Abdominal obezite ve önemi

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Endokrinoloji Metabolizma ve Diyabet BD

Obezite

Subkutan yağ dokusu artışı

İntra-abdominal yağ dokusu artışı

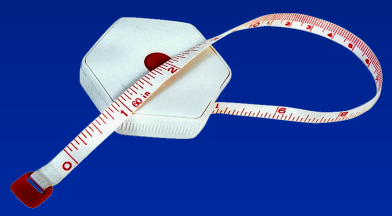
Ektopik yağ depolanması

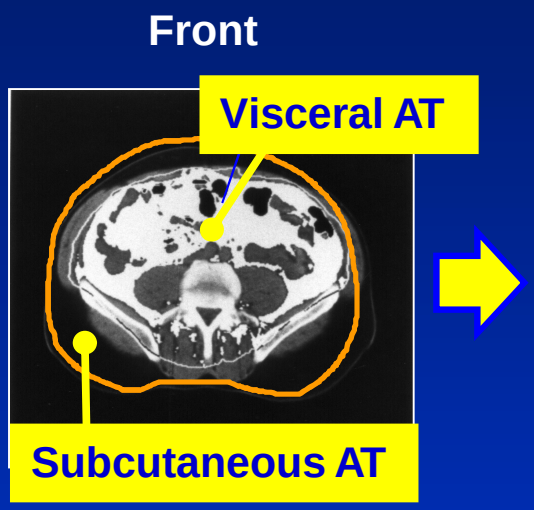
Abdominal Obesity

- as indicated by increased waist circumference
- is the strongest obesity-related parameter associated with metabolic risk factors

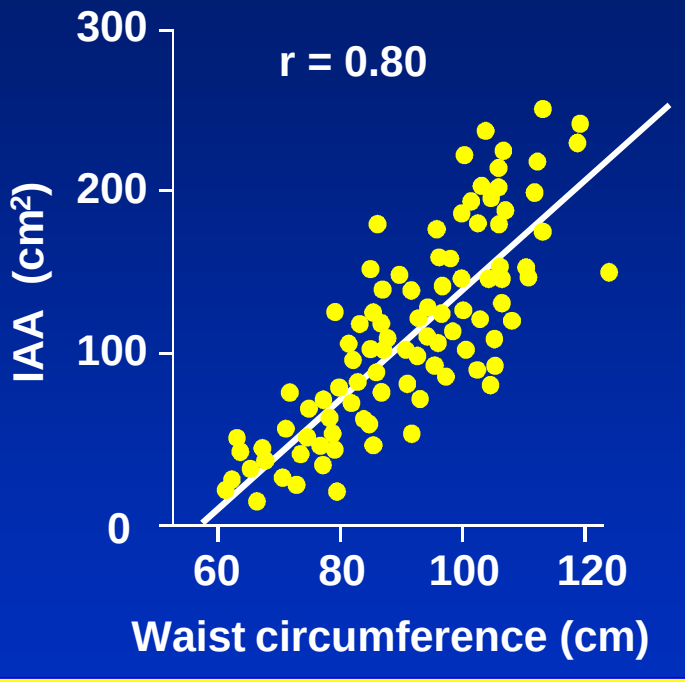
Grundy SM et al. *Circulation.* 2005. Oct 25;112(17):2735-52.

Waist Circumference Correlates with Intra-abdominal Adiposity (IAA)





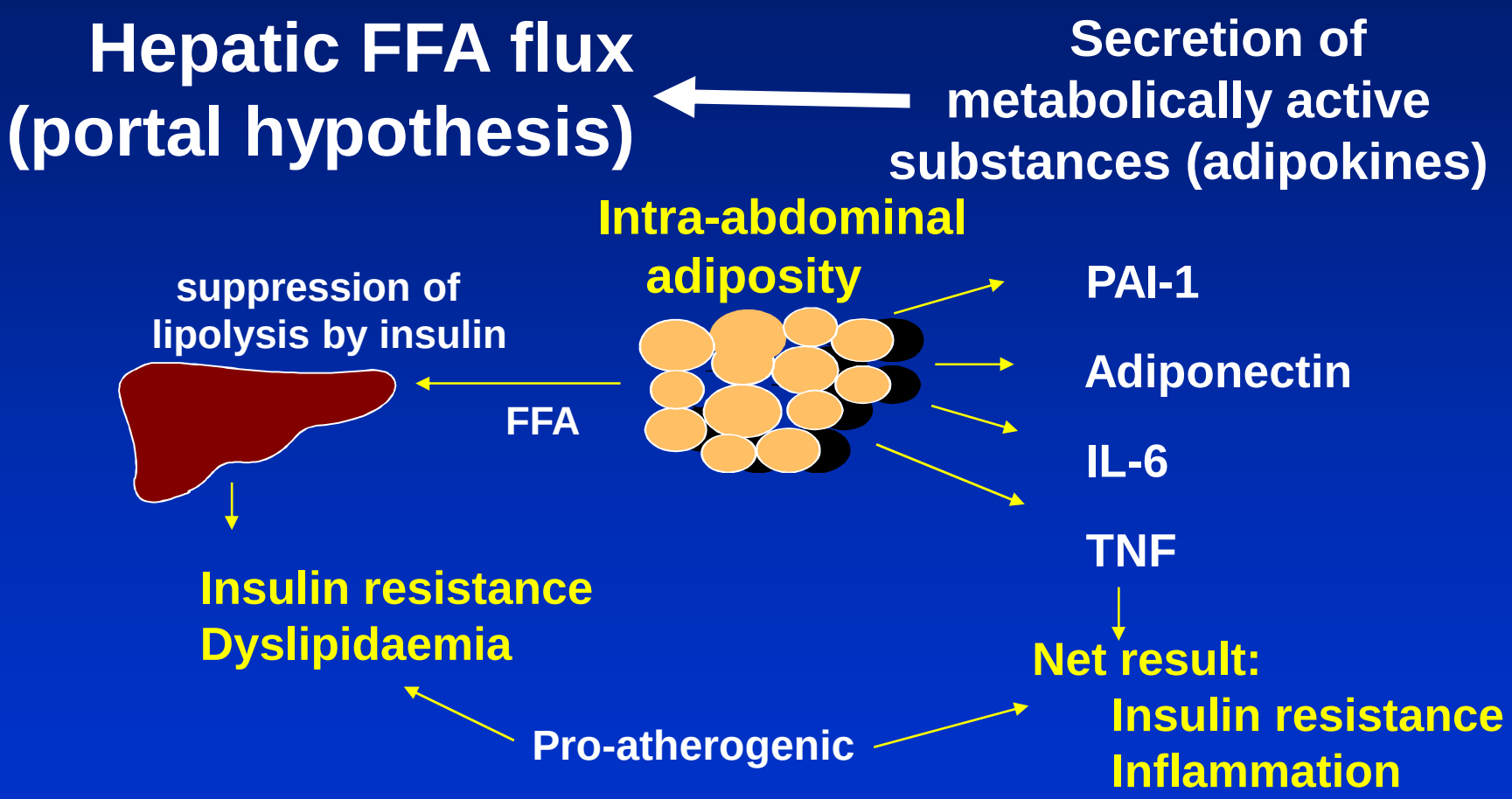
AT: adipose tissue



To assess IAA, the simplest anthropometric index is the measurement of waist circumference, which is strongly correlated with direct measurement of IAA by CT scan or MRI, considered to be the gold standard

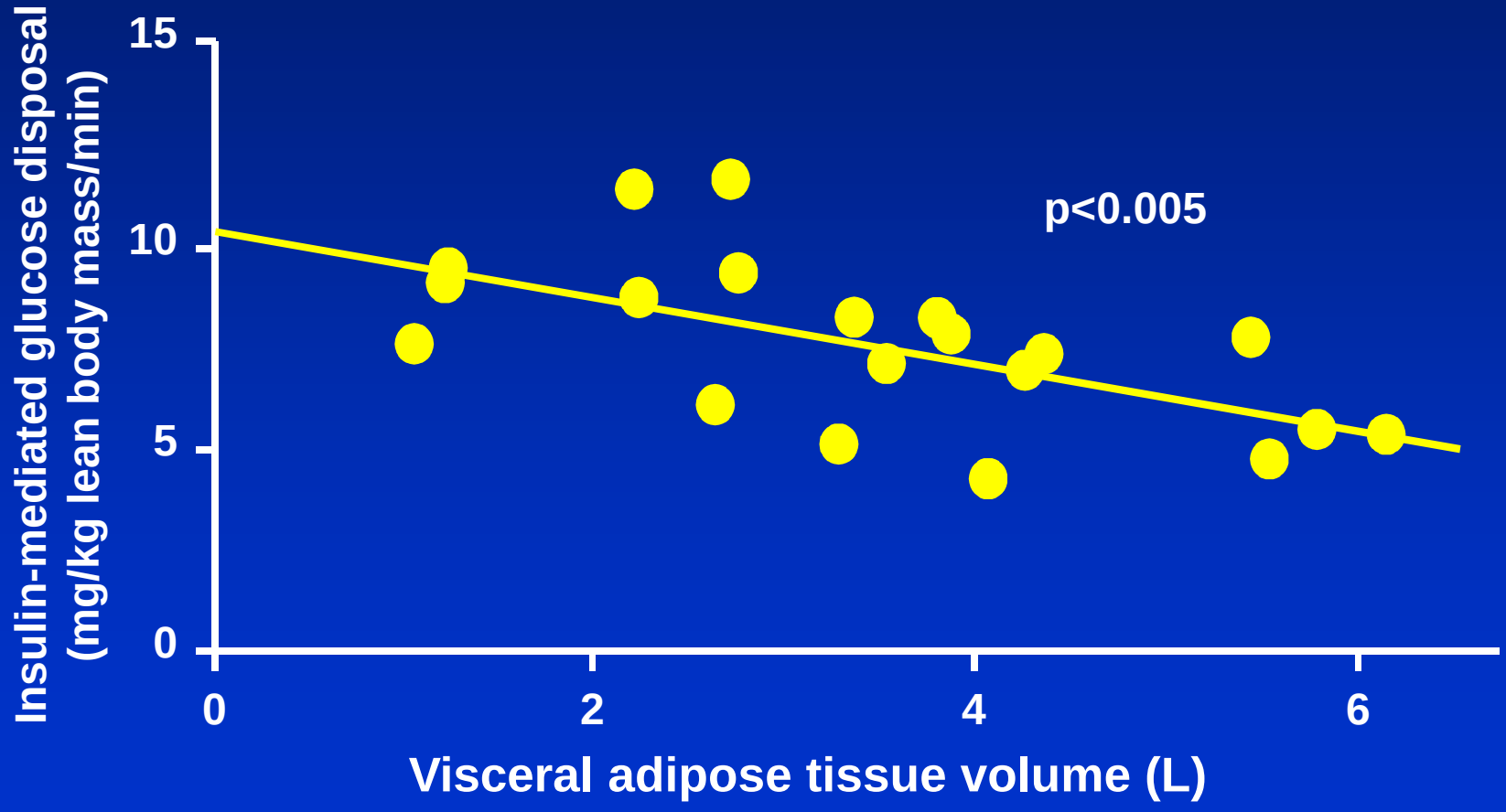
Pouliot MC et al. *Am J Cardiol.* 1994;73:460-8.
Després JP et al. 2001 *BMJ*. 2001;322:716-20.

Intra-abdominal Adiposity Feeds Directly into the Liver



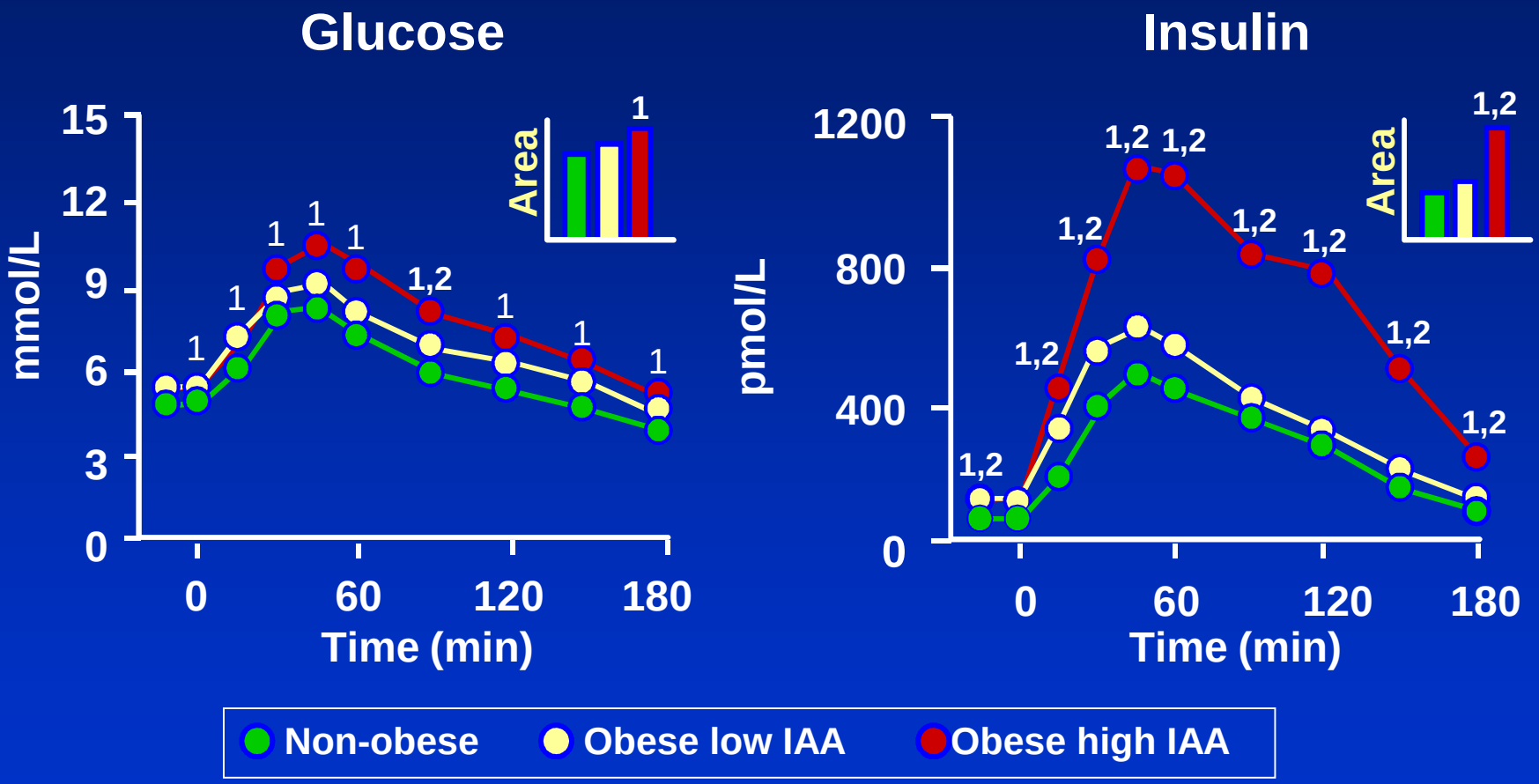
Heilbronn L et al. *Int J Obes Relat Metab Disord.* 2004;28 Suppl 4:S12-21.
Coppack SW. *Proc Nutr Soc*. 2001;60:349-56.
Skurk T & Hauner H. *Int J Obes Relat Metab Disord.* 2004;28:1357-64.

Intra-abdominal Adiposity Associates with Reduced Insulin-Mediated Glucose Disposal



Banerji MA et al. *J Clin Endocrinol Metab.* 1999;84:137-44.

High Intra-abdominal Adiposity (IAA) Associates with Insulin Resistance



IAA: intra-abdominal adiposity
Significantly different from [1]non-obese, [2]obese with low visceral AT levels

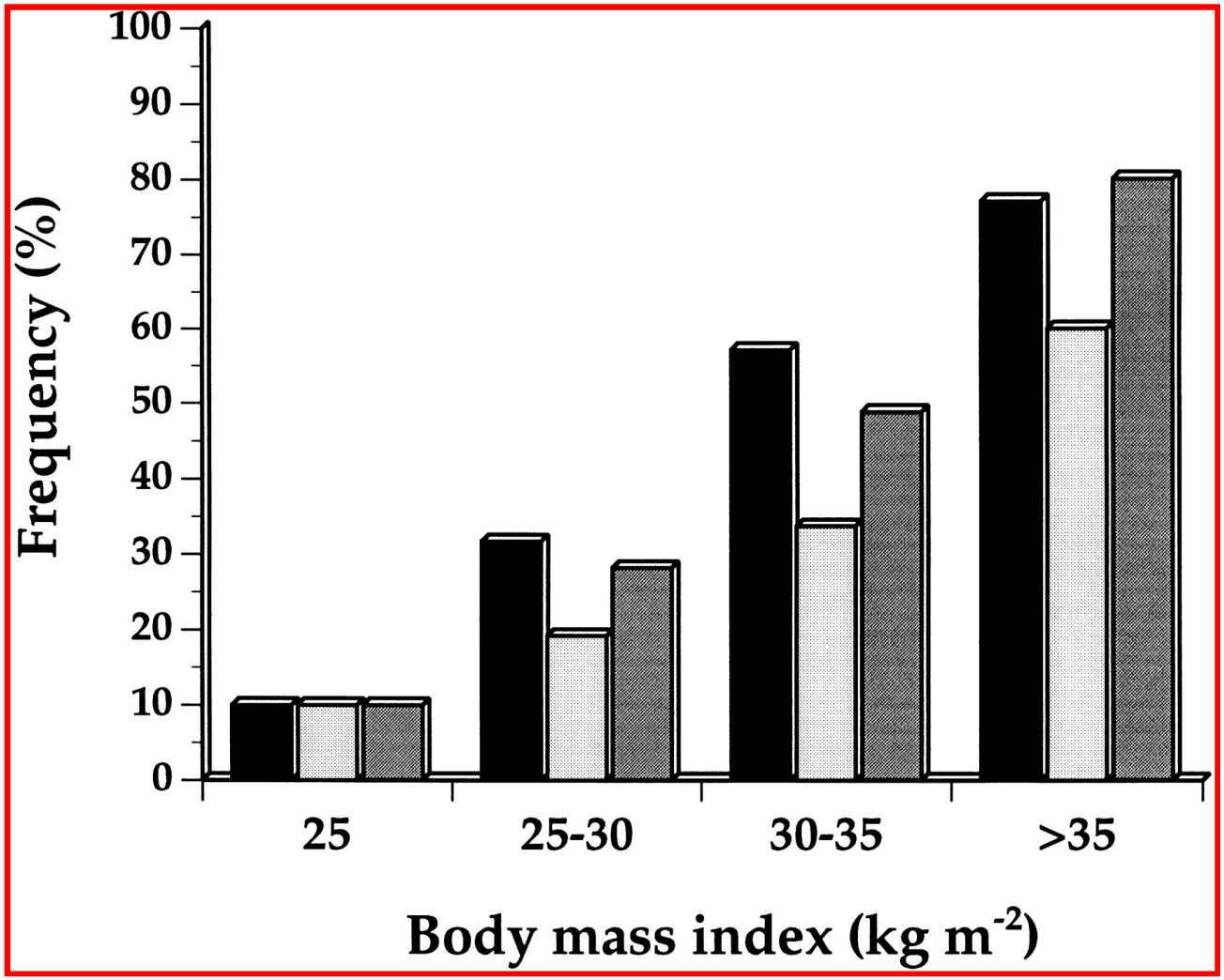
Pouliot MC et al. *Diabetes.* 1992;41:826-34.

Abdominal Obesity: Reaching Epidemic Proportions Worldwide

	Men (%)	Women (%)	Total (%)
US[a]	36.9	55.1	46.0
Spain[b]	30.5	37.8	34.7
Italy[c]	24.0	37.0	31.5
UK[d]	29.0	26.0	27.5
France[e]	–	–	26.3
Netherlands[f]	14.8	21.1	18.2
Germany[g]	20.0	20.5	20.3

High waist circumference: ≥102 cm (≥40 in) in men or ≥88 cm (≥35 in) in women except in Germany (>103 cm [41 in] and >92 cm [36 in], respectively)

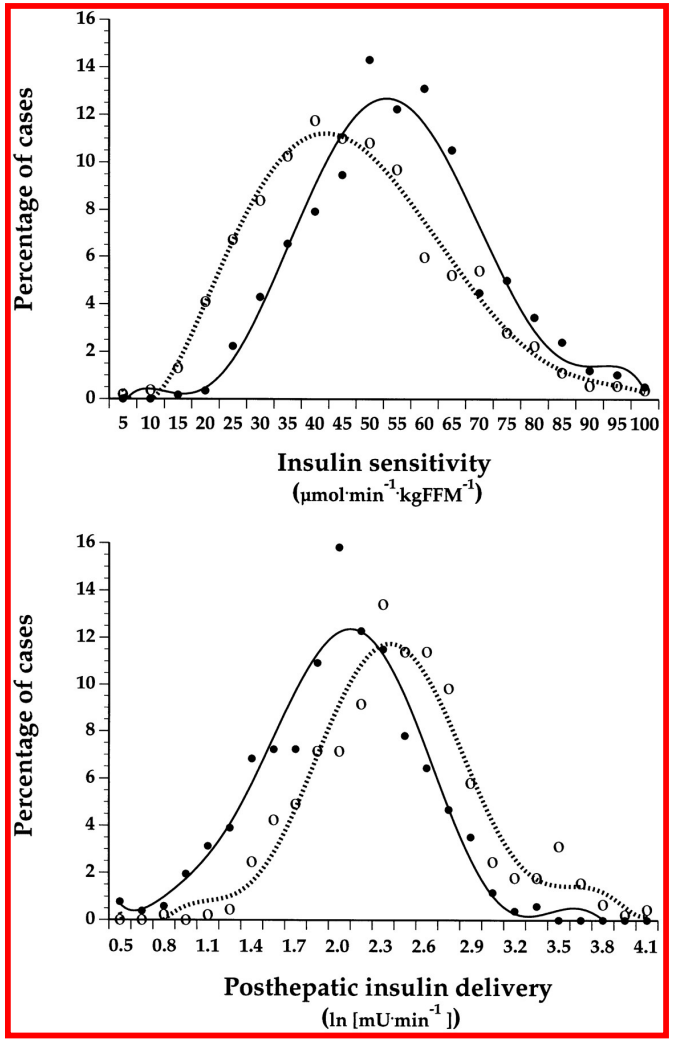
[a]Ford ES et al. *Obes Res.* 2003;11:1223-31. ; [b]Alvarez-Leon EE et al. *Med Clin. (Barc)* 2003;120:172-4.; [c]OECI *Ital Heart J.* 2004,5(suppl.3):49-92.; [d]Ruston D et al. Office of National Statistics (UK), 2004, *National Diet and Nutrition Survey*, vol. 4.; [e]Obepi 2003; [f]Visscher TLS & Seidell JC. *Int J Obes*. 2004;28:1309-16. ; [g]Liese AD et al. *Eur J Nutr.* 2001;40: 282-8.



Prevalence rates of insulin resistance, hyperinsulinemia, and insulin hypersecretion (all defined as the top decile of the respective distributions in lean subjects) as a function of the BMI. *Black bars*, hyperinsulinemia; *light gray bars*, insulin resistance; *dark gray bars*, hypersecretion.

