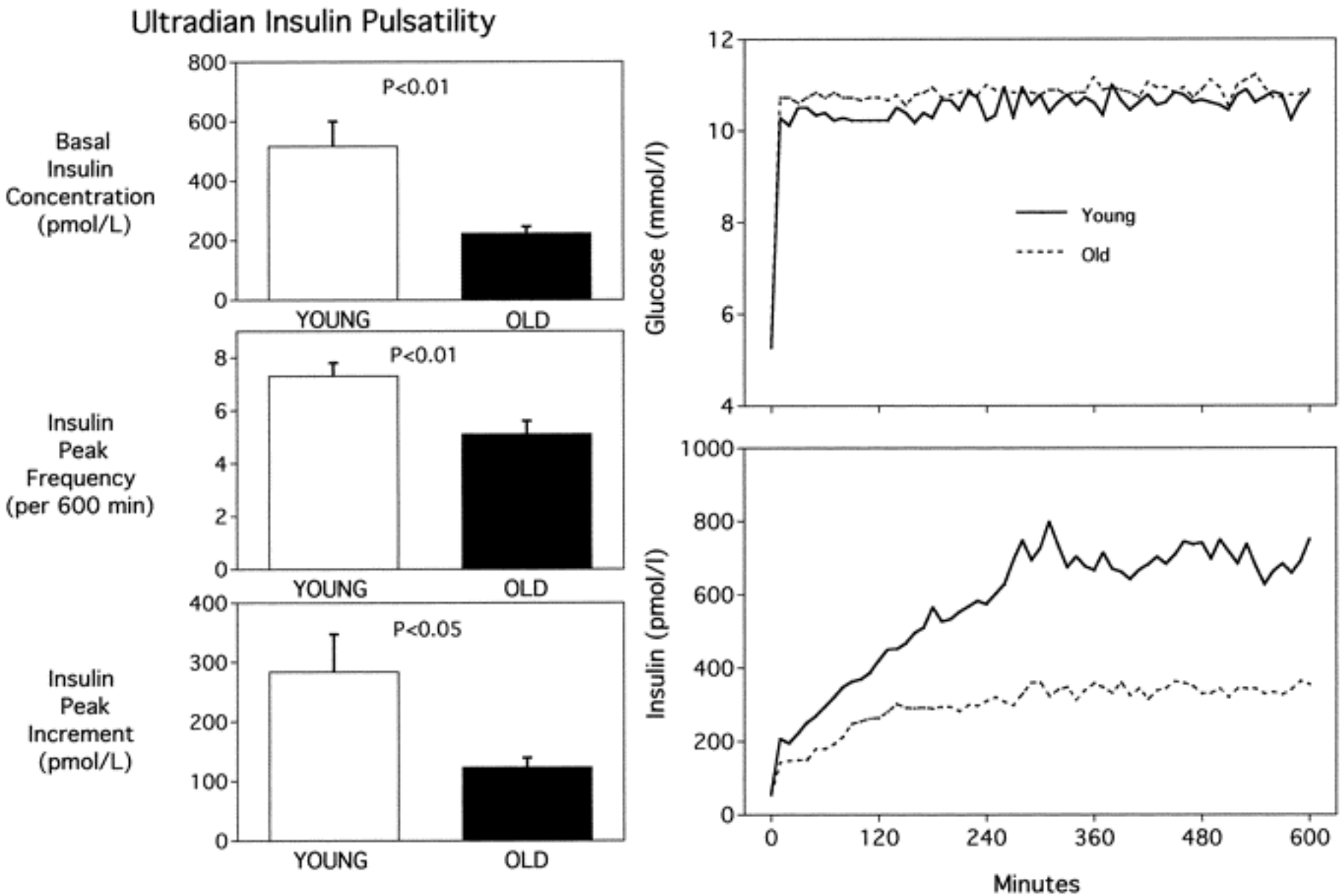


1. Insulin is secreted in a pulsatile fashion
2. 7-8 pulses/hr are evident

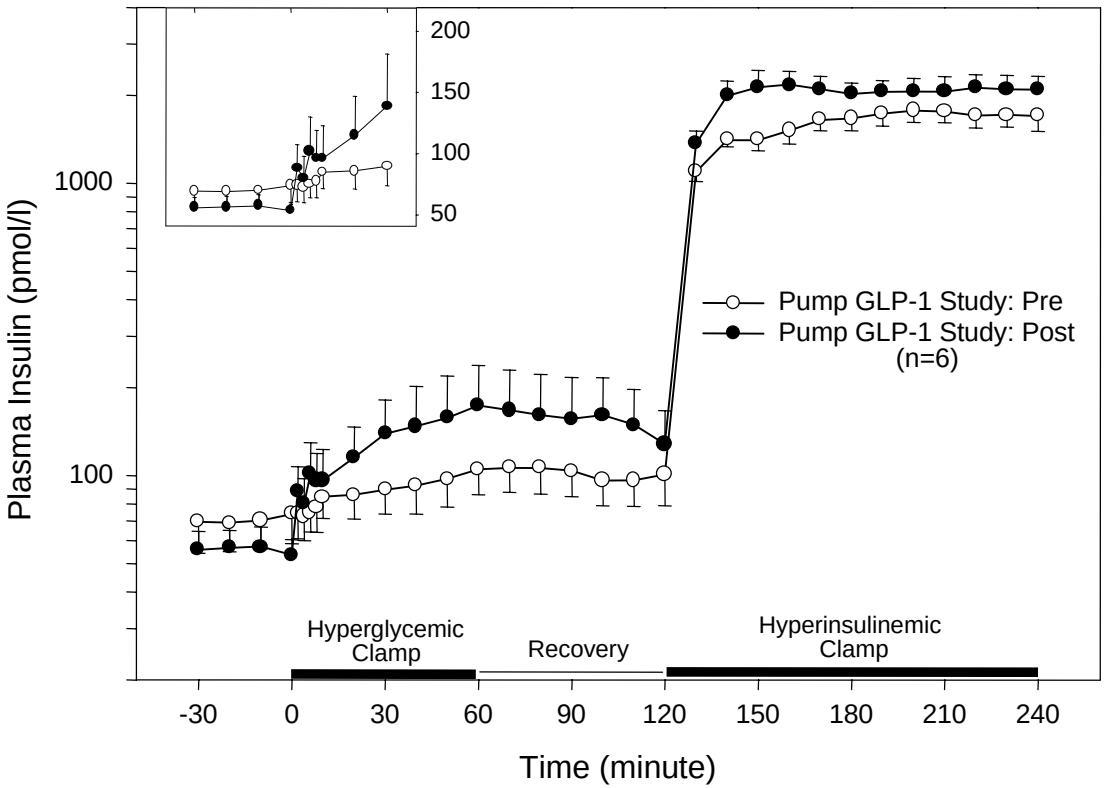

Young
Old
Insulin (pmol/l)
Insulin (pmol/l)
1500
1000
500
0
1500
1000
500
0
0
120
240
360
480
600
Minutes


12
10
8
6
4
Glucose (mmol/l)
Young
Old
1000
800
600
400
200
0
Insulin (pmol/l)
0
120
240
360
480
600
Minutes


Rapid Insulin Pulsatility
Basal Insulin Secretory Rate (pmol/L/min)
150
100
50
0
P<0.01
YOUNG
OLD
Insulin Burst Mass (pmol/L)
800
600
400
200
0
P<0.01
YOUNG
OLD
Insulin Pulse Frequency (per 120 min)
15
10
5
0
P=NS
YOUNG
OLD
Young
Old
Insulin (pmol/l)
1500
1000
500
0
0
120
240
360
480
600
Minutes


Ultradian Insulin Pulsatility
Basal Insulin Concentration (pmol/L)
800
600
400
200
0
P<0.01
YOUNG
OLD
Insulin Peak Frequency (per 600 min)
8
6
4
2
0
P<0.01
YOUNG
OLD
Insulin Peak Increment (pmol/L)
400
300
200
100
0
P<0.05
YOUNG
OLD
Glucose (mmol/l)
12
10
8
6
4
Young
Old
Insulin (pmol/l)
1000
800
600
400
200
0
0
120
240
360
480
600
Minutes