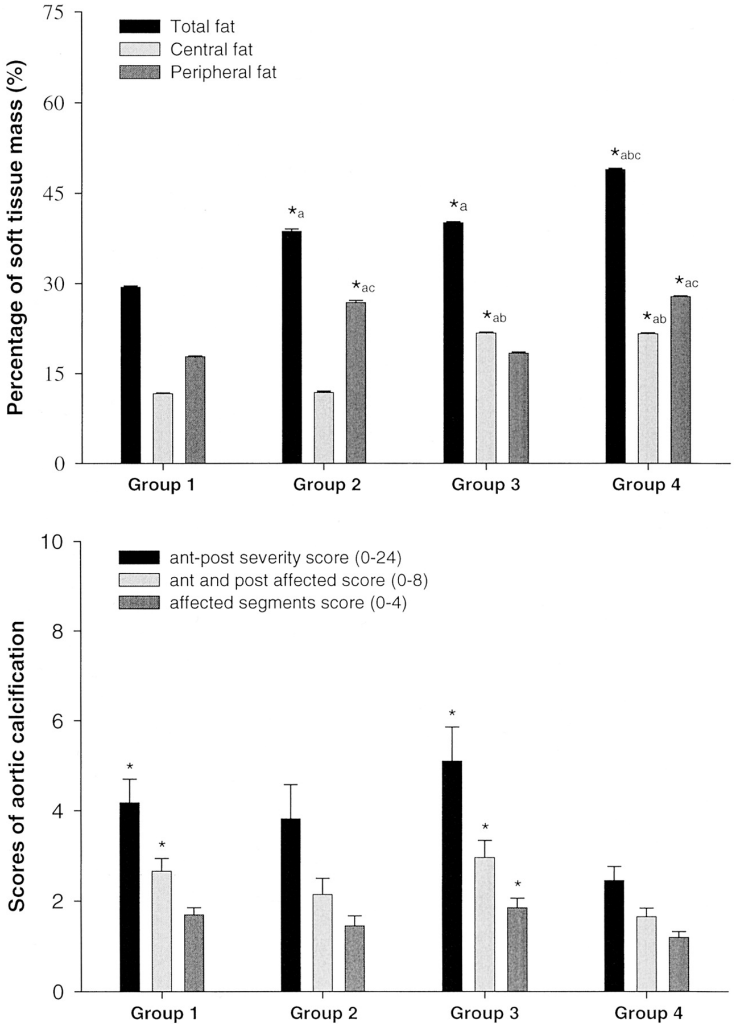
J. Clin. Invest. 1997;100:1166-1173

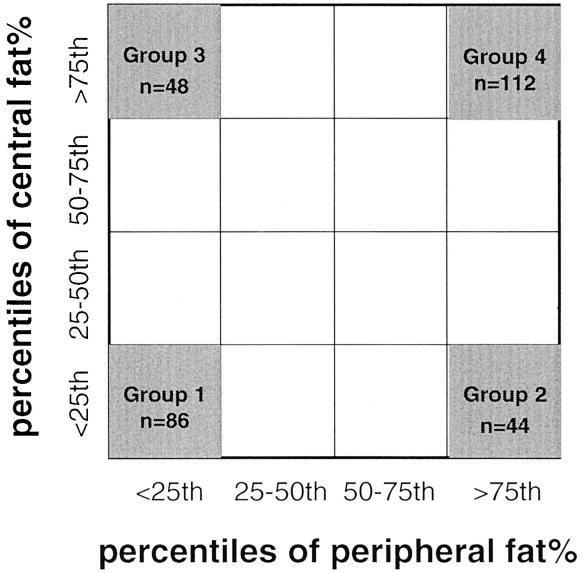
Frequency distribution plots of insulin sensitivity (as the Mffm, *top*) and fasting posthepatic insulin delivery rate (as the natural logarithm of IDR, *bottom*) in lean and obese subjects. Lines are polynomial functions only used for the purpose of outlining the two distributions. By the Shapiro-Wilk W test, the distribution function of insulin sensitivity deviates from normality in both obese and lean subjects, whereas the corresponding functions for log-transformed IDR do not. *Filled circles*, lean; *open circles*, obese.



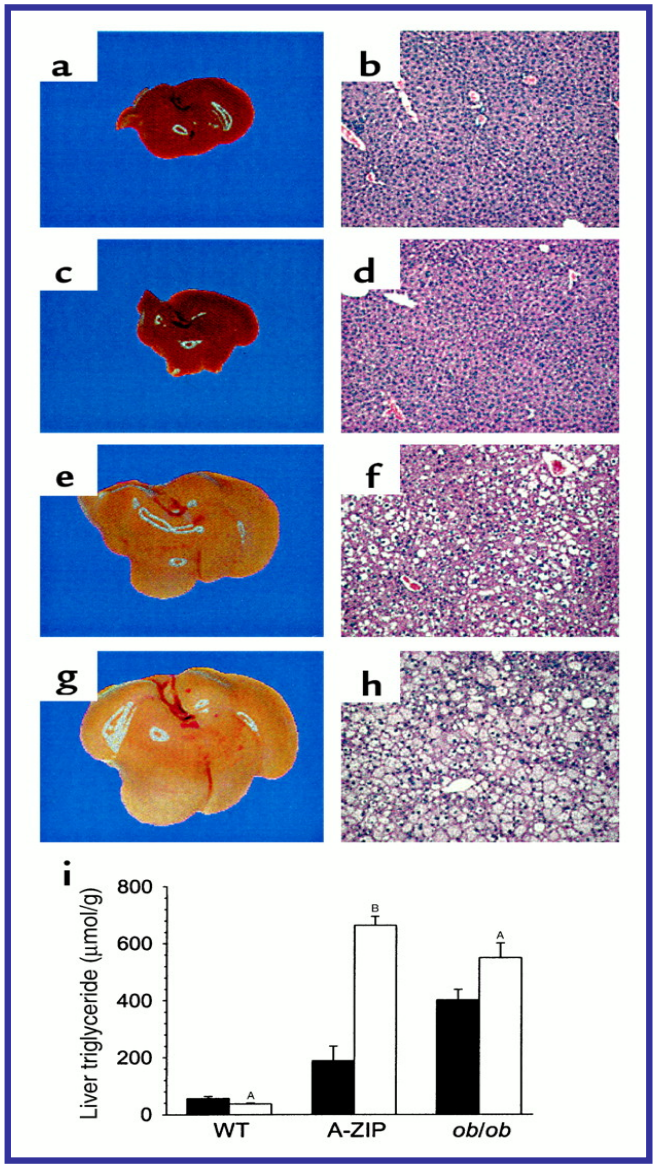
J. Clin. Invest. 1997;100:1166-1173

Total, peripheral, and central fat% (A) and severity scores of aortic calcification (B) in elderly women with various extremes of body fat distribution



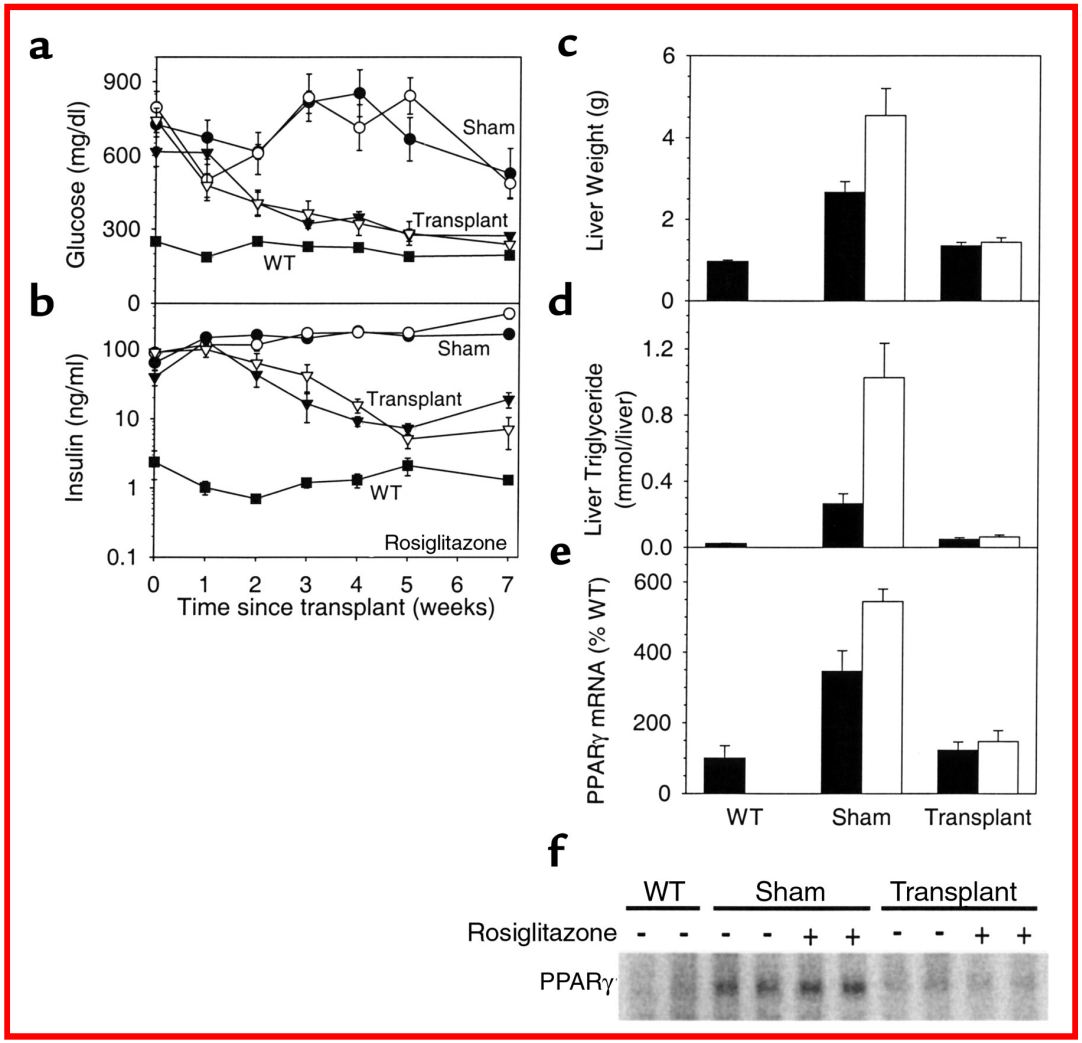


Tanko, L. B. et al. Circulation 2003;107:1626-1631



Rosiglitazone exacerbates hepatic steatosis. Livers from WT (**a**–**d**) and A-ZIP/F-1 (**e**–**h**) mice, either treated with rosiglitazone (**c**, **d**, **g**, **h**) or not (**a**, **b**, **e**, **f**) for 5 weeks, are shown at the same magnification. Hematoxylin and eosin–stained sections of the same livers (original magnification, x100) show steatosis of the control A-ZIP/F-1 mice, which worsens with rosiglitazone treatment. Liver triglyceride content (**i**) is shown for control (filled bars) and rosiglitazone-treated (open bars) mice (after 5 weeks of treatment for the A-ZIP/F-1 mice and 2 weeks for the *ob/ob* mice). Data are mean ± SEM (n = 5–6). A$P < 0.05$ for differences within each genotype between control and rosiglitazone-treated mice. B$P < 0.005$ for differences within each genotype between control and rosiglitazone-treated mice.

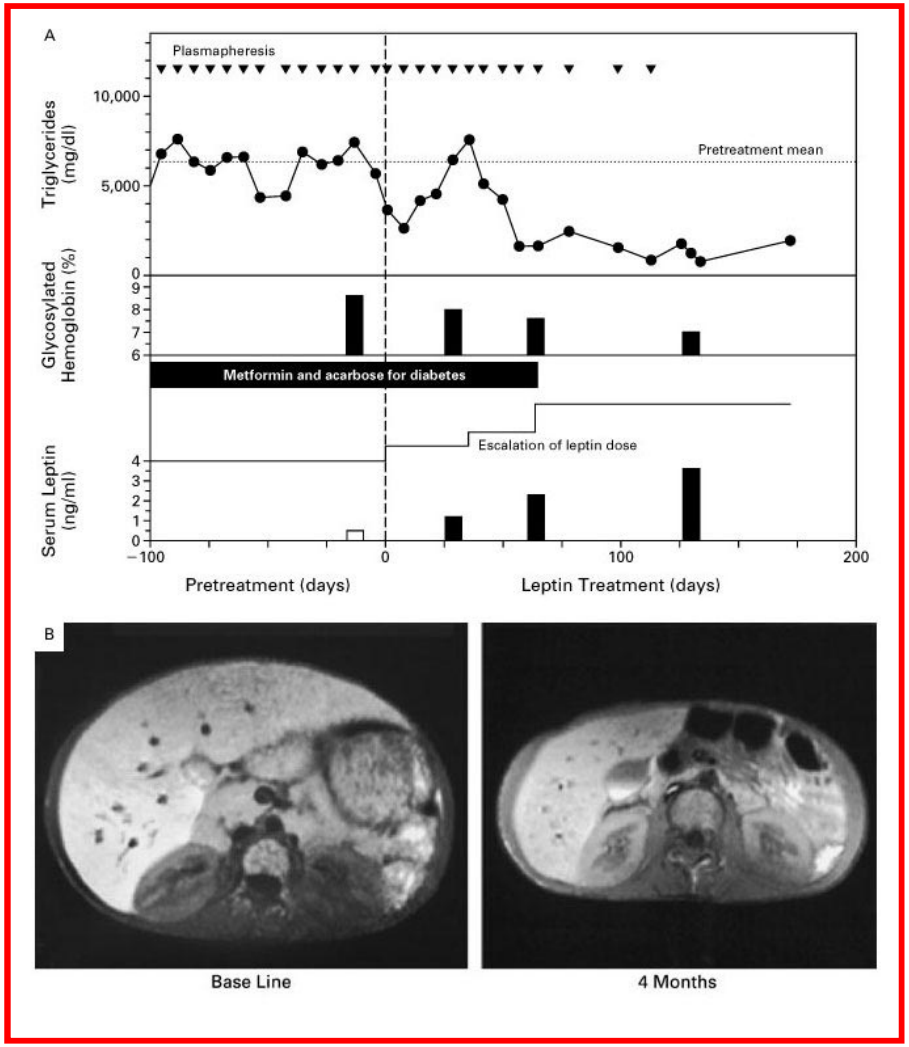
Chao, L. et al. J. Clin. Invest. 2000;106:1221-1228



Effect of rosiglitazone treatment on fat-transplanted A-ZIP/F-1 mice. WAT (400 mg) was transplanted into A-ZIP/F-1 mice at 5 weeks of age. Serum glucose (**a**) and insulin (**b**) were measured weekly (note that the insulin scale is logarithmic). Rosiglitazone (or control) treatment was begun 2 weeks after transplantation. Symbols are filled circles, sham-operated A-ZIP/F-1; open circles, sham-operated, rosiglitazone-treated A-ZIP/F-1; filled triangles, transplanted A-ZIP/F-1; open triangles, transplanted, rosiglitazone-treated A-ZIP/F-1; and filled squares, WT FVB/N. Hepatic weight (**c**), triglyceride content (**d**), and PPAR mRNA (**e**, **f**) levels in control (filled bars) or rosiglitazone-treated (open bars) mice at 8 weeks after transplant. WAT transplants increased to 329 ± 59% and 398 ± 87% of initial weight in the control and rosiglitazone-treated groups, respectively. mRNA levels are expressed as a percent of WT levels. Each lane of the Northern blot is from a different mouse. Data are mean ± SEM (n = 5–6).

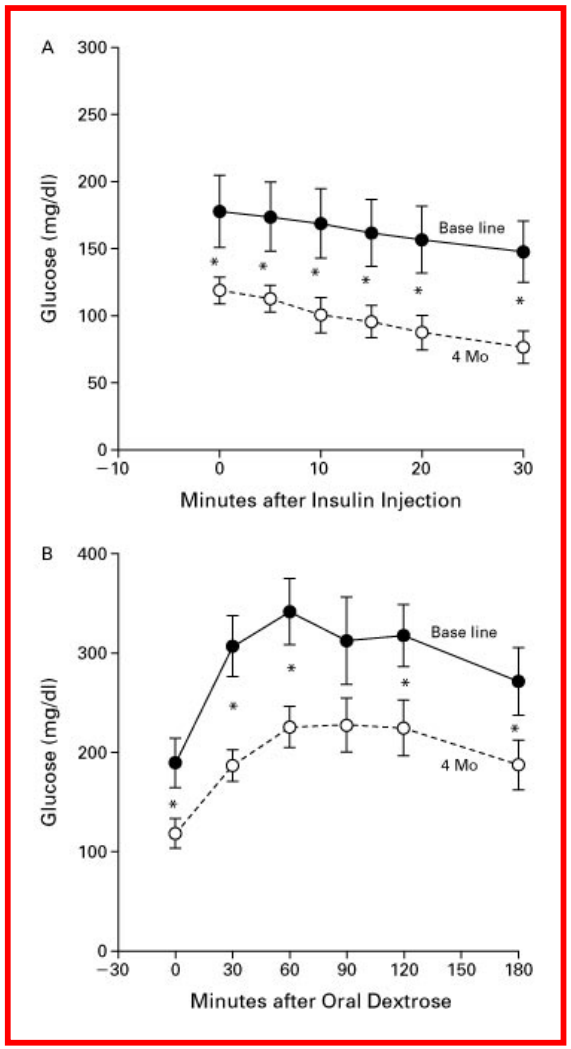
Chao, L. et al. J. Clin. Invest. 2000;106:1221-1228

Clinical Course of Patient 1, as Assessed by Changes in Mean Triglyceride Levels, Glycosylated Hemoglobin Values, and Serum Leptin Values

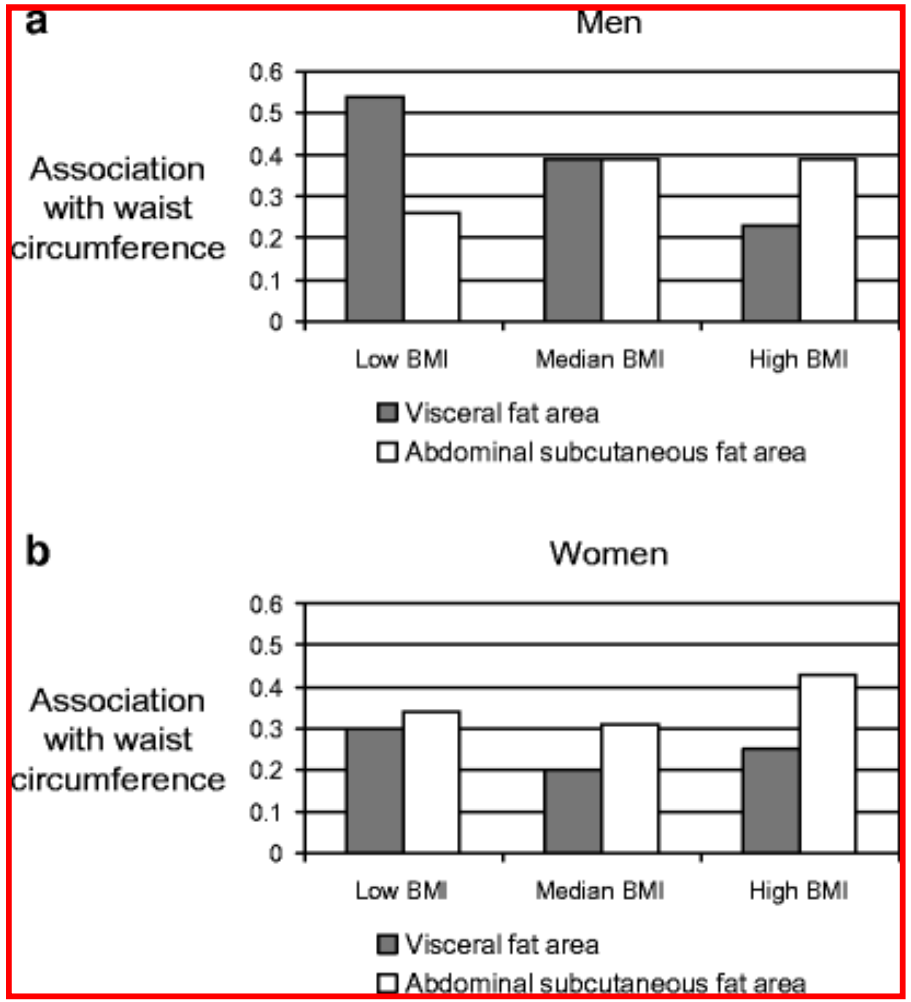


Oral E et al. N Engl J Med 2002;346:570-578

Mean ({+/-}SE) Plasma Glucose Levels in Response to an Insulin-Tolerance Test (Panel A) and an Oral Glucose-Tolerance Test (Panel B) in Nine Patients at Base Line and after Four Months of Leptin-Replacement Therapy



Oral E et al. N Engl J Med 2002;346:570-578



Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study.
Diabetologia. 2005 Feb;48(2):301-8. Epub 2005 Jan 20.

Independent associations (regression coefficients) of CT visceral fat area and CT abdominal subcutaneous fat area (adjusted for each other) with anthropometrically derived waist circumference, adjusted for CT abdominal muscle area, age, site (Pittsburgh or Memphis), and race, stratified by tertiles of BMI and separately for men (**a**) and women (**b**)

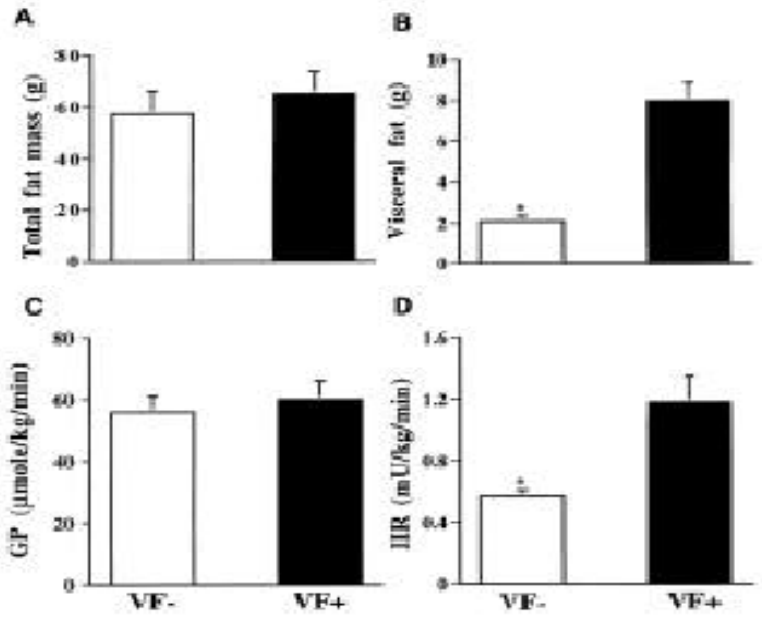


FIG. 1. Total fat mass, total visceral fat (epididymal, perinephric, and mesenteric fat), hepatic GP, and insulin infusion rate (IIR) during the hepatic-pancreatic clamp. Studies were performed in rats from which visceral fat was removed (VF^-) and from sham-operated control rats (VF^+). Fat mass was calculated from the whole-body volume of distribution of water, estimated by ^3H_2O bolus injection in each experimental rat (*A*). Total visceral fat was removed and weighed at the end of the study (*B*). After the basal turnover period of a primed-continuous infusion of [^{3}H-3]glucose to determine HGP (*C*), somatostatin was infused (1.5 μg · kg^{-1} · min^{-1}) to suppress endogenous insulin secretion. Insulin was then infused peripherally at variable rates in the 1st hour to determine the rate required to clamp the plasma glucose levels at fasting levels and maintained at that rate for an additional hour, at which time IIR was determined (*D*). $^*P < 0.001$ vs. VF^+.