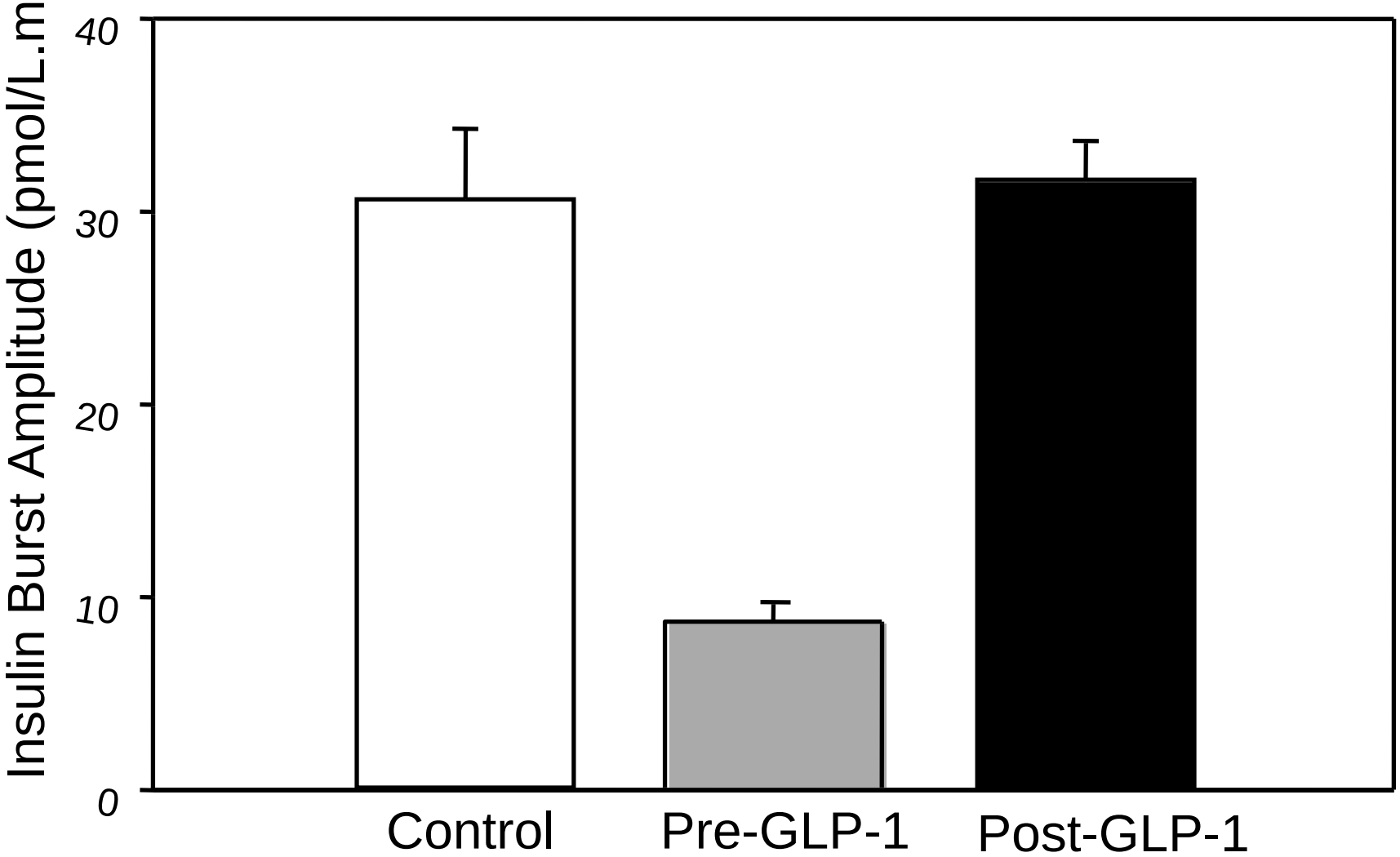
Plasma Insulin Levels during a Hyperglycemic / Hyperinsulinemic Clamp in Diabetic Patients with a Continuous Pump Infusion of GLP-1