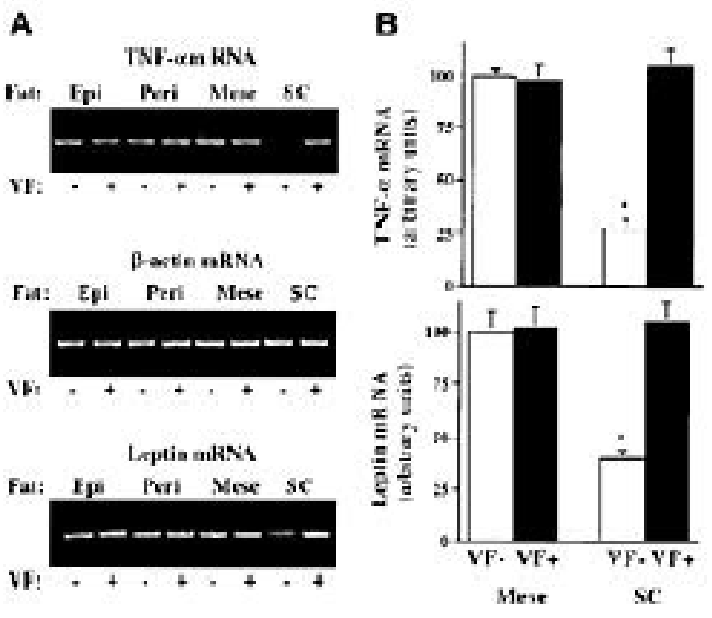
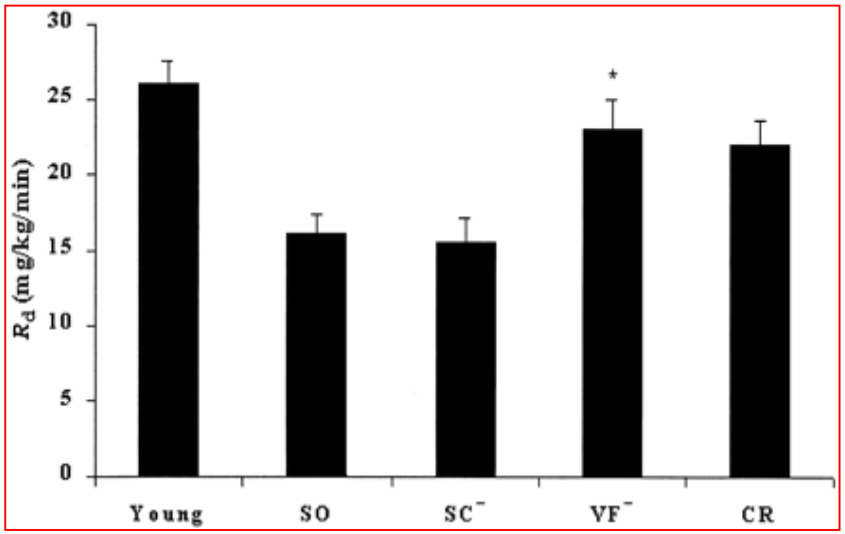
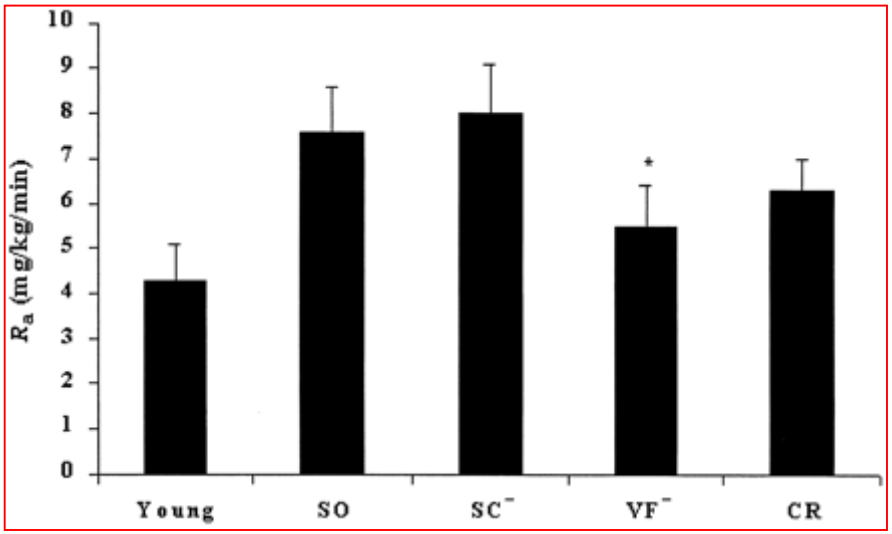


FIG. 4. Gene expression of TNF-■ and leptin in Epi, Peri, mesenteric (Mese), and subcutaneous (SC) fat after extraction of visceral fat (VF^-) or sham operation (VF^+). Individual fat depots from each of the rats were rapidly obtained, clamp-frozen with liquid nitrogen, and stored at −80°C for subsequent analysis. Epi and Peri fats were obtained from VF^- during the surgery (~3 weeks previously); all other fat depots were obtained after the study. RT-PCR analysis for TNF-■, leptin, and ■-actin is described in METHODS. *A*: Example of RT-PCR analysis from different fat depots from one VF^- and one VF^+ rat. *B*: Analysis of all RT-PCR data obtained from all rats (VF^-, $n = 6$; VF^+, $n = 8$), corrected for intensity of ■-actin and presented in arbitrary units. $^*P < 0.001$ vs. VF^+.

Diabetes. 1999 Jan;48(1):94-8.



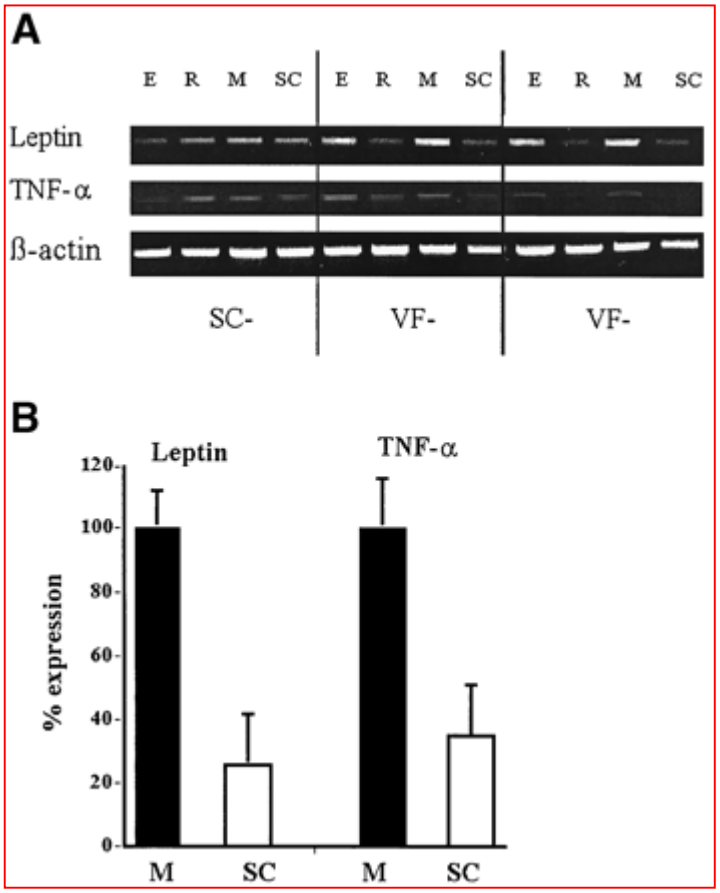
Peripheral insulin sensitivity in aging rats. Shown are results for young (2-month-old) and old (20-month-old) F1 hybrids of F344 and Brown Norway rats. The old rats underwent VF removal (VF-), SC fat removal (SC-), or sham operation (SO), or they were calorically restricted Glucose uptake (*R*d) during hyperinsulinemic (6 mU · kg-1 · min-1) pancreatic clamps is shown. **P* < 0.001 vs. SC- and SO rats.



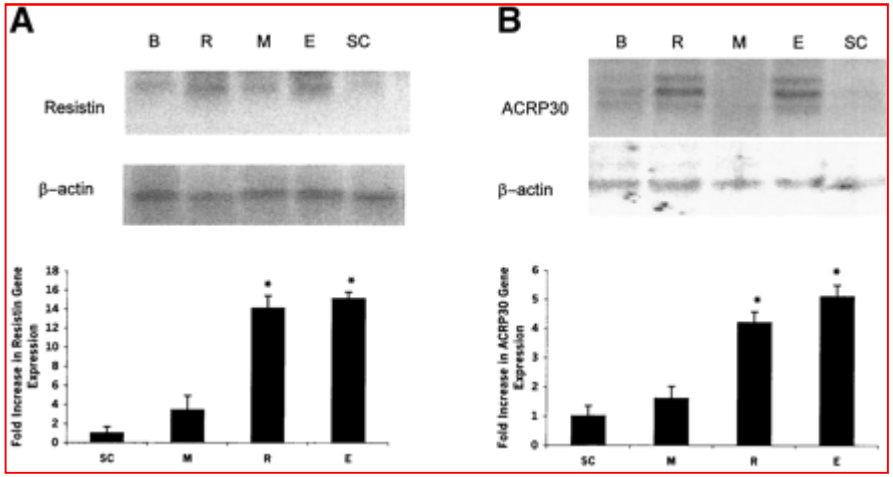
Hepatic insulin sensitivity in aging rats. The ability of insulin to suppress EGP was studied using glucose tracer methodology

Diabetes 51:2951-2958, 2002

Removal of Visceral Fat Prevents Insulin Resistance and Glucose Intolerance of Aging



Gene expression of TNF- and leptin. Measurements were performed in epididymal (E), perinephric (R), mesenteric (M), and SC fat after extraction of VF (VF-) or SC fat (SC-). RT and real-time PCR analysis for TNF- , leptin, and ß-actin are described in RESEARCH DESIGN AND METHODS. *A*: Example of agarose gel analysis of RT-PCR products from different fat depots in SC- and VF- rats. *B*: Analysis of all real-time PCR data obtained in all rats, corrected for intensity of ß-actin and presented in arbitrary units. $P <$ 0.001 vs. mesenteric fat.

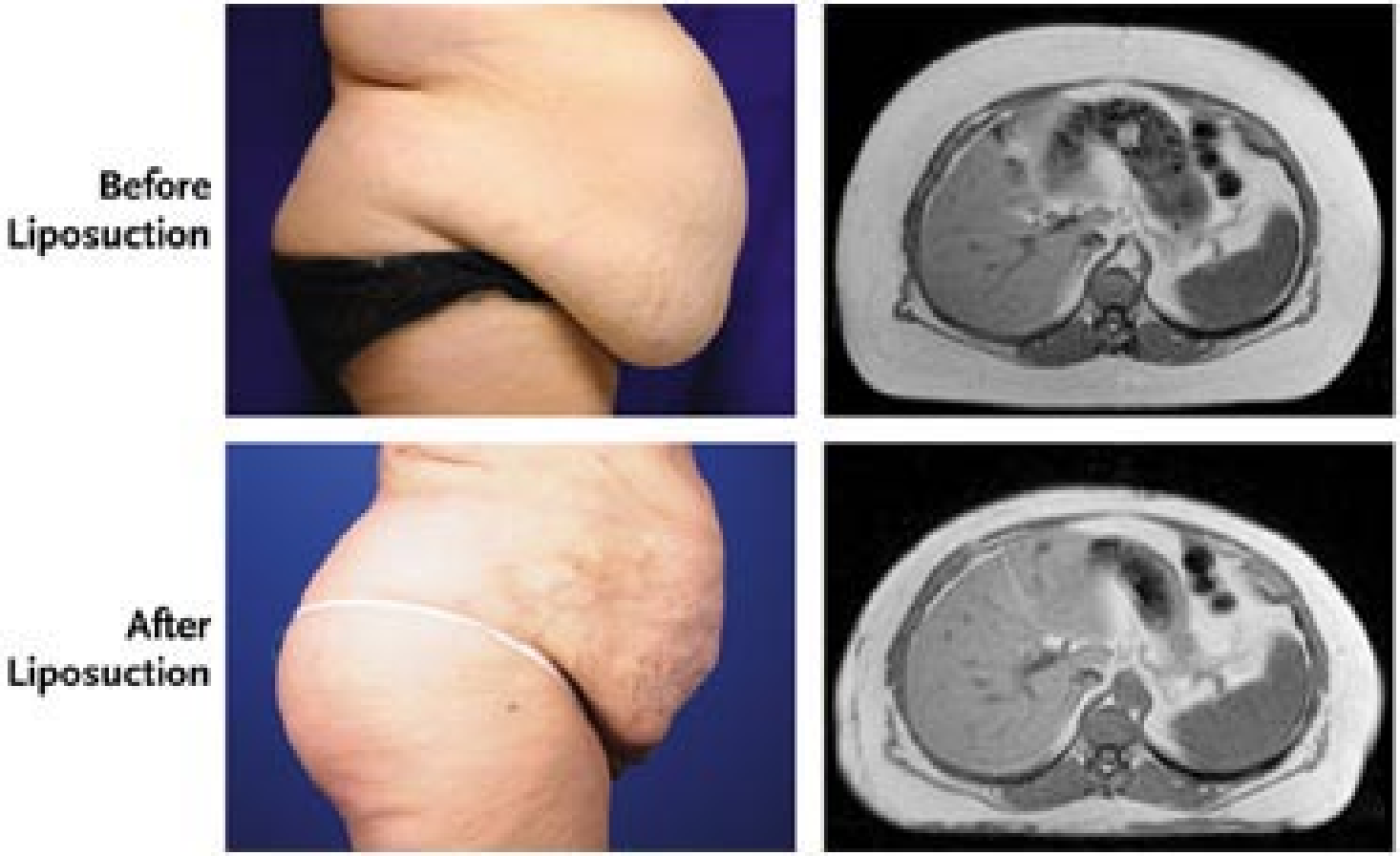


Gene expression of resistin (*A*) and ACRP30 (*B*). A: Northern blot analysis of brown (B), epididymal (E), perinephric (R), mesenteric (M), and SC fat obtained from SC- rats. *B*: Real-time PCR data obtained from all rats corrected for the intensity of ß-actin and presented in arbitrary units. *$P < 0.01$ vs. M and SC

Diabetes 51:2951-2958, 2002

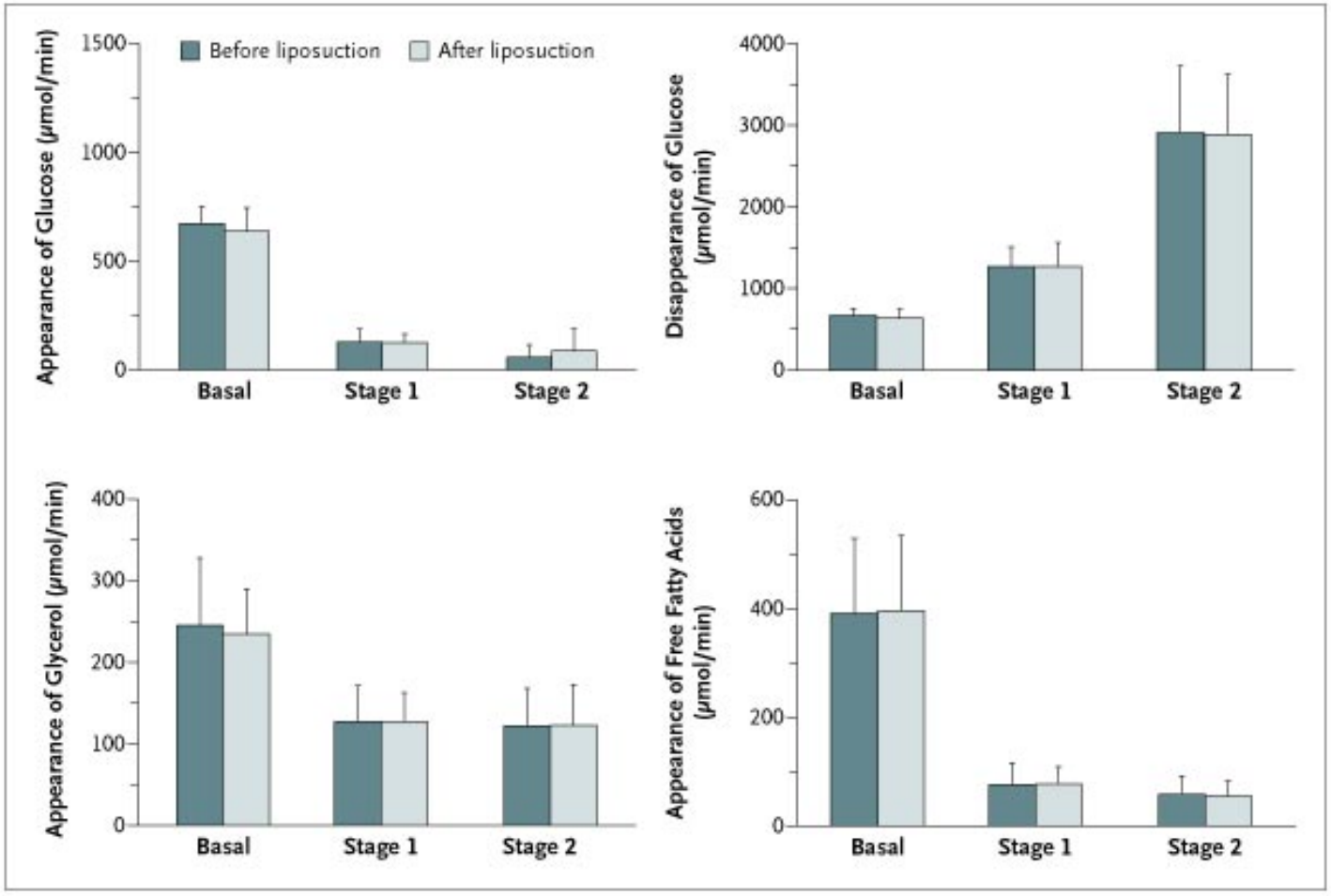
Removal of Visceral Fat Prevents Insulin Resistance and Glucose Intolerance of Aging

Photographs and Abdominal Magnetic Resonance Images Obtained before and after Liposuction



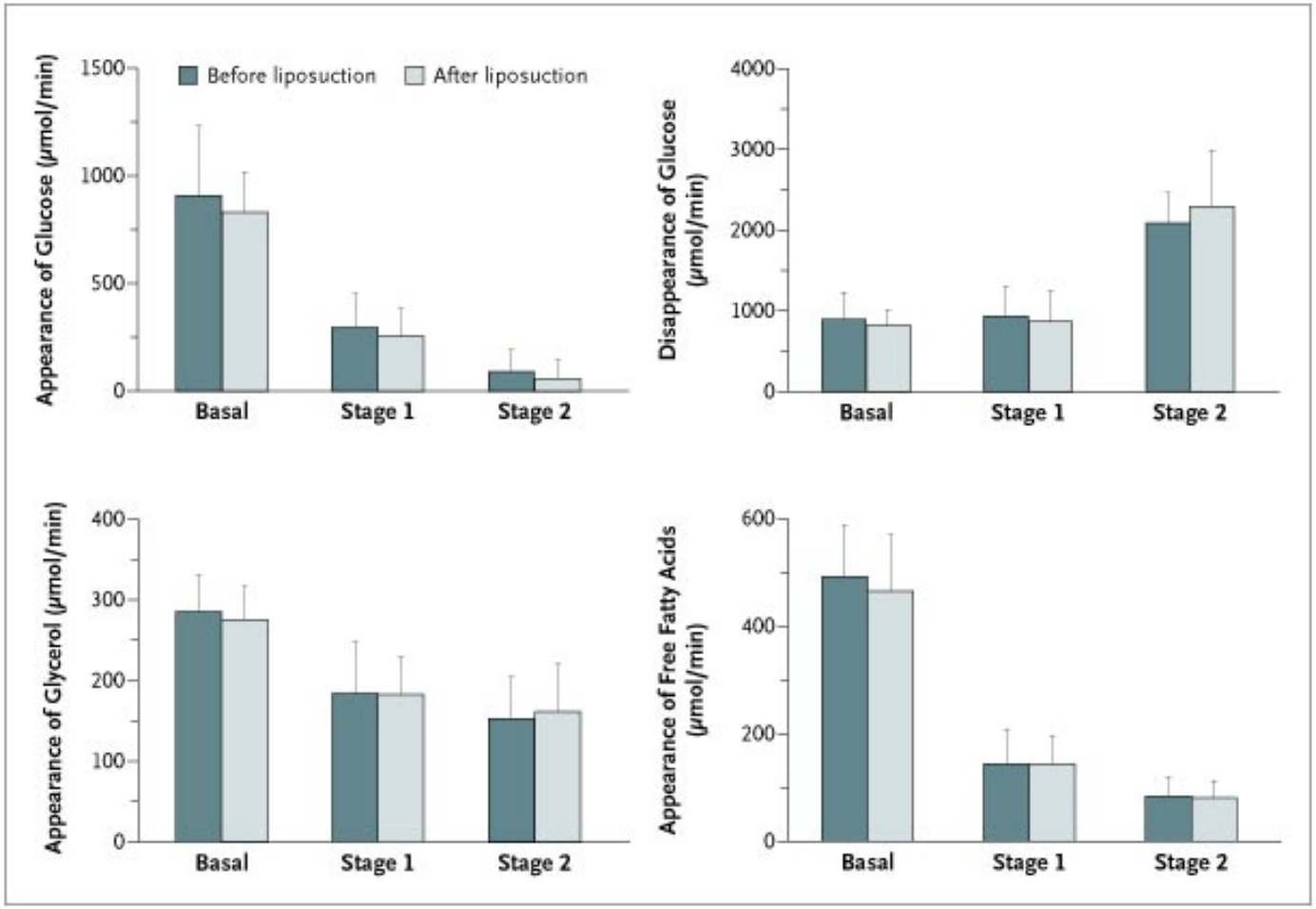
Klein, S. et al. N Engl J Med 2004;350:2549-2557

Mean Rates of Appearance and Disappearance of Glucose and Rates of Appearance of Glycerol and Free Fatty Acids in the Basal State and during the Euglycemic-Hyperinsulinemic Clamp Procedure in Obese Women with Normal Glucose Tolerance before and after Liposuction



Klein, S. et al. N Engl J Med 2004;350:2549-2557

Mean Rates of Appearance and Disappearance of Glucose and Rates of Appearance of Glycerol and Free Fatty Acids in the Basal State and during the Euglycemic-Hyperinsulinemic Clamp Procedure in Obese Women with Diabetes before and after Liposuction



Klein, S. et al. N Engl J Med 2004;350:2549-2557

Effects of Liposuction on Mediators of Inflammation in Obese Women with Normal Glucose Tolerance or Type 2 Diabetes

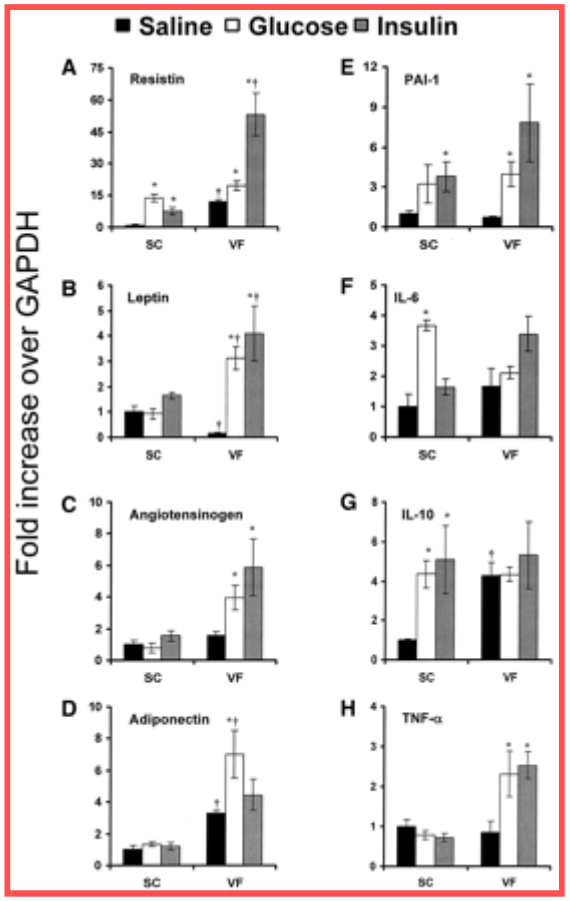
Table 3. Effects of Liposuction on Mediators of Inflammation in Obese Women with Normal Glucose Tolerance or Type 2 Diabetes.*

Variable	Normal Glucose Tolerance (N=8)				Type 2 Diabetes (N=7)			
	Before Liposuction	After Liposuction	Change (95% CI)	P Value	Before Liposuction	After Liposuction	Change (95% CI)	P Value
Leptin (ng/ml)	31.7±12.0	23.5±5.4	–8.2 (–15.9 to –0.4)	0.05	35.7±13.5	30.2±12.6	–5.5 (–1.1 to –9.8)	0.05
Adiponectin (ng/ml)	5.0±2.2	4.5±2.2	–0.5 (–0.8 to ±0.1)	0.13	4.3±2.3	3.6±2.2	–0.7 (–1.5 to +0.1)	0.13
Tumor necrosis factor α (pg/ml)	3.5±5.8	2.8±3.3	–0.7 (–2.8 to +1.4)	0.54	7.6±8.3	7.7±7.8	+0.2 (–0.5 to +0.9)	0.60
Interleukin-6 (pg/ml)†	1.5±0.6	2.4±0.9	+0.9 (0 to +1.7)	0.10	3.8±3.8	3.2±2.5	–0.7 (–1.7 to +0.3)	0.24
C-reactive protein (μg/ml)	6.9±6.7	6.7±6.5	–0.2 (–1.1 to +0.8)	0.74	8.2±7.2	7.7±6.9	–0.5 (–1.3 to +0.4)	0.30

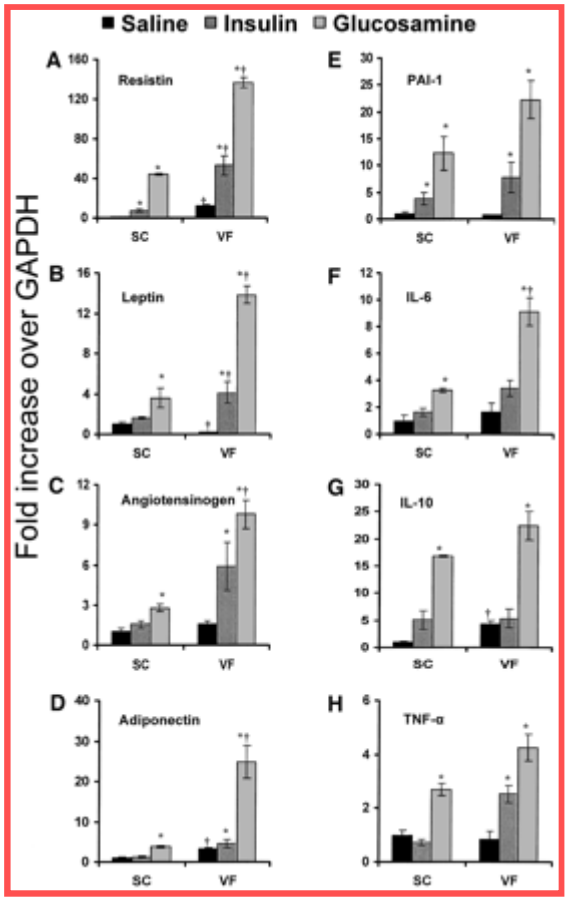
* Plus–minus values are means ±SD. The measurements were made within 9 days before liposuction and again 10 to 12 weeks after liposuction. CI denotes confidence interval, minus signs decreases, and plus signs increases.
† Values were obtained from six subjects in each group.

Klein, S. et al. N Engl J Med 2004;350:2549-2557

The NEW ENGLAND JOURNAL of MEDICINE



Selected gene expression of adipokines during hyperglycemia and hyperinsulinemia in subcutaneous fat and visceral fat. Acute increase (5 h) in glucose and insulin infusion. Four rats from each group were studied, and subcutaneous fat and visceral fat of each rat were studied separately. *Significant difference of at least $P < 0.05$ vs. saline; † significant difference of at least $P < 0.05$ vs. same study in subcutaneous fat.



Selected gene expression of cytokines during hyperinsulinemia and glucosamine infusion in subcutaneous fat and visceral fat

Diabetes 54:672-678, 2005

Differential Responses of Visceral and Subcutaneous Fat Depots to Nutrients

Differences in metabolic characteristics in MHO individuals and at risk obese individuals

Metabolically Healthy Obese (MHO)	"At Risk" Obese
	
Low Visceral Fat	High Visceral Fat
High BMI	High BMI
High Fat mass	High Fat mass
High Insulin Sensitivity	Low Insulin Sensitivity
High HDL	Low HDL
Low Triglycerides	High Triglycerides

Karelis, A. D. et al. J Clin Endocrinol Metab 2004;89:2569-2575

Insulin sensitivity indexes of MHO and at risk individuals

Insulin sensitivity indexes	MHO (n = 22)	At risk (n = 22)
Fasting glucose (mmol/liter)	4.90 ± 0.48	5.13 ± 0.55
Fasting insulin (μU/ml) (n = 22, 21)	12.11 ± 4.5[1]	20.53 ± 8.4
HOMA (n = 22, 21)	2.70 ± 1.2[1]	4.68 ± 1.9
QUICKI (n = 22, 21)	0.335 ± 0.02[1]	0.309 ± 0.02
$IS_{(clamp)}$ (n = 22, 21)	309.7 ± 86.5[1]	163.2 ± 38.7
$M_{(clamp)}$ (mg/min · kg)	7.98 ± 1.4[1]	4.20 ± 0.76
$M/FFM_{(clamp)}$ (mg/min · kg FFM)	15.35 ± 2.3[1]	7.69 ± 1.3
$Glycemia_{(steady\text{-}state)}$ (mmol/liter)	4.86 ± 0.47	4.77 ± 0.38
$Insulin_{(steady\text{-}state)}$ (μU/ml) (n = 22, 21)	198.5 ± 21.9	219.6 ± 35.5

Values are means ± SD.

[1] Significantly different from the at risk group ($P < 0.05$).

Metabolic and body composition factors in subgroups of obesity: what do we know?

J Clin Endocrinol Metab. 2004 Jun;89(6):2569-75. Review.

Body fat distribution of MHO and at risk individuals

Variables	MHO (n = 22)	At risk (n = 22)
SAT area (L4/L5, cm^2)	490.9 ± 128	512.9 ± 122
Superficial SAT area (cm^2)	250.1 ± 79.8	257.1 ± 68.0
Deep SAT area (cm^2) (n = 22, 21)	239.9 ± 56.8	257.4 ± 66.6
Abdominal fat (cm^2)	670.8 ± 149	740.0 ± 161
Visceral fat content (cm^2)	179.9 ± 53.9[1]	227.0 ± 64.6
Muscle attenuation	49.6 ± 3.7	54.7 ± 29.9

Values are means ± SD.
[1] Significantly different from the at risk group ($P < 0.05$).

Metabolic and body composition factors in subgroups of obesity: what do we know?

J Clin Endocrinol Metab. 2004 Jun;89(6):2569-75. Review.

Table I
Physical characteristics of MHO and at risk obese postmenopausal women.

Parameters	MHO (n = 19)	At risk (n = 135)
Age (years)	56.9 ± 5.9	57.0 ± 5.3
Height (m)	1.63 ± 0.05	1.61 ± 0.06
Weight (kg)	89.6 ± 16.4	89.1 ± 15.8
Body Mass Index	33.5 ± 5.2	34.4 ± 5.5
Fat Mass (kg)	41.4 ± 8.7	40.8 ± 10.2
Fat Free Mass (kg)	44.7 ± 6.6	45.4 ± 6.0
Waist Circumference (cm) (n = 8/60)	91.5 ± 5.9	98.5 ± 9.7
Systolic Blood Pressure (mm Hg)	129.4 ± 19.3	126.7 ± 15.9
Diastolic Blood Pressure (mm Hg)	75.3 ± 10.8	72.8 ± 9.9

Values are means ± SD.

Table II
Metabolic markers that identify metabolically healthy but obese individuals.

Metabolic markers	Defining level	MHO (n = 19)	At risk (n = 135)
HOMA Index (n = 16/118)	≤ 1.95	2.30 ± 1.2*	3.26 ± 1.8
Triglycerides (mmol/l)	≤ 1.7	1.1 ± 0.4*	1.8 ± 0.7
Total cholesterol (mmol/l)	≤ 5.2	4.3 ± 0.5*	5.4 ± 0.9
LDL cholesterol (mmol/l)	≤ 2.6	2.6 ± 0.4*	3.4 ± 0.8
HDL cholesterol (mmol/l)	≥ 1.3	1.5 ± 0.2*	1.3 ± 0.3

Values are means ± SD. *Significantly different from at risk group ($P < 0.05$). When 4 out of 5 criteria are met, a diagnosis of the MHO individual could be made.

Can we identify metabolically healthy but obese individuals (MHO)?

Diabetes Metab. 2004 Dec;30(6):569-72.

Differences in metabolic characteristics in MONW individuals and normal healthy individuals

Metabolically Obese Normal Weight (MONW)	Metabolically Healthy
	
High Visceral Fat	Low Visceral Fat
Low BMI	Low BMI
High Fat mass	Low Fat mass
Low Lean Body Mass	High Lean Body Mass
Low Insulin Sensitivity	High Insulin Sensitivity
High Liver Fat	Low Liver Fat
High Triglycerides	Low Triglycerides

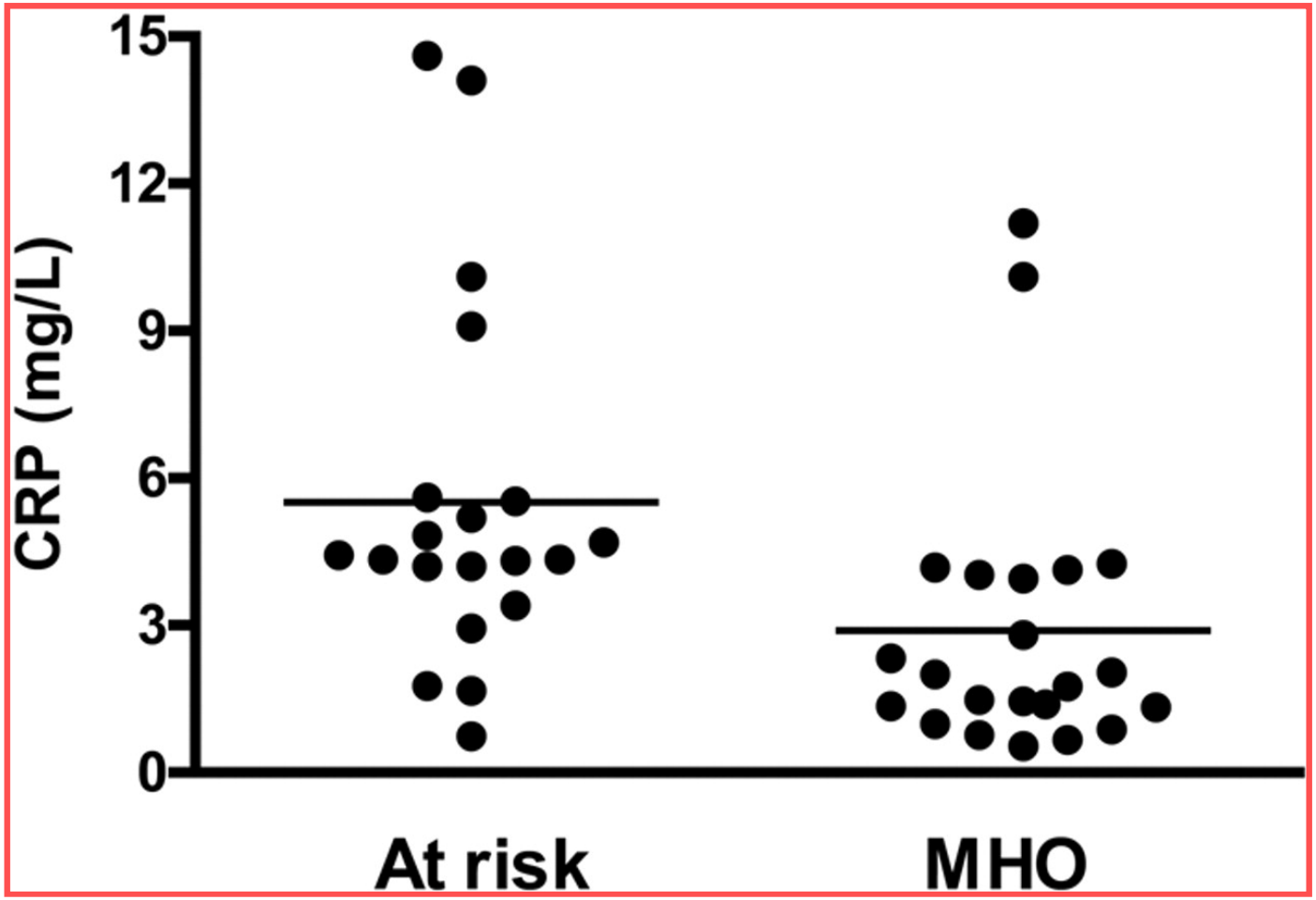
Karelis, A. D. et al. J Clin Endocrinol Metab 2004;89:2569-2575

Several selected metabolic characteristics in MONW and metabolically healthy individuals

	MONW (n = 13)	Metabolically healthy (n = 58)
Age (yr)	29 ± 3	28 ± 4
Insulin sensitivity	6.5 ± 1.7[1]	11.0 ± 2.2
Fat free mass (kg)	38.9 ± 5.1	40.3 ± 4.0
Fat mass (kg)	18.4 ± 5.2[1]	15.3 ± 4.4
% Body fat	31.8 ± 5.9[1]	27.4 ± 5.5
Subcutaneous fat (cm^2)	213 ± 61[1]	160 ± 78
Visceral fat (cm^2)	44 ± 16[1]	35 ± 14
Total cholesterol (mmol/liter)	5.3 ± 0.9[1]	4.5 ± 0.7
Physical activity energy expenditure (kcal/d)	633 ± 219[1]	1045 ± 357

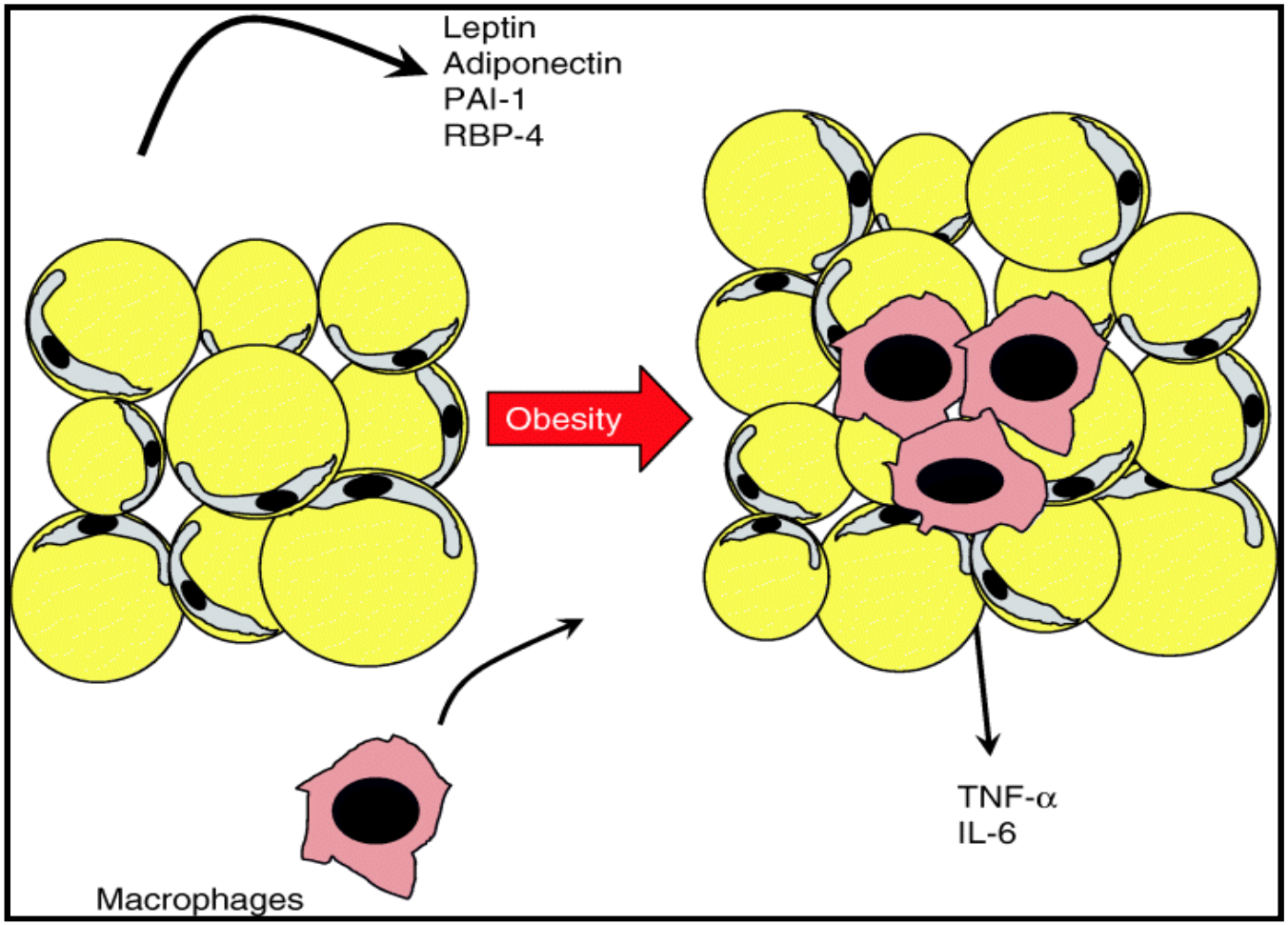
Values are the mean ± SD. Data were adapted from Dvorak *et al*. (21). M/LBM, Glucose disposal/lean body mass.
[1] Significantly different from metabolically healthy subjects ($P < 0.05$).

Distribution and means of hsCRP levels in MHO and at risk subjects

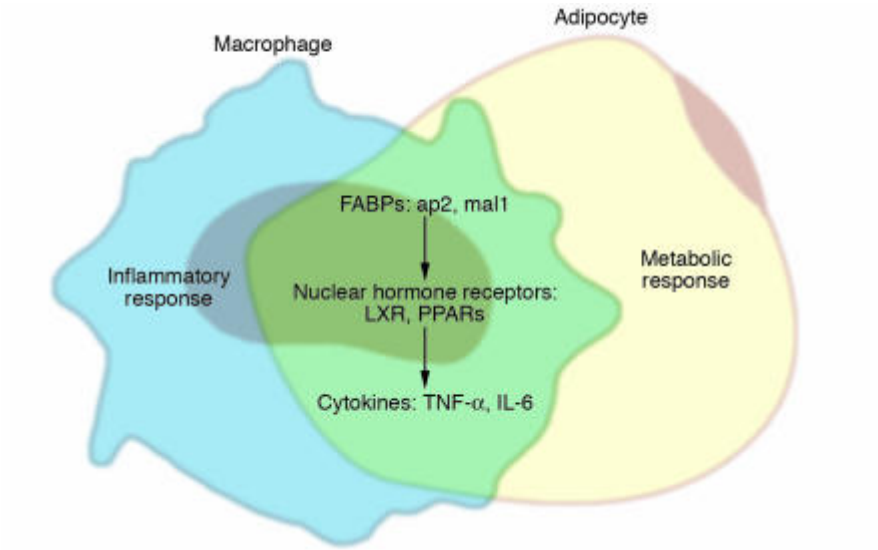


Karelis, A. D. et al. J Clin Endocrinol Metab 2005;90:4145-4150

Infiltration of adipose tissue with macrophages. With progressive obesity, adipose tissue of some subjects accumulates resident tissue macrophages, which then secrete inflammatory cytokines and account for much of the inflammatory condition associated with metabolic syndrome

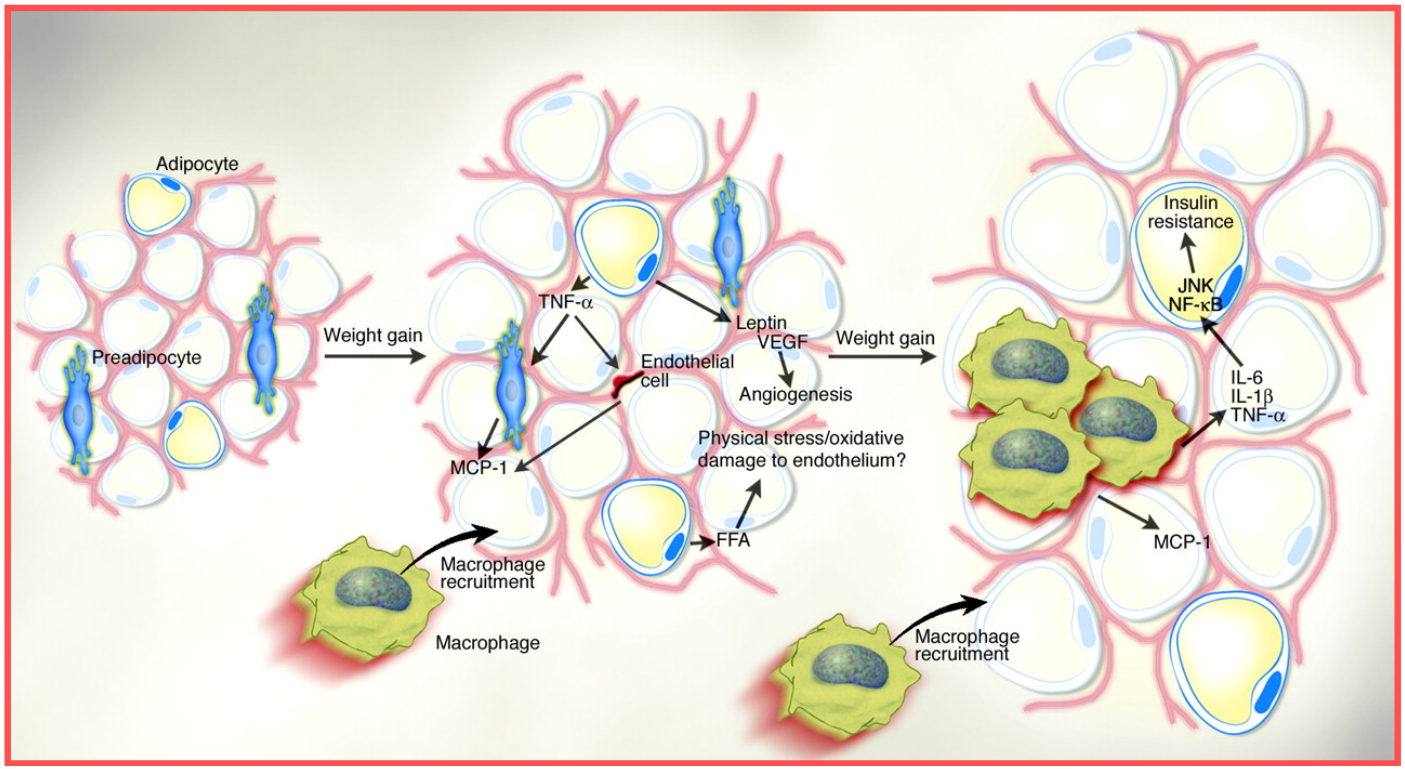


Diabetes, Obesity and Metabolism **9** (1), 1-10.

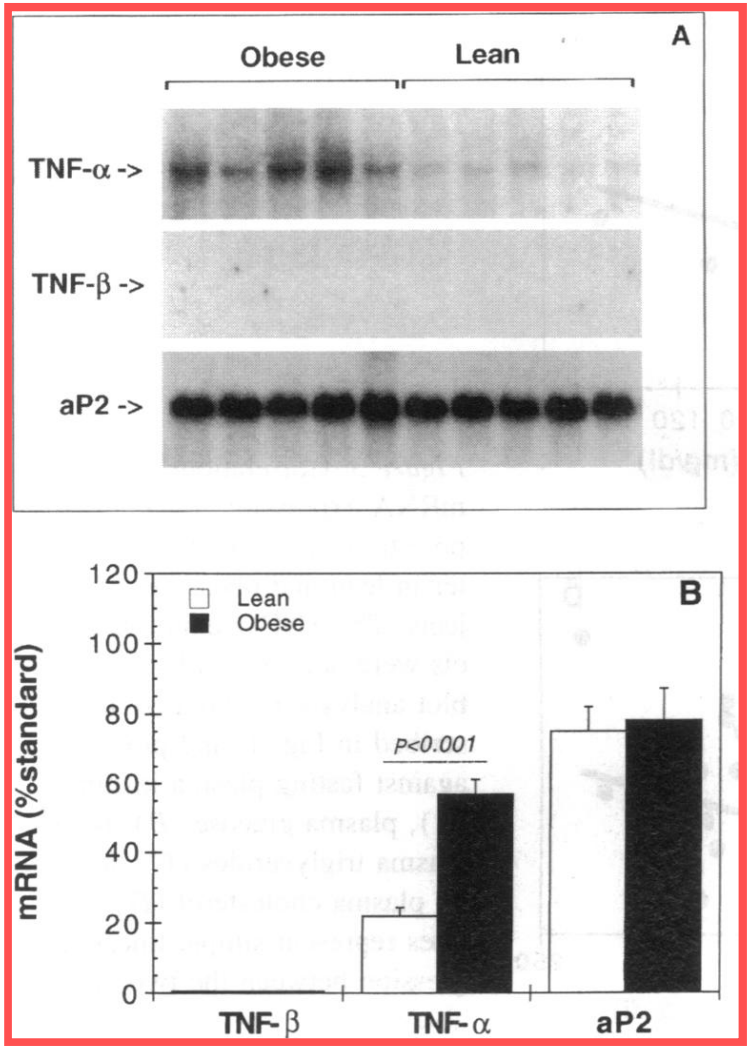


Clin Invest. 2005 May 2; 115(5): 1111–1119.

Obese adipose tissue is characterized by inflammation and progressive infiltration by macrophages as obesity develops



Wellen, K. E. et al. J. Clin. Invest. 2003;112:1785-1788

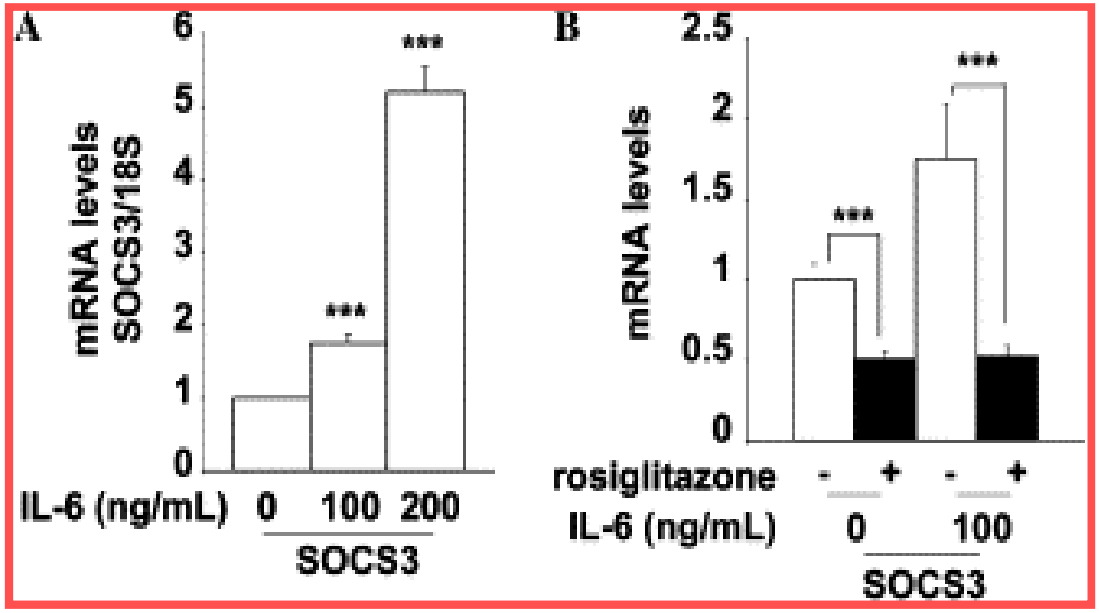


J Clin Invest. 1995 May; 95(5): 2409–2415.