1.) First-phase insulin response returns after 3 months GLP-1 treatment

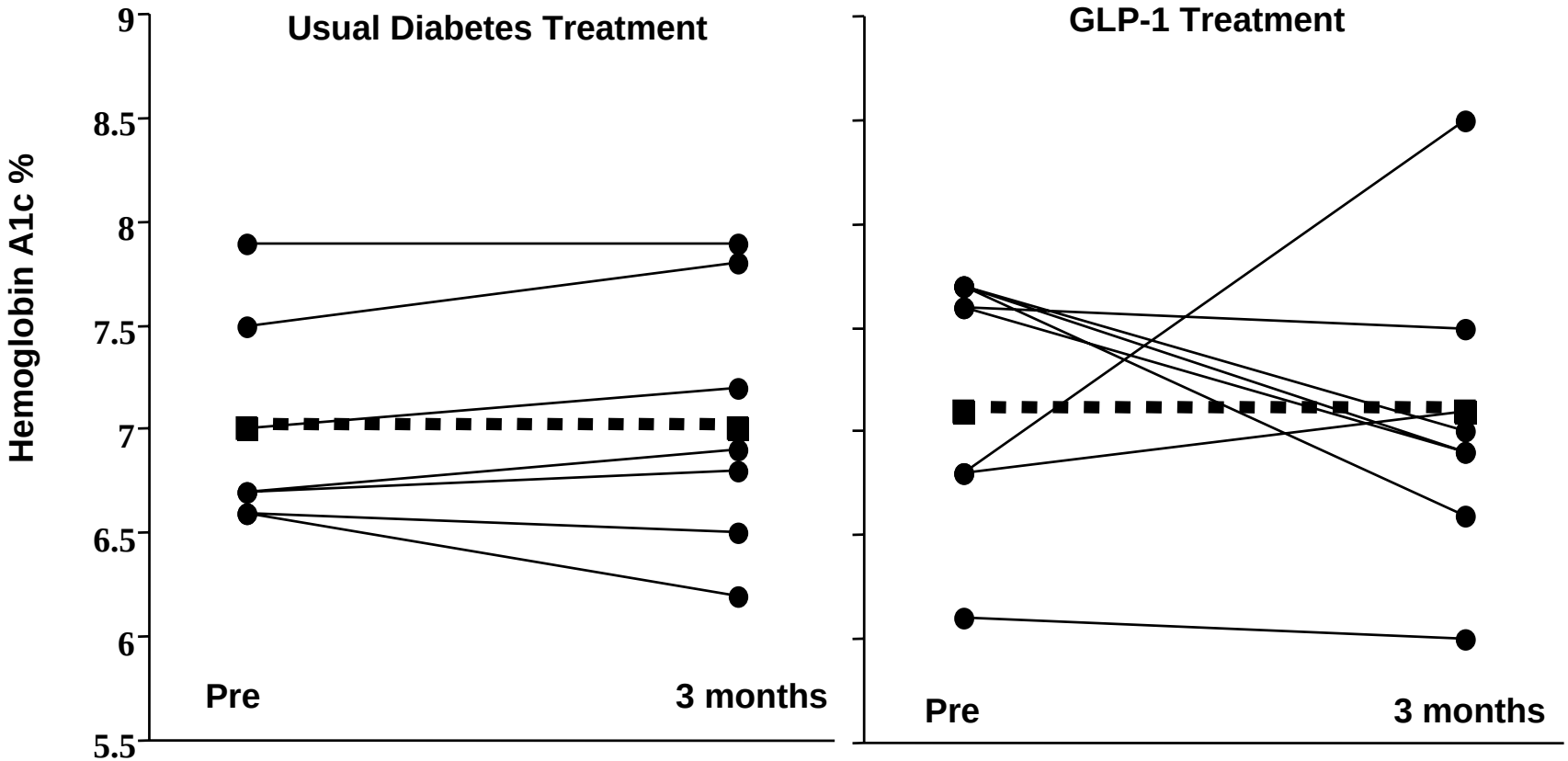
2.) Plateau-phase returns after 3 months GLP-1 treatment

Insulin Burst Amplitude Ascertained from One Minute Plasma Insulin Levels Over 4 Hour Sampling Period



Six-week GLP-1 treatment significantly increased insulin burst amplitude

Pre- and Post Hemoglobin A_{1c} Levels



Hemoglobin A_{1c} levels are maintained over 3 month GLP-1 treatment