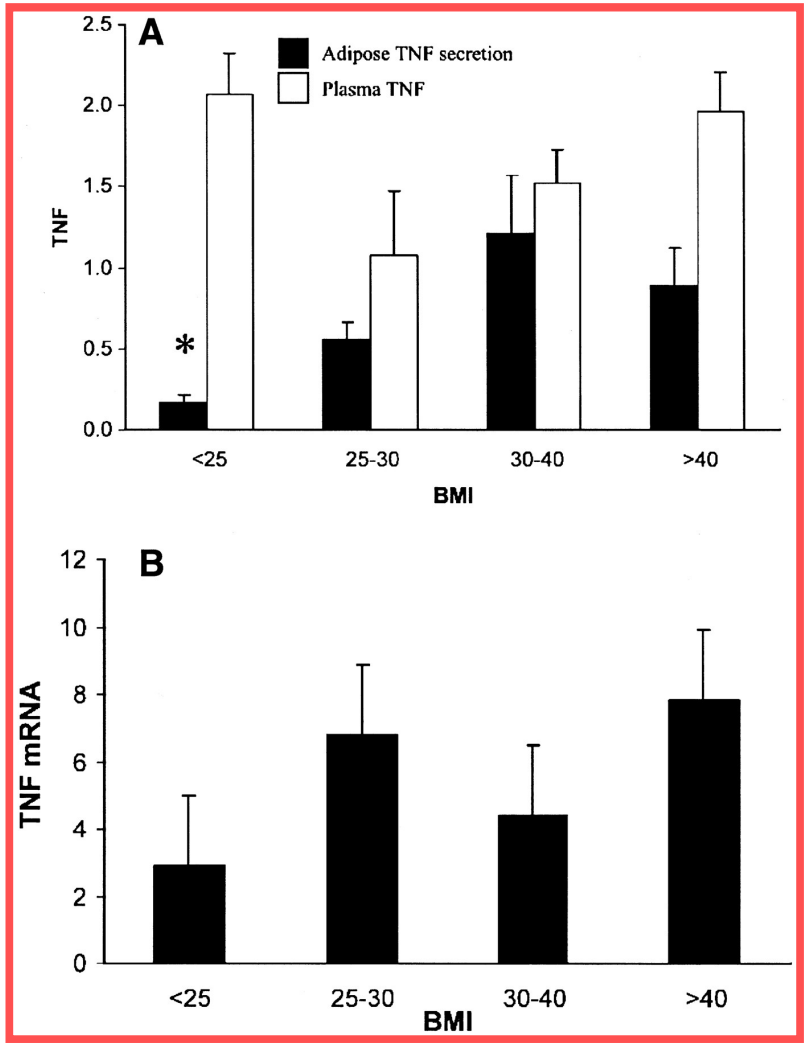
Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance.

Biochemical and Biophysical Research Communications
Volume 311, Issue 2, 14 November 2003, Pages 372-379

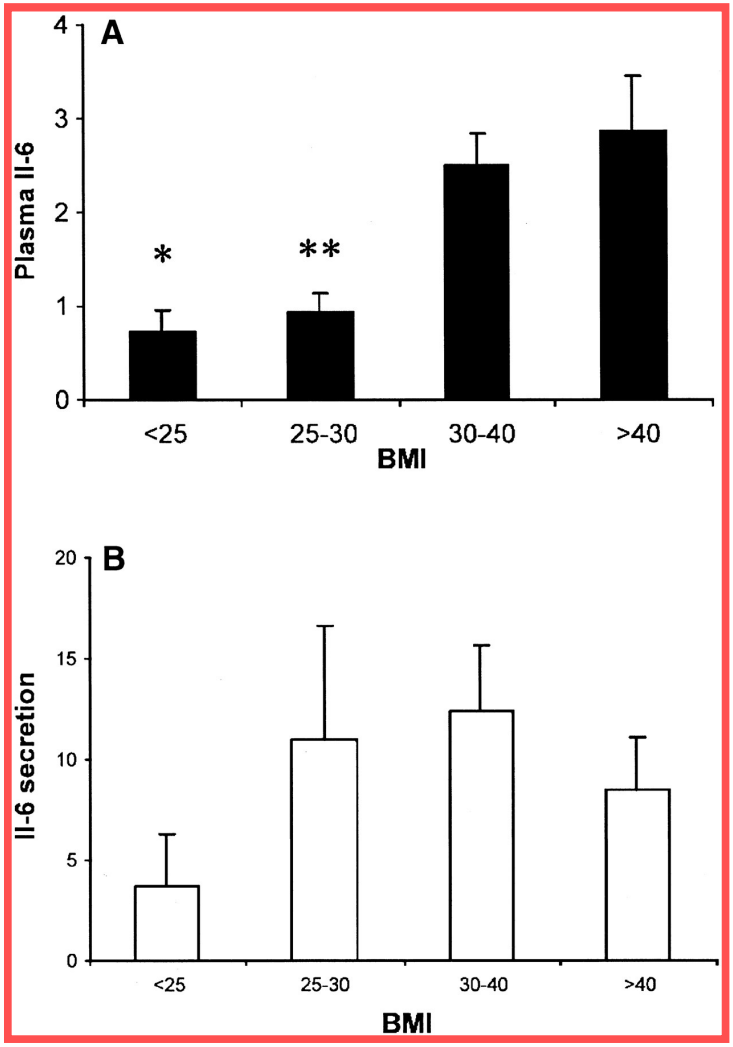
Chronic interleukin-6 (IL-6) treatment increased IL-6 secretion and induced insulin resistance in adipocyte: prevention by rosiglitazone



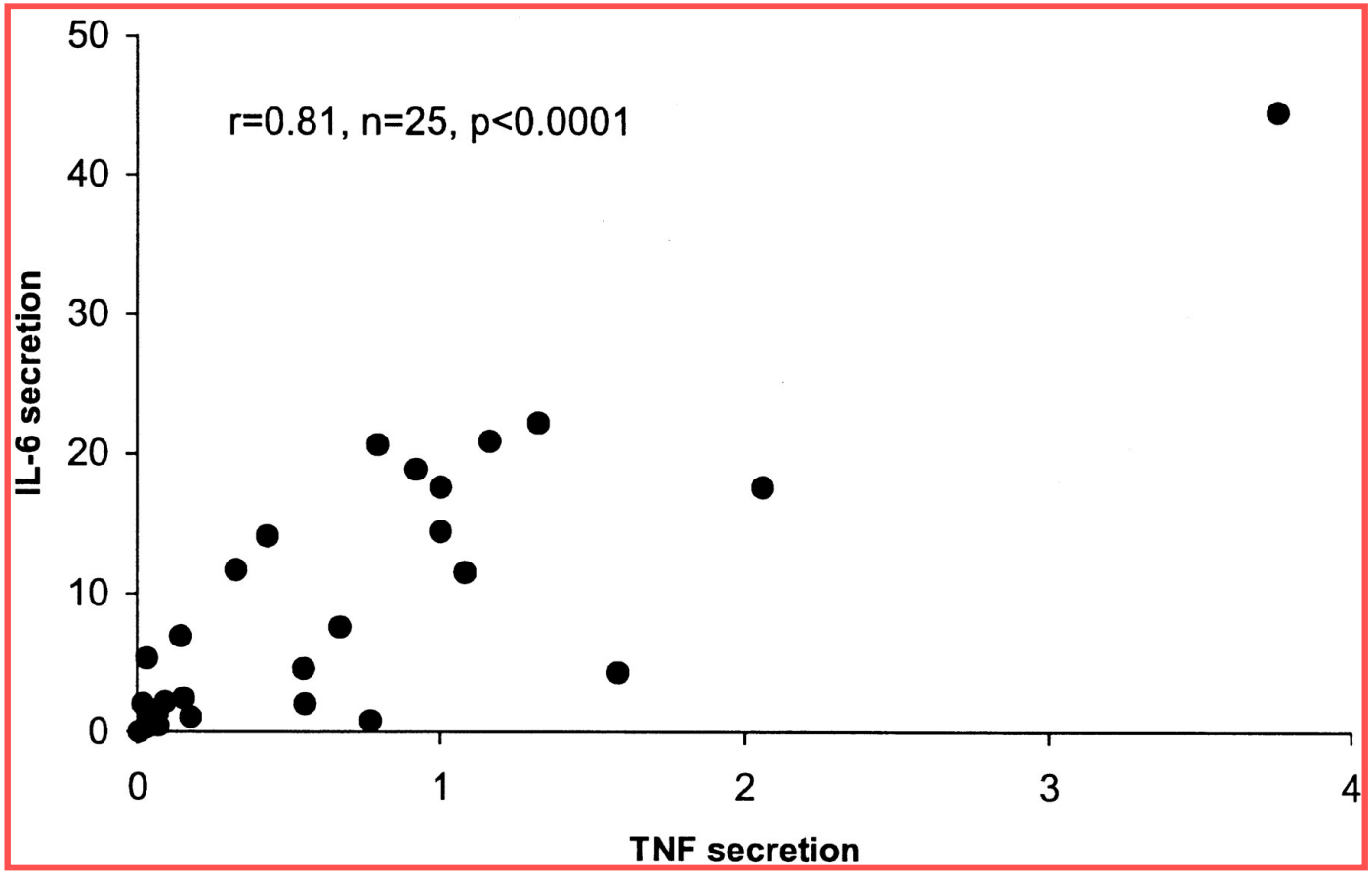
Rosiglitazone inhibits SOCS-3 expression and its induction by IL-6. 3T3-F442A preadipocytes were differentiated in the presence of the indicated concentration of IL-6 (open bars) (A) and/or 1 μM of rosiglitazone (dark bars) (B). At day 8 of differentiation, total RNA was extracted and subjected to real-time PCR. SOCS-3 mRNA levels normalized to 18S expression were determined relative to untreated cells (1.0). Results are means ± SEM of 4–6 experiments performed in triplicate. ***P<0.001.



Kern, P. A. et al. Am J Physiol Endocrinol Metab 280: E745-E751 2001



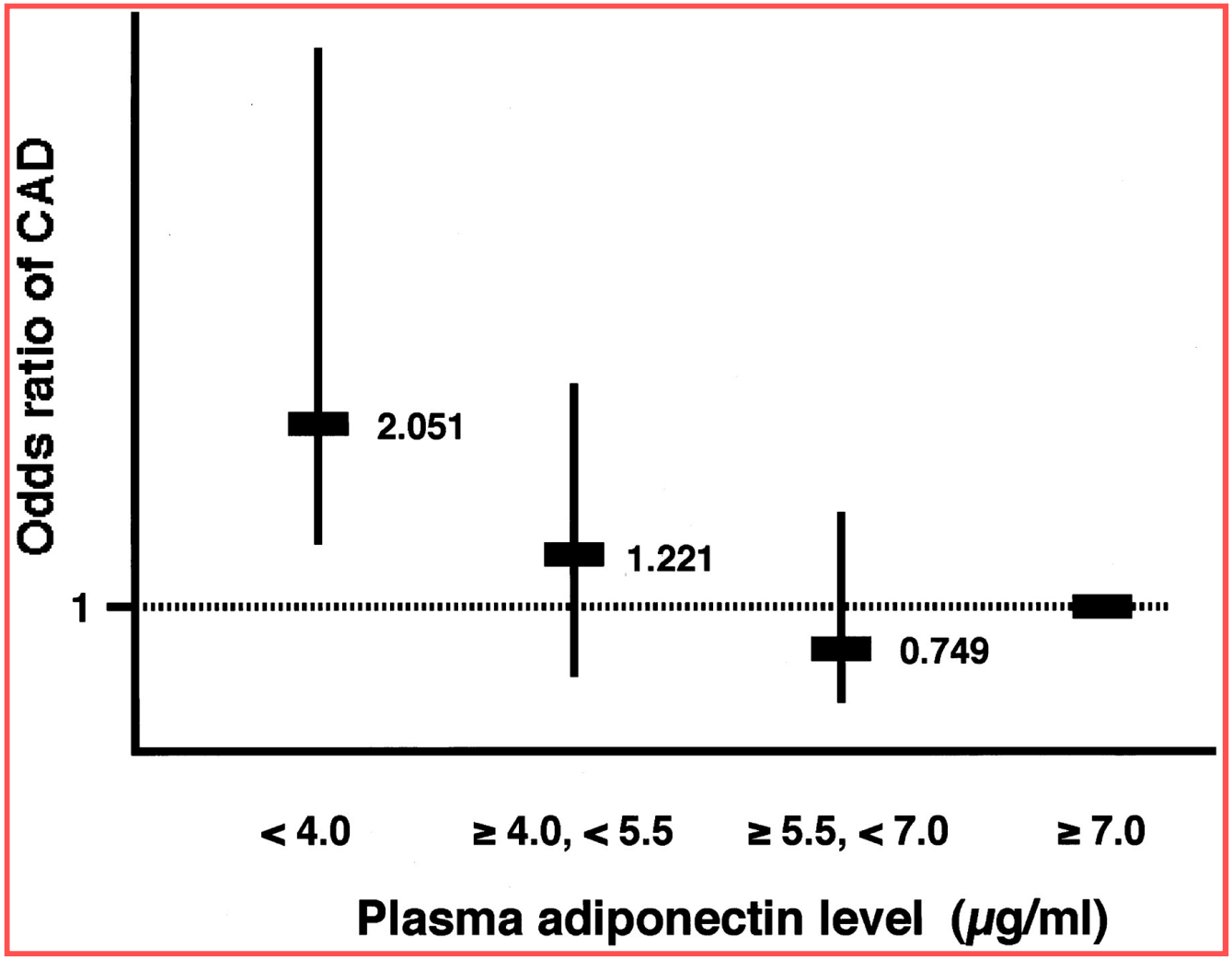
Kern, P. A. et al. Am J Physiol Endocrinol Metab 280: E745-E751 2001



Kern, P. A. et al. Am J Physiol Endocrinol Metab 280: E745-E751 2001

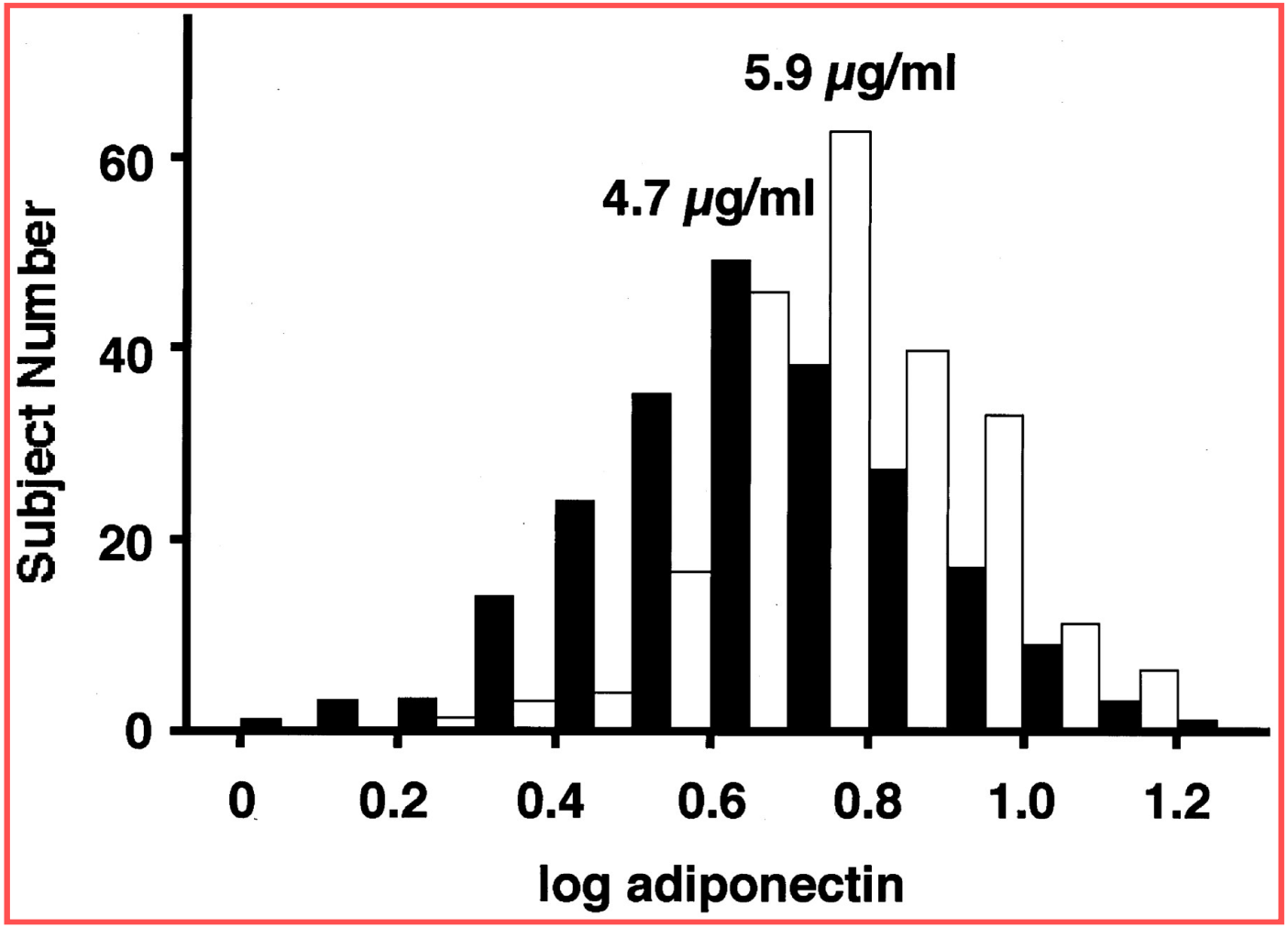
AJP - Endocrinology and Metabolism

ORs for CAD in the first, second, and third quartiles compared with the fourth quartile

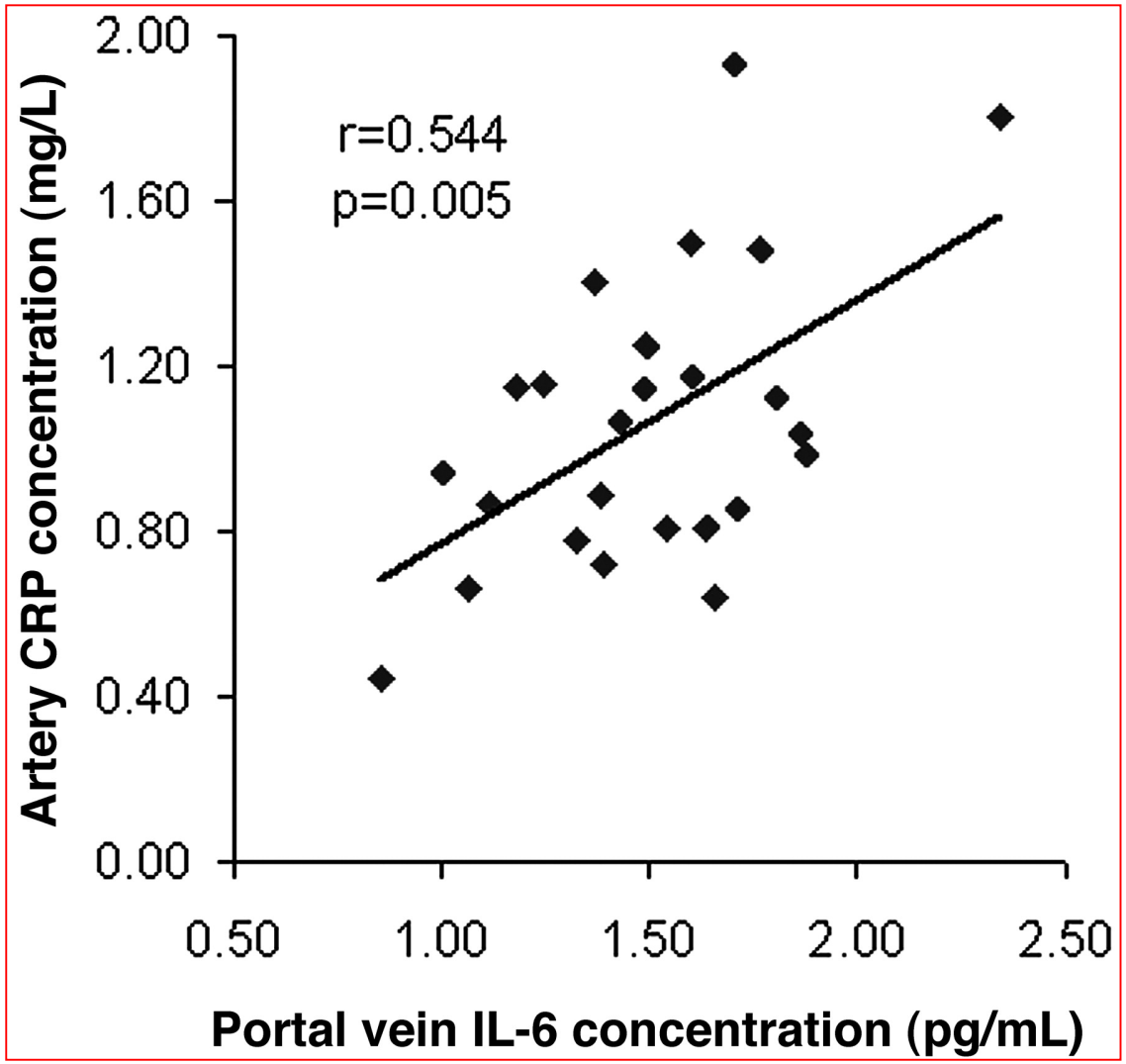


Kumada, M. et al. Arterioscler Thromb Vasc Biol 2003;23:85-89

The number of subjects according to log adiponectin levels in patients with CAD (solid bars) and control subjects (open bars)



Kumada, M. et al. Arterioscler Thromb Vasc Biol 2003;23:85-89



Relationship between portal vein IL-6 and systemic CRP concentrations in extremely obese subjects. Data are log transformed.

Diabetes 56:1010-1013, 2007

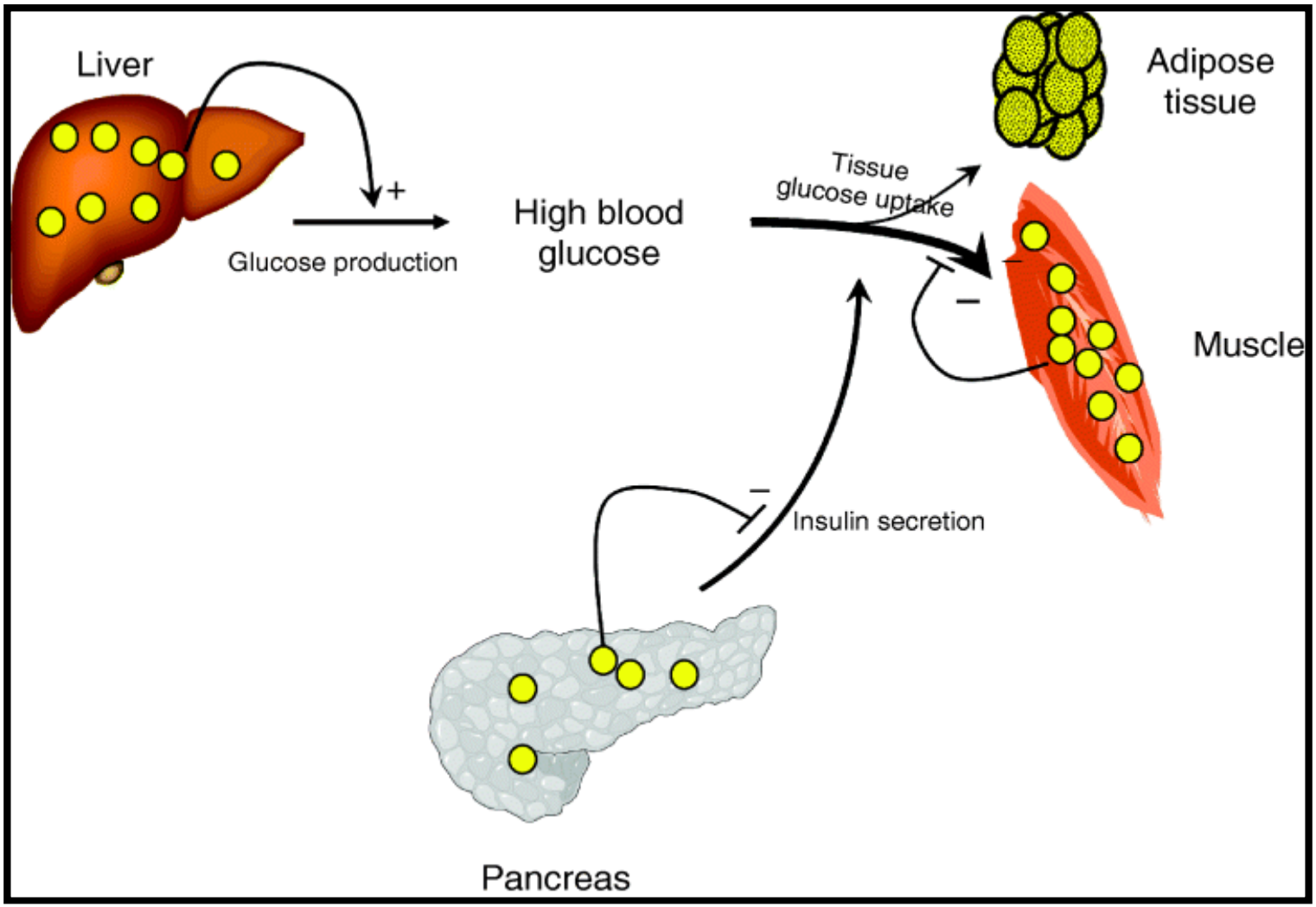
Radial artery and portal vein plasma adipokine concentrations in obese subjects

	Radial artery	Portal vein	
IL-6 (pg/ml)	28.5 ± 27.6	42.1 ± 41.8*	13.6 ± 23.3 (–16.0 to 60.4)
TNF- (pg/ml)	1.87 ± 0.8	1.93 ± 0.8	0.06 ± 0.2 (–0.4 to 0.6)
MCP-1 (pg/ml)	205 ± 88	190 ± 99	–14.7 ± 82.2 (–202 to 198)
Resistin (pg/ml)	18.5 ± 11	18.1 ± 11	–0.4 ± 2.6 (–8.1 to 4.2)
Leptin (ng/ml)	101 ± 51	81 ± 42 †	–19 ± 21 (–80.0 to 16.0)
Total adiponectin (µg/ml)	14.3 ± 10	14.7 ± 11	0.4 ± 3.1 (–7.0 to 7.1)

Data are means ± SD. Significantly different from corresponding radial artery value,
* $P = 0.007$;
† $P = 0.0002$.

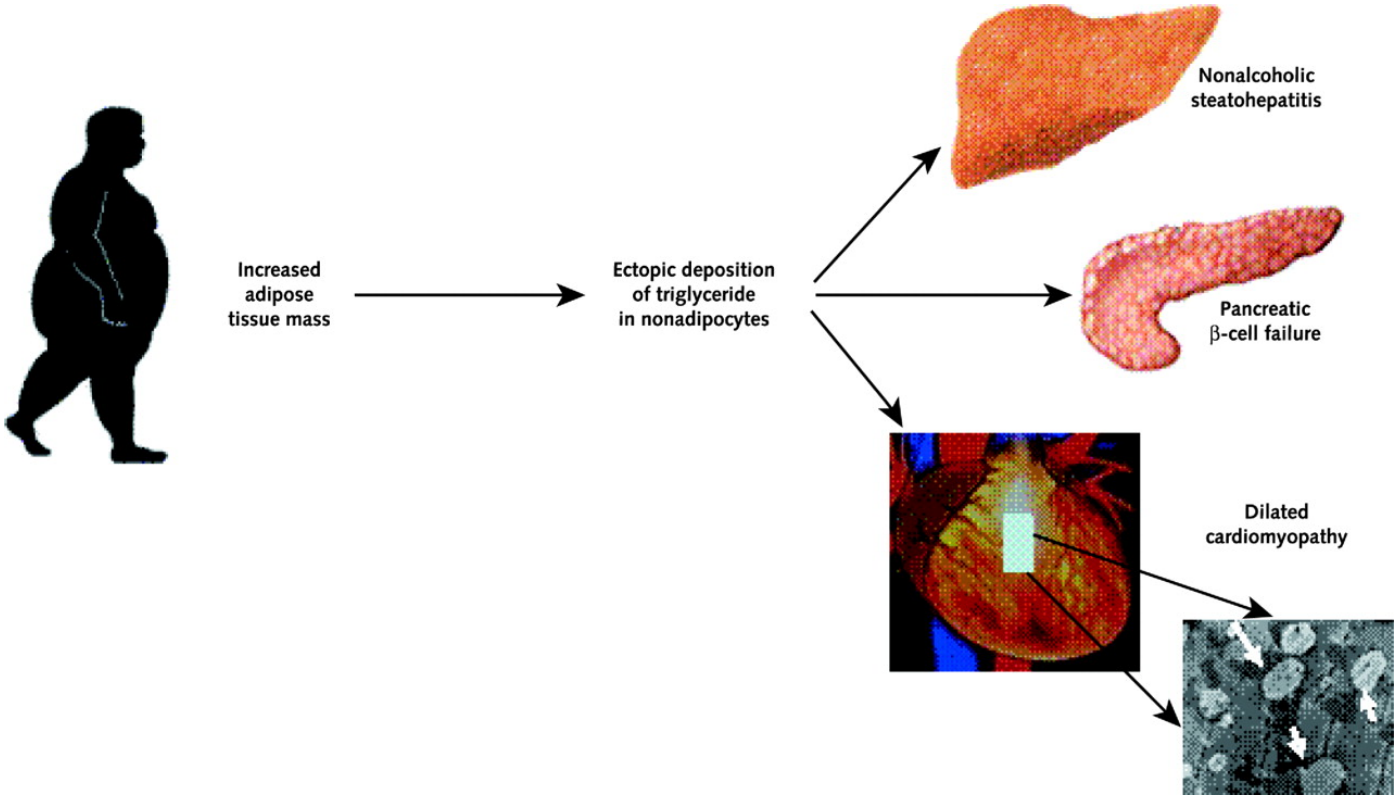
Diabetes 56:1010-1013, 2007

Ektopik yağ depolanması



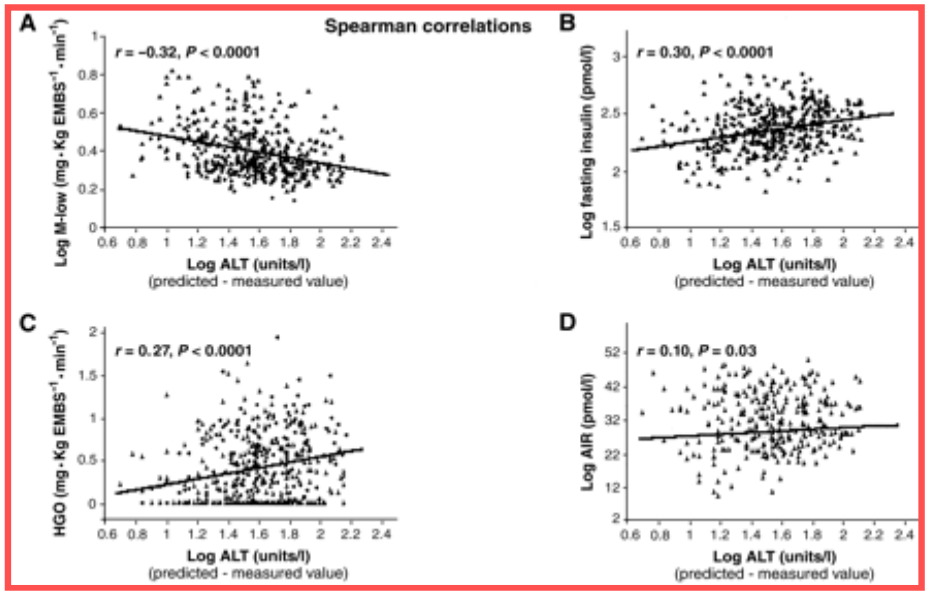
Diabetes, Obesity and Metabolism **9** (1), 1-10.

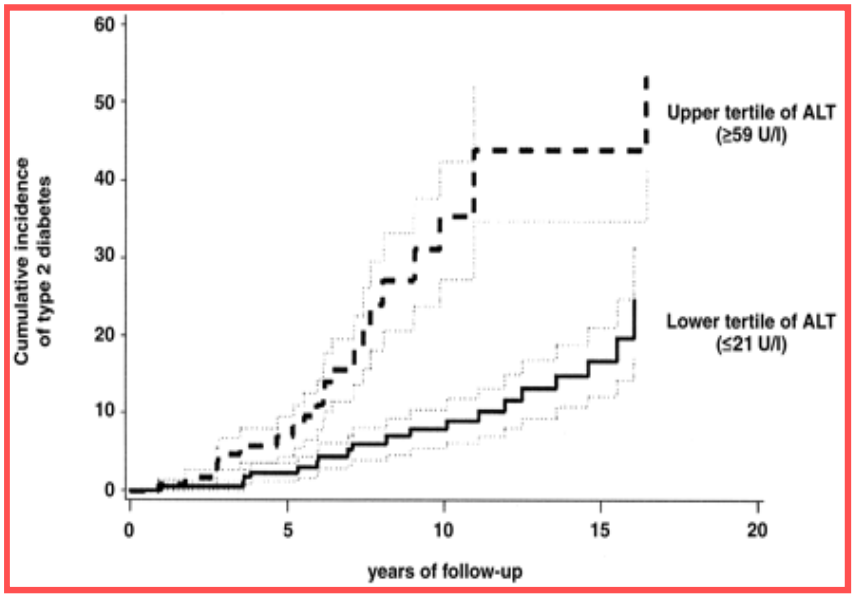
Concept of lipotoxicity

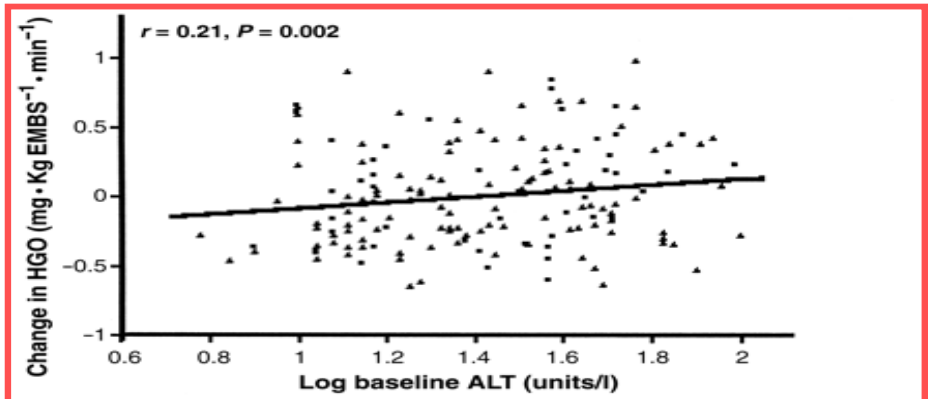


McGavock, J. M. et. al. Ann Intern Med 2006;144:517-524

Karaciğer



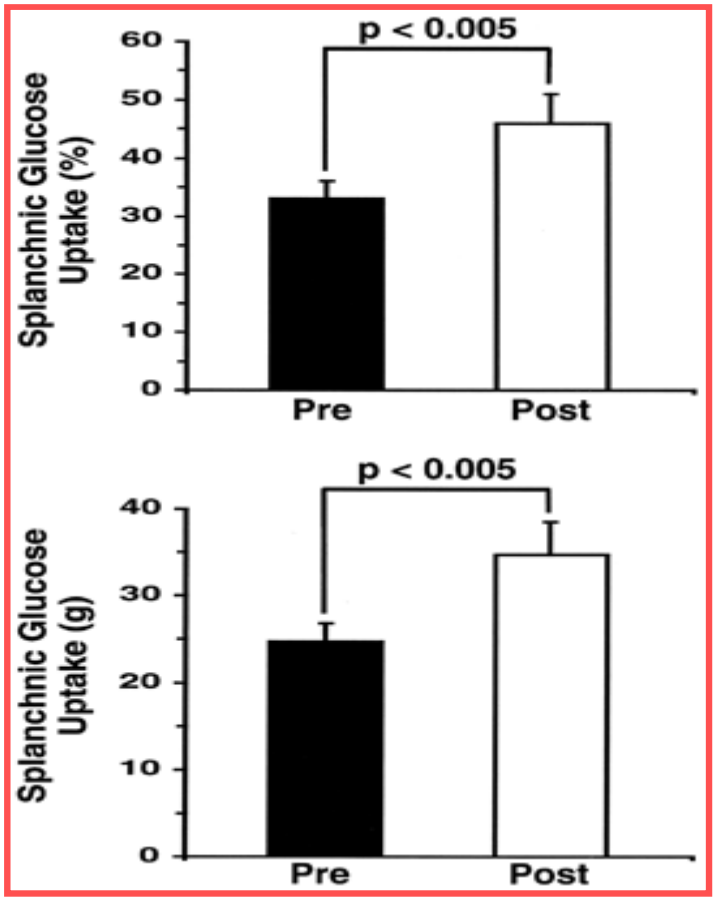




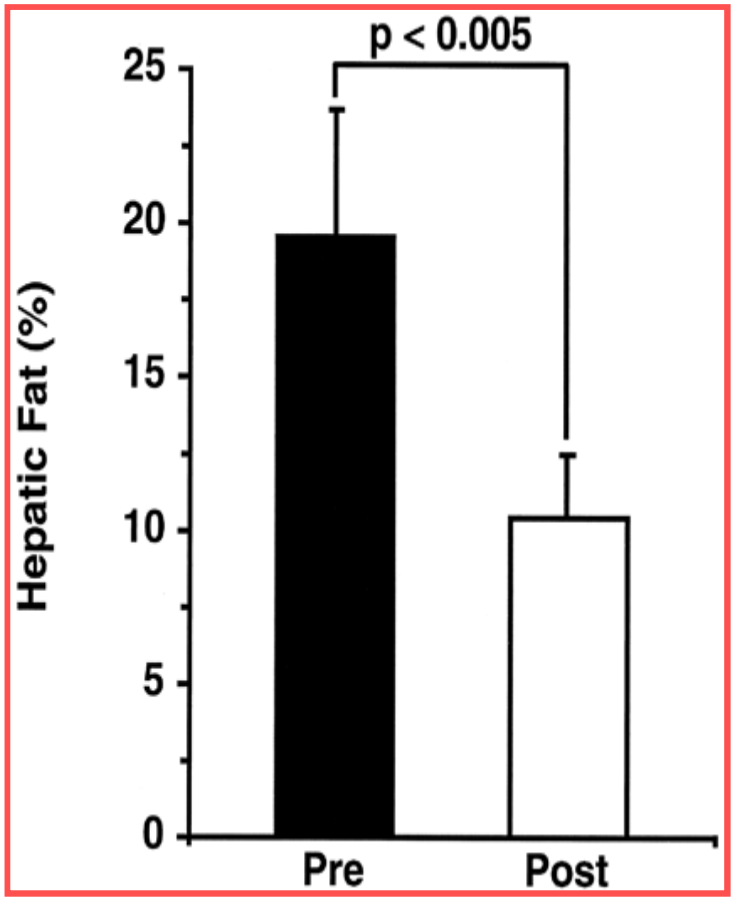
HGO at follow-up	Determinant	Estimate	Standard error	p-value
	Intercept	−0.47	0.19	0.02
	Age follow-up	0.005	0.004	0.18
	Sex	−0.19	0.06	0.003
	Body fat at follow-up	0.03	0.006	0.0001
	Body fat at baseline	−0.008	0.006	0.15
	HGO at baseline	0.28	0.07	0.0001
	ALT at baseline	0.17	0.08	0.001
	Time of follow-up	0.00004	0.00002	0.06

Diabetes 51:1889-1895, 2002

High Alanine Aminotransferase Is Associated With Decreased Hepatic Insulin Sensitivity and Predicts the Development of Type 2 Diabetes



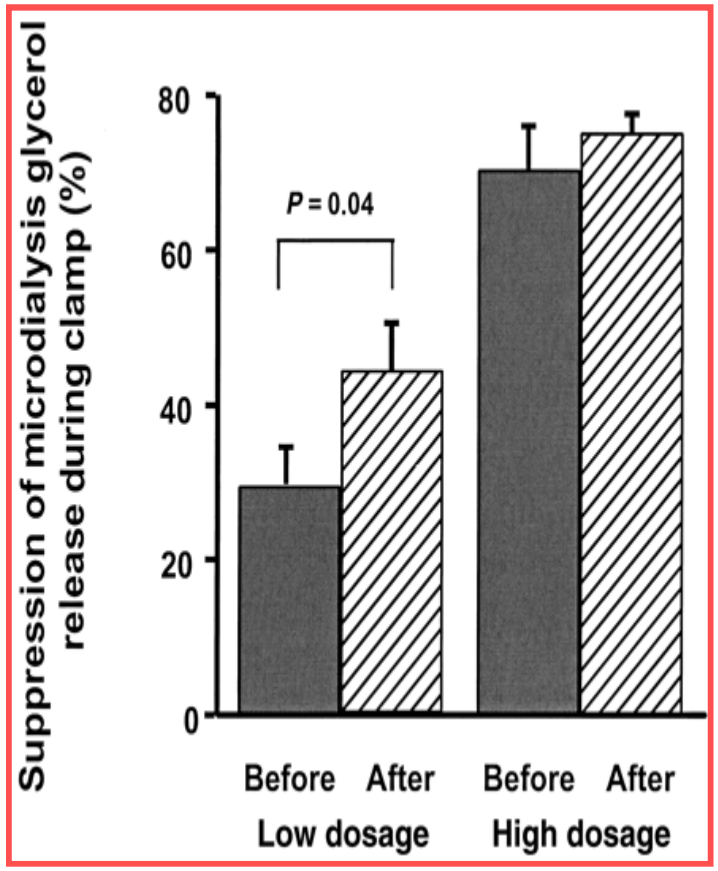
SGU (absolute and percentage of ingested glucose load) during the oral glucose load-insulin clamp studies performed before (pre) and after (post) pioglitazone treatment.



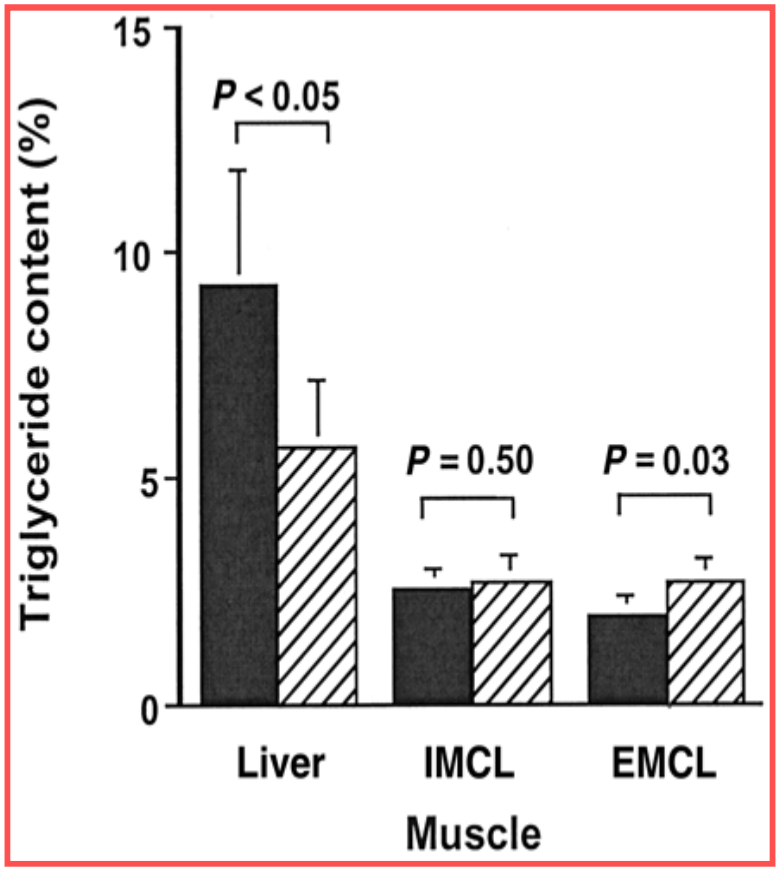
Hepatic fat content before (pre) and after (post) pioglitazone treatment

Diabetes 52:1364-1370, 2003

Pioglitazone Reduces Hepatic Fat Content and Augments Splanchnic Glucose Uptake in Patients With Type 2 Diabetes



Effects of 3 months of rosiglitazone treatment on insulin suppression of peripheral adipocyte lipolysis during the two-step hyperinsulinemic-euglycemic clamp.



Effects of 3 months of rosiglitazone treatment on hepatic triglyceride, IMLC, and EMLC content. , before rosiglitazone; , after rosiglitazone

Diabetes 51:797-802, 2002

The Effects of Rosiglitazone on Insulin Sensitivity, Lipolysis, and Hepatic and Skeletal Muscle Triglyceride Content in Patients With Type 2 Diabetes

ß-hücresi

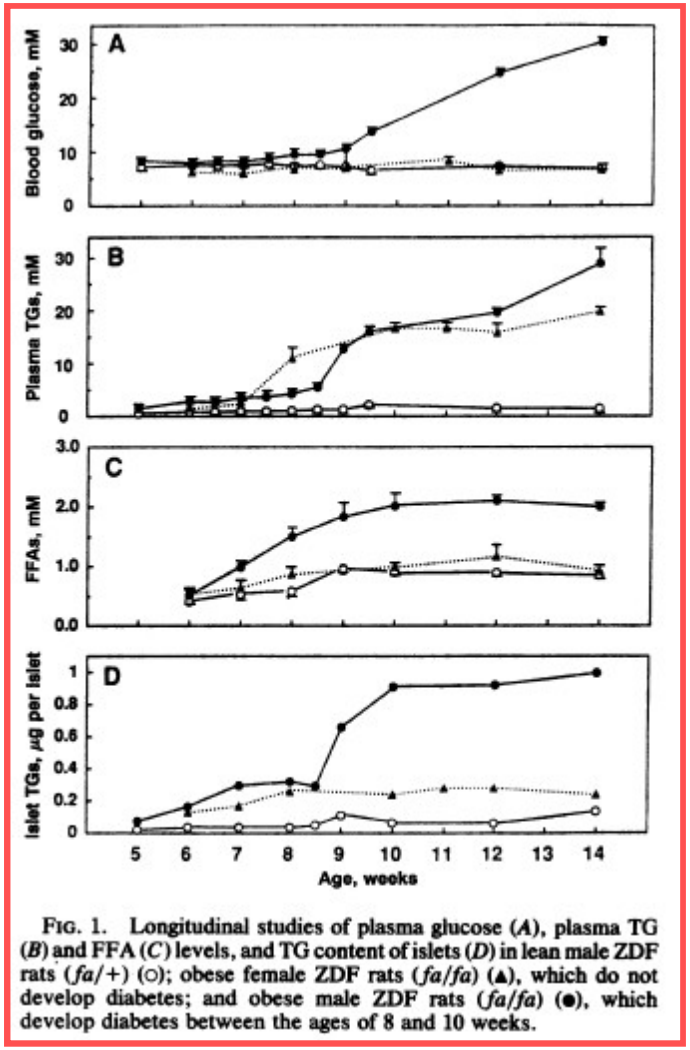
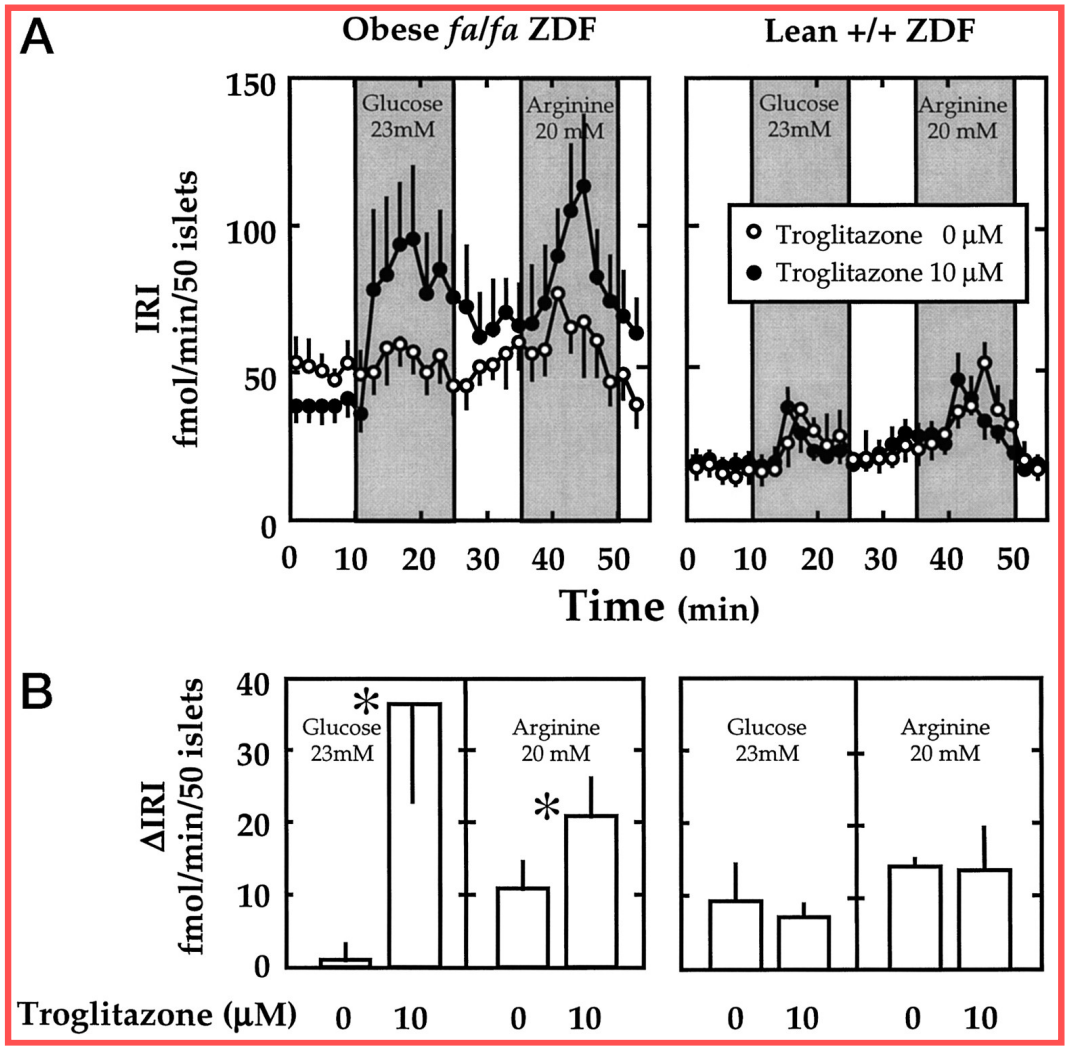


FIG. 1. Longitudinal studies of plasma glucose (*A*), plasma TG (*B*) and FFA (*C*) levels, and TG content of islets (*D*) in lean male ZDF rats (*fa*/+) (○); obese female ZDF rats (*fa*/*fa*) (▲), which do not develop diabetes; and obese male ZDF rats (*fa*/*fa*) (●), which develop diabetes between the ages of 8 and 10 weeks.

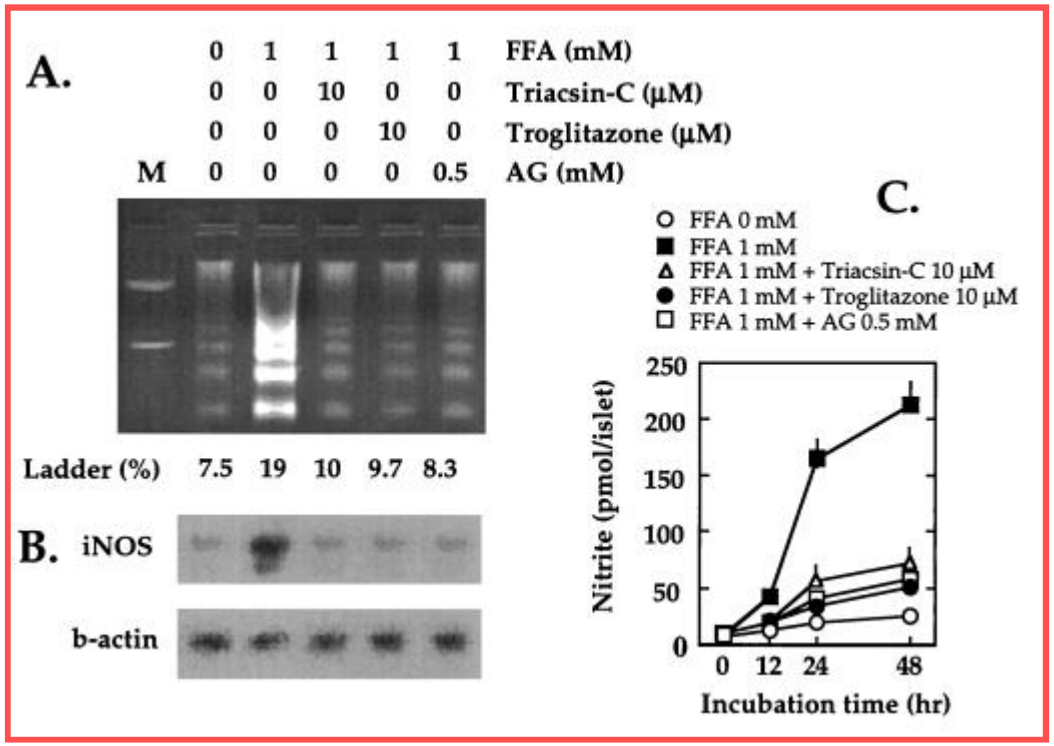
Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 10878–10882, November 1994
Medical Sciences

β-Cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: Impairment in adipocyte–β-cell relationships

A, effect of troglitazone on insulin secretion in islets isolated from obese (fa/fa) (left panel) and lean (+/+) (right panel) ZDF rats cultured for 48 h with or without troglitazone



Shimabukuro, M. et al. J. Biol. Chem. 1998;273:3547-3550

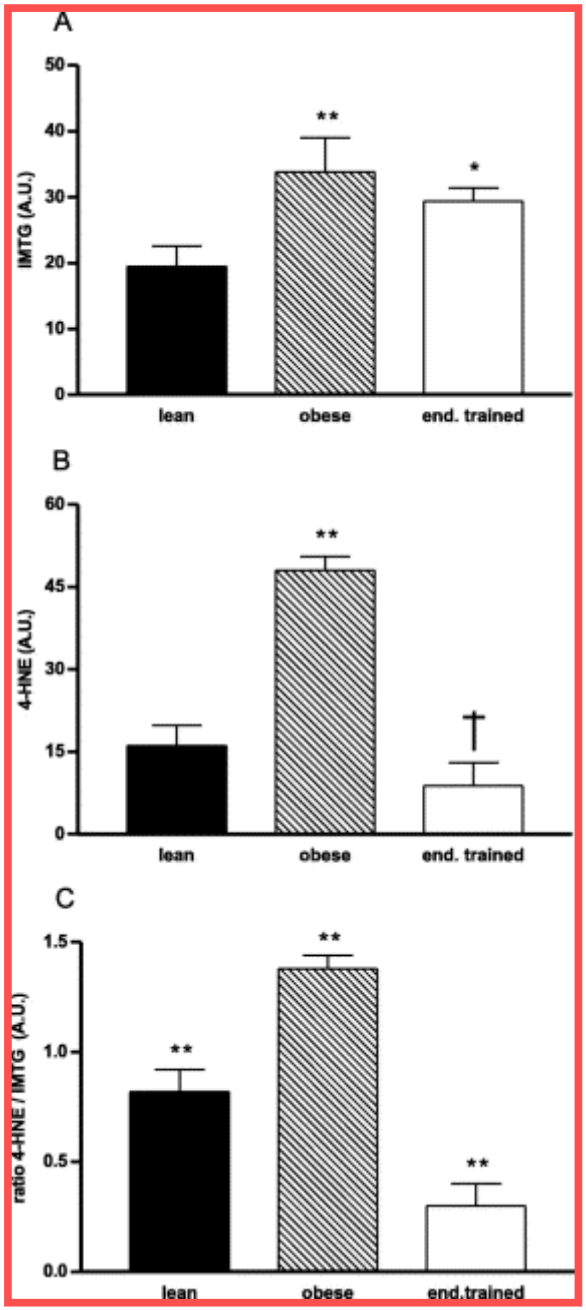


Inhibitory effect of triacsin C, troglitazone, and aminoguanidine on FFA-induced DNA fragmentation in islets from obese *fa/fa* ZDF rats. Islets isolated from 7-week-old *fa/fa* ZDF rats were cultured for 24 hr at 0 or 1 mM FFA with 10 μM triacsin C, 10 μM troglitazone, or 0.5 mM aminoguanidine. M, 100-bp DNA size marker. (*B*) Inhibitory effect of triacsin C, troglitazone, and aminoguanidine on FFA-induced iNOS mRNA induction. (*C*) FFA-induced NO production in islets of obese *fa/fa* ZDF rats. Effect of triacsin C, troglitazone, and aminoguanidine on islets cultured as described in *A* except for 48 hr

Proc Natl Acad Sci U S A. 1998 March 3; 95(5): 2498–2502.

Fatty acid-induced β cell apoptosis: A link between obesity and diabetes

Kas



FABS letters
Volume 551, Issues 1-3, 11
September 2003, Pages 104-106

Level of IMTG in muscle biopsies of lean (*n*=6), obese (*n*=5) and ET (*n*=6) subjects; ***P*<0.001 and **P*<001 vs. lean levels. B: Levels of the lipid peroxidation by-product, anti-4-HNE-lysine in muscle biopsies of lean, obese and ET subjects; ***P*<0.001 vs. lean and ET subjects; †*P*<0.05 vs. lean subjects. C: The relative amount of peroxidized IMTG expressed as the 4-HNE/IMTG ratio in muscle biopsies of lean, obese and ET subjects; ***P*<0.001 for all comparisons. The results are means±S.E.M.

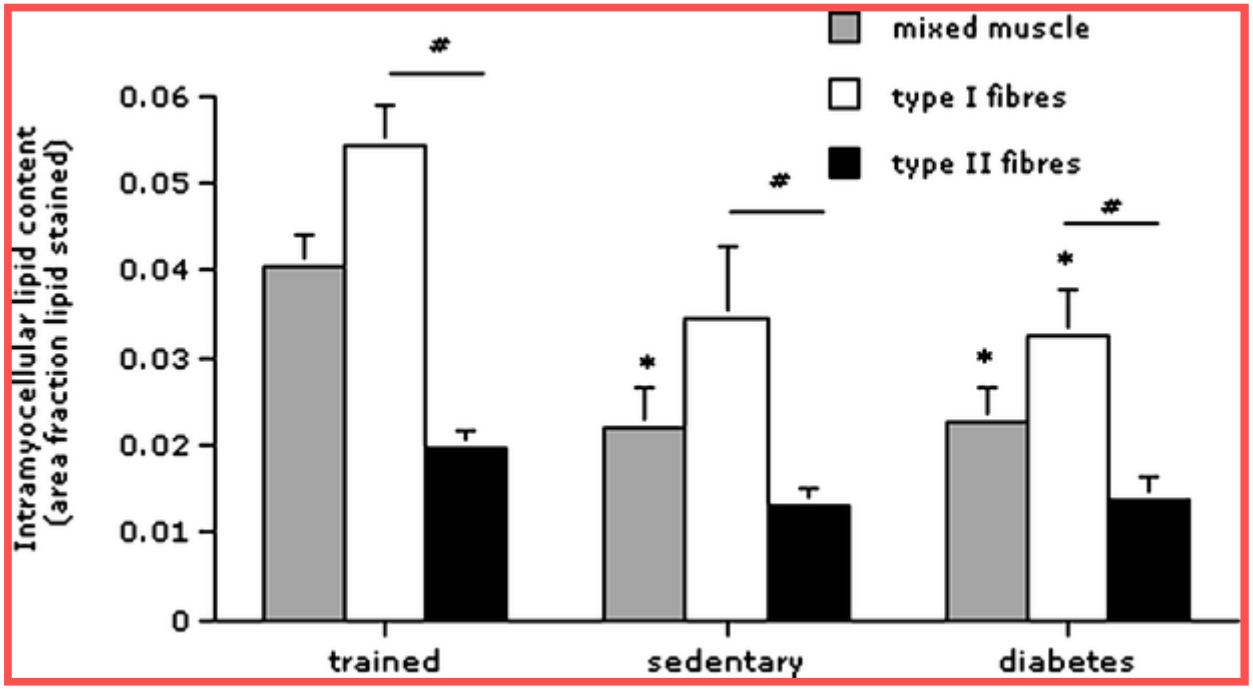
Condition	Intermuscular adipose tissue	Triglycerides	Diacylglycerol	Ceramides	Triglyceride fatty acid composition
Obesity	↑ [a,b]	↑ [c]	↑ [d]	↑ [c]	?
Insulin resistance	↑ [a,b]	↑ [c]	↑ [d]	↑ [c]	?
Type 2 diabetes	↑ [a]	[c]	?	?	?
Aging	↑ [a,b]	?	?	?	?
Weight loss	↓ [a,b]	↓ [c]	?	?	?
Acute exercise	?	↓ [c]	?	?	?
Chronic exercise	↓ [a]	↑ [c]	↓ [c]	↓ ?	altered[c]

[a] In-vivo computed tomography.
[b] In-vivo magnetic resonance imaging.
[c] Muscle biopsy.
[d] Lipid infusion.

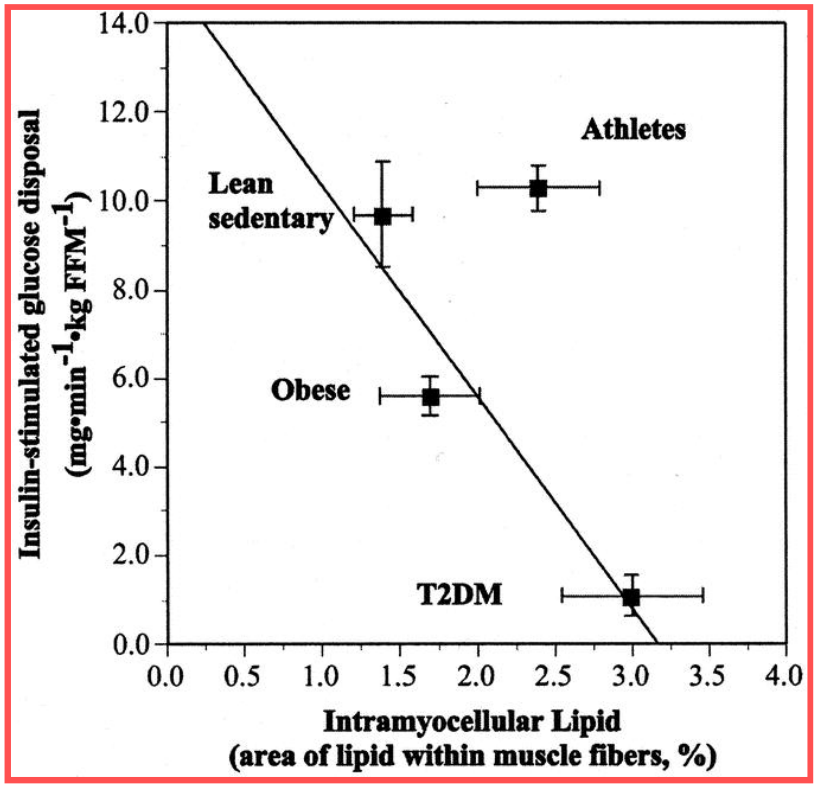
Assessment of intramuscular triglycerides: contribution to metabolic abnormalities. Curr Opin Clin Nutr Metab Care, Volume 9(5).September 2006.553–559

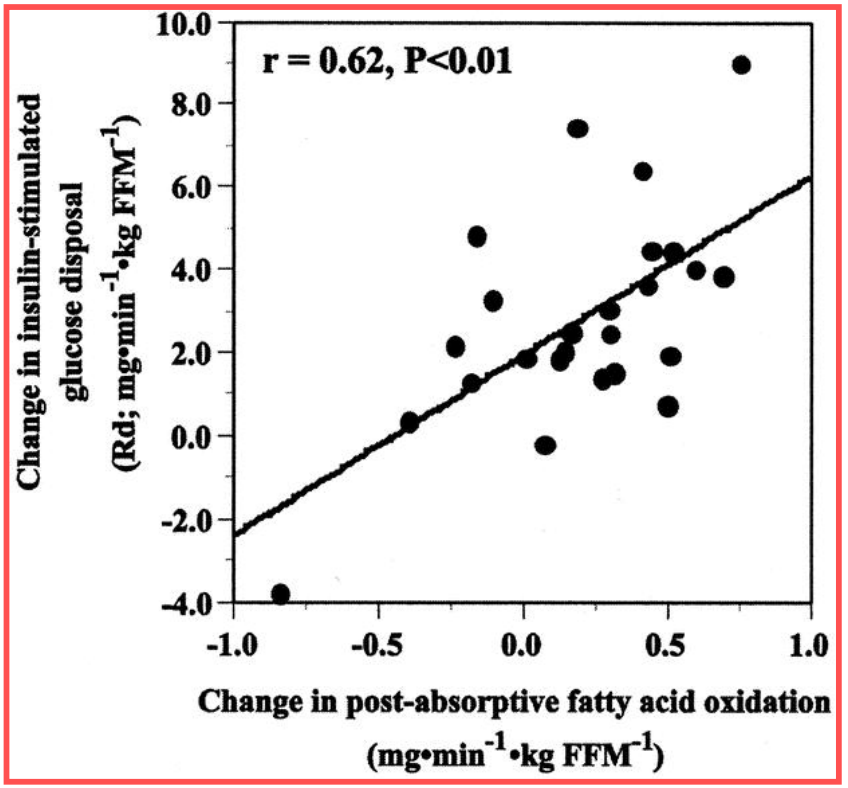
Increased intramuscular lipid storage in the insulin-resistant and endurance-trained state.

Pflugers Arch. 2006 Feb;451(5):606-16.



Fibre type-specific intramyocellular lipid content (expressed as % area lipid stained) in type I, type II and mixed (average) muscle fibres in endurance-trained athletes, type 2 diabetes patients and weight-matched, sedentary men. Data obtained by using fluorescence microscopy on oil red O stained muscle cross-sections. Data provided are mean + SEM; *: significantly lower compared to values observed in the trained athletes; #: significant difference between type I and II muscle fibres ($P<0.05$)

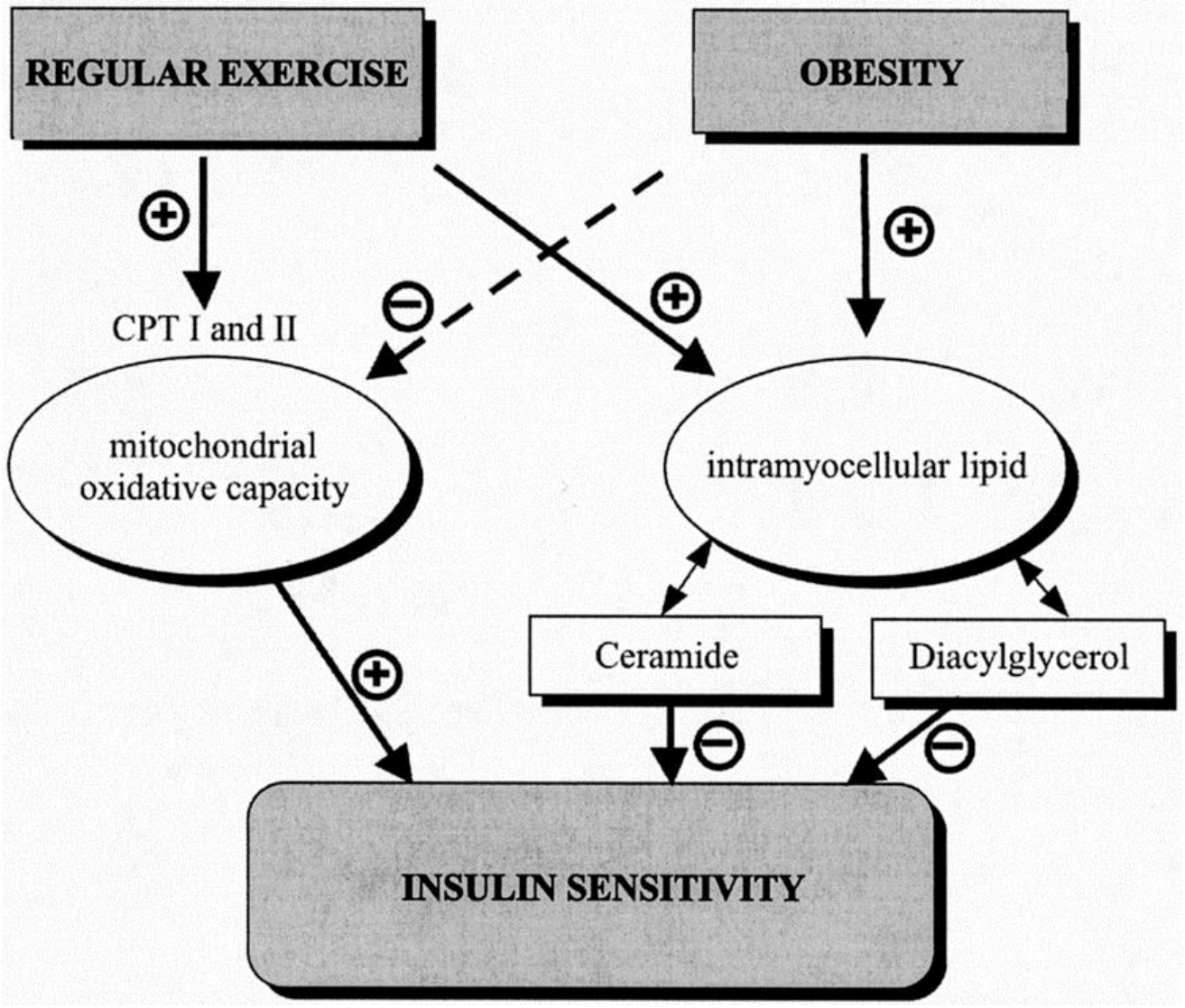




The amount of lipid contained within skeletal muscle as triglycerides (intramyocellular lipid) is negatively correlated with insulin sensitivity (low rates of insulin-stimulated glucose disposal, that is, insulin resistance) in sedentary subjects. There is an apparent paradox in this often-cited association such that endurance-trained athletes, who are markedly insulin-sensitive, have intramyocellular lipid levels higher than lean sedentary subjects and similar to that of subjects with severe insulin resistance. Units of insulin-stimulated glucose disposal reported as mg·min-1·kg-1 fat-free mass (FFM)

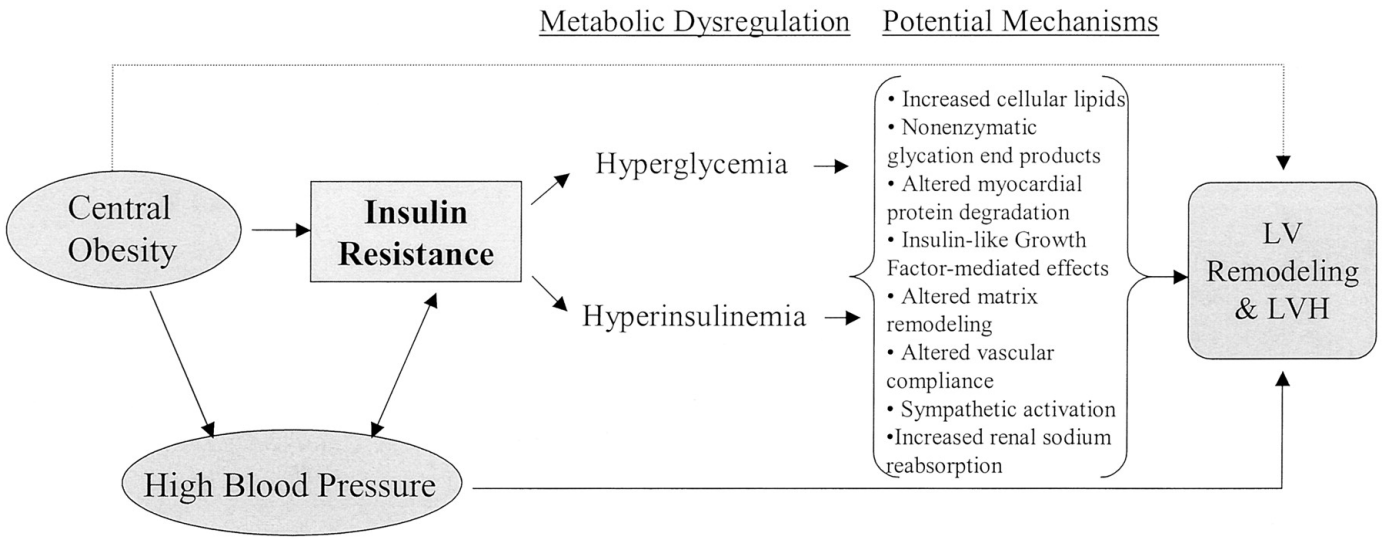
The degree of enhanced fat oxidation during postabsorptive (fasting, resting) conditions resulting from increased physical activity is directly associated with improved insulin sensitivity.

Skeletal muscle lipid and its association with insulin resistance: what is the role for exercise? Exerc Sport Sci Rev. 2005 Jul;33(3):150-4.

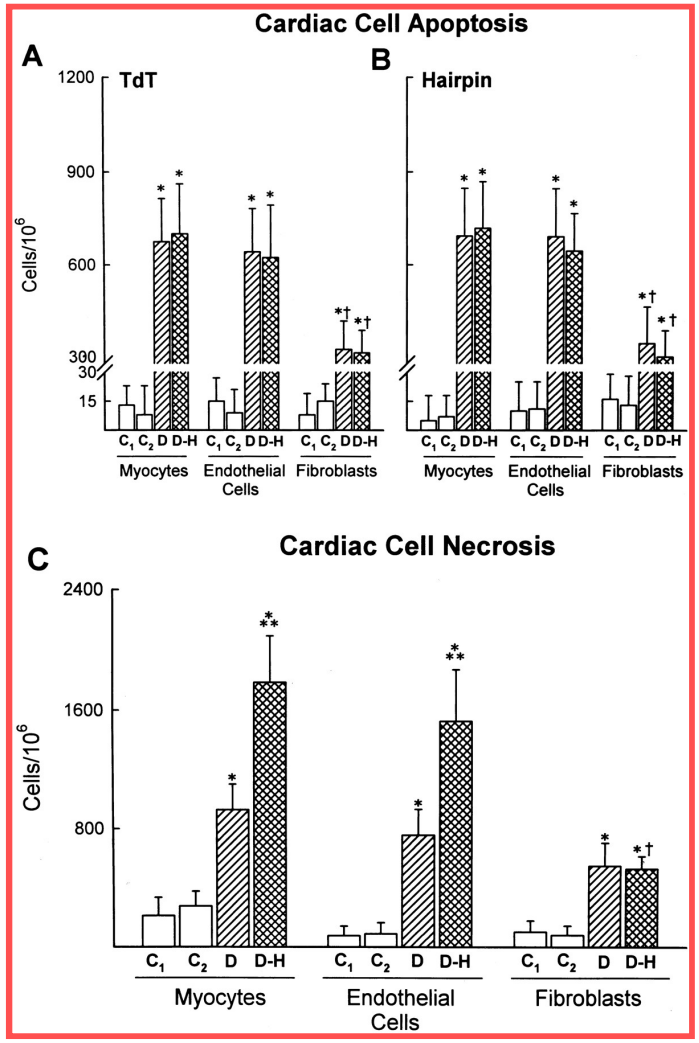

REGULAR EXERCISE
OBESITY
CPT I and II
mitochondrial oxidative capacity
intramyocellular lipid
Ceramide
Diacylglycerol
INSULIN SENSITIVITY

Kalp

Potential mechanisms by which insulin resistance and its precursors/correlates are associated with LV hypertrophy (LVH) (see reference 26 for review)

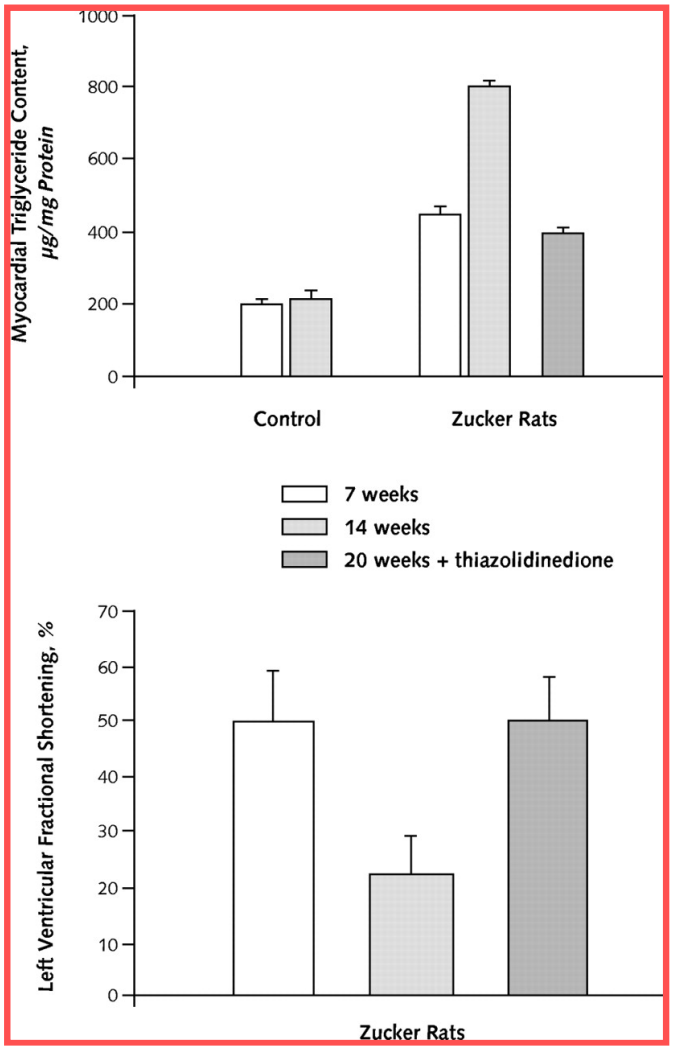


Rutter, M. K. et al. Circulation 2003;107:448-454



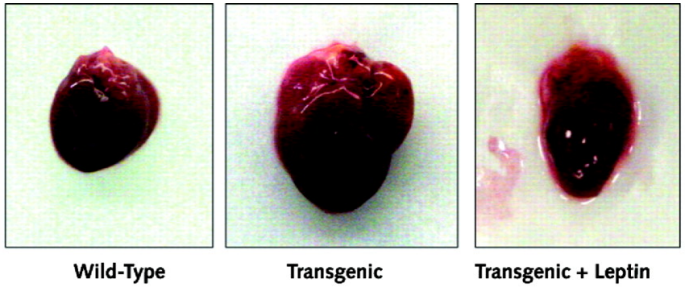
Frustaci, A. et al. Circ Res 2000;87:1123-1132

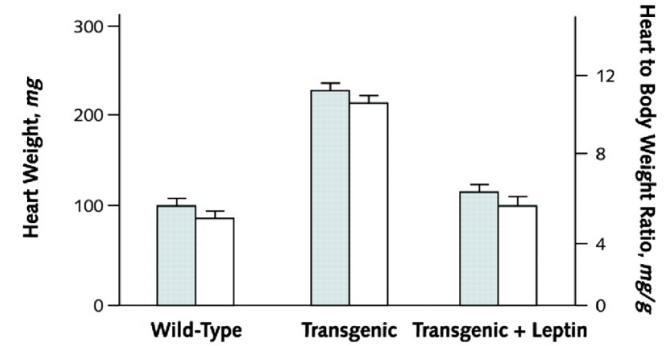
Myocardial lipotoxicity in the Zucker diabetic fatty rat

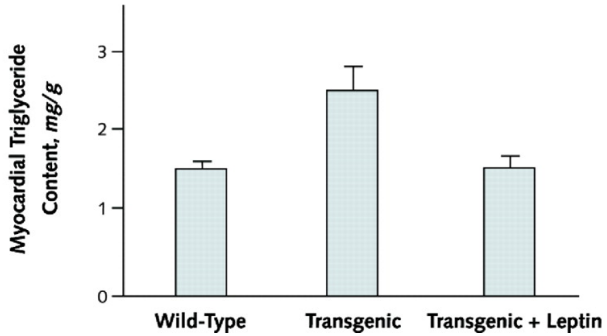


McGavock, J. M. et. al. Ann Intern Med 2006;144:517-524

Myocardial-specific lipotoxicity

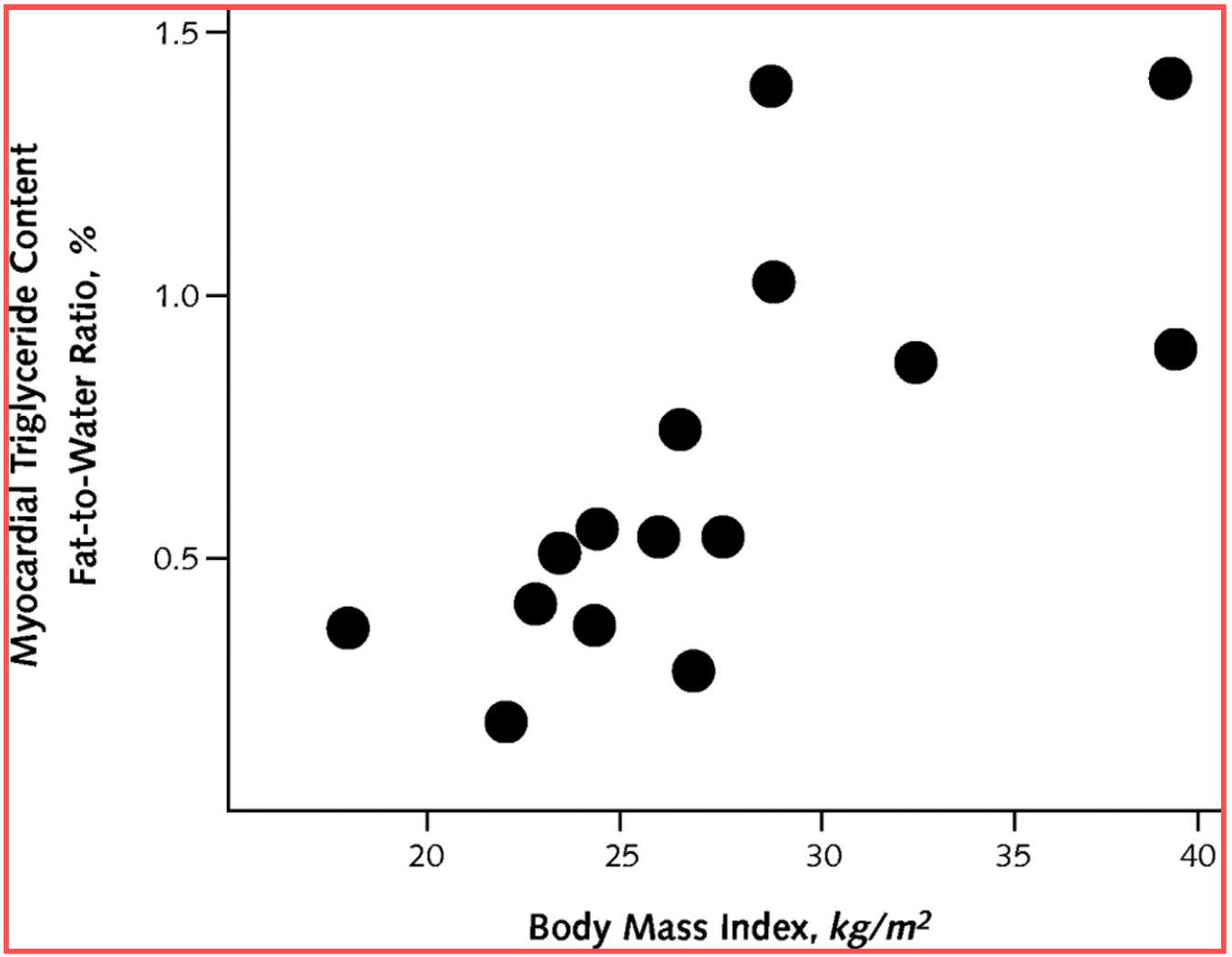






McGavock, J. M. et. al. Ann Intern Med 2006;144:517-524

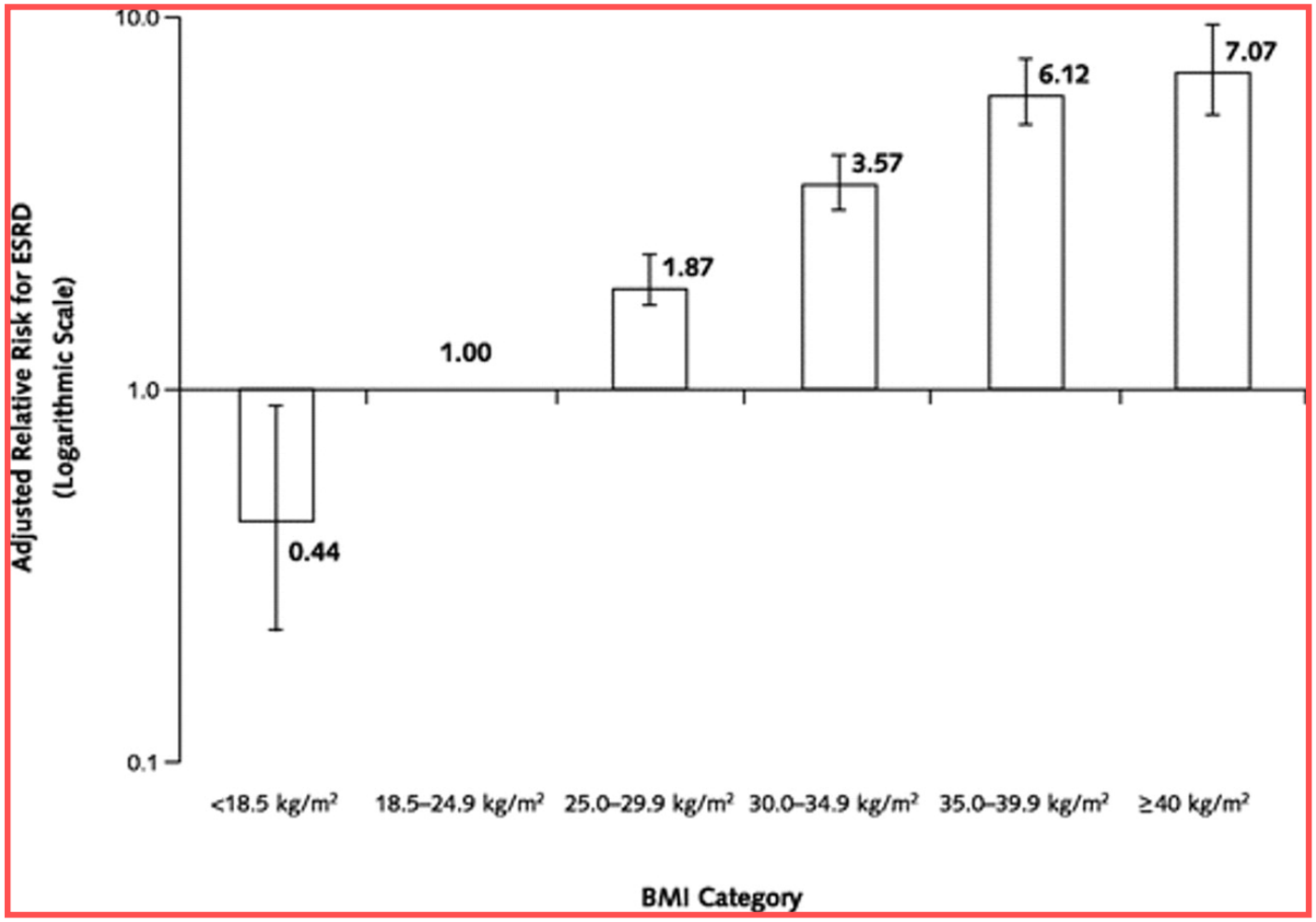
Myocardial triglyceride levels correlate positively with body mass index



McGavock, J. M. et. al. Ann Intern Med 2006;144:517-524

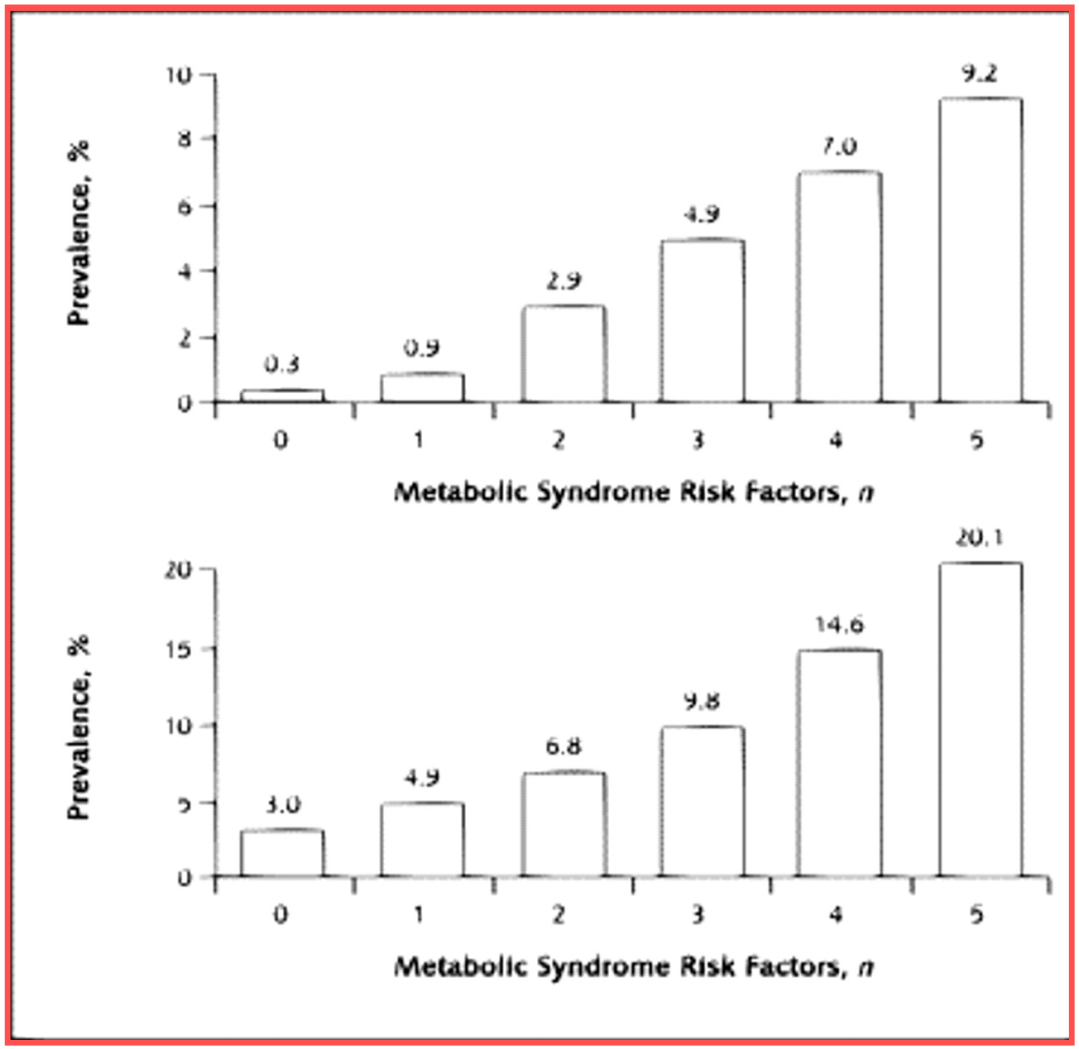
Böbrek

Adjusted relative risk for end-stage renal disease (ESRD) by body mass index (BMI)

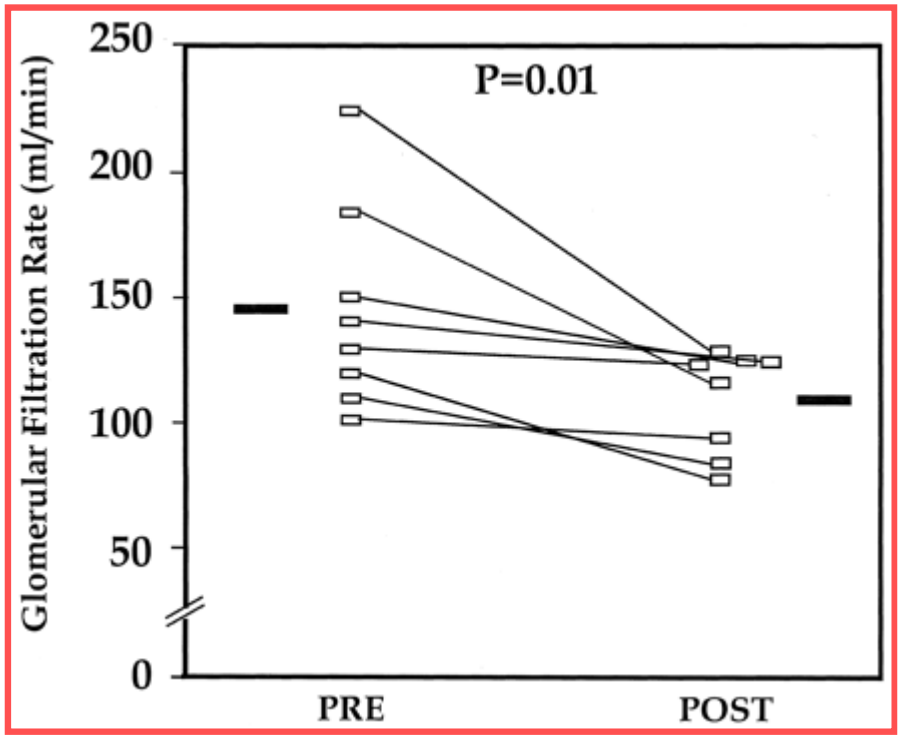


Hsu, C.-y. et. al. Ann Intern Med 2006;144:21-28

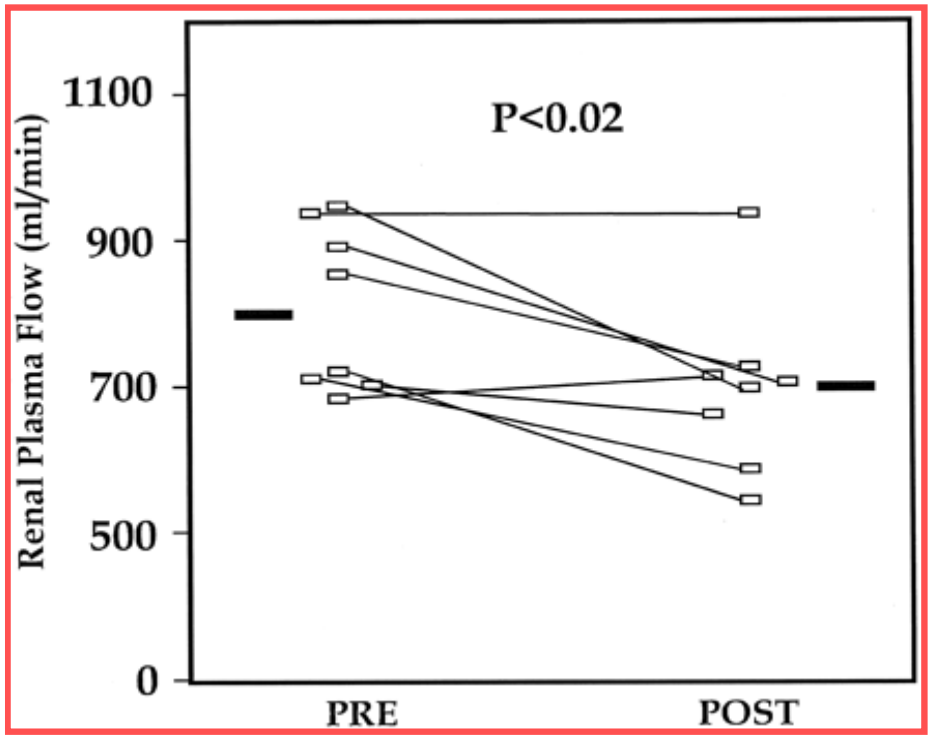
Prevalence of chronic kidney disease (top) and microalbuminuria (bottom) by number of the metabolic syndrome components



Chen, J. et. al. Ann Intern Med 2004;140:167-174



GFR in the obese group before and after weight loss.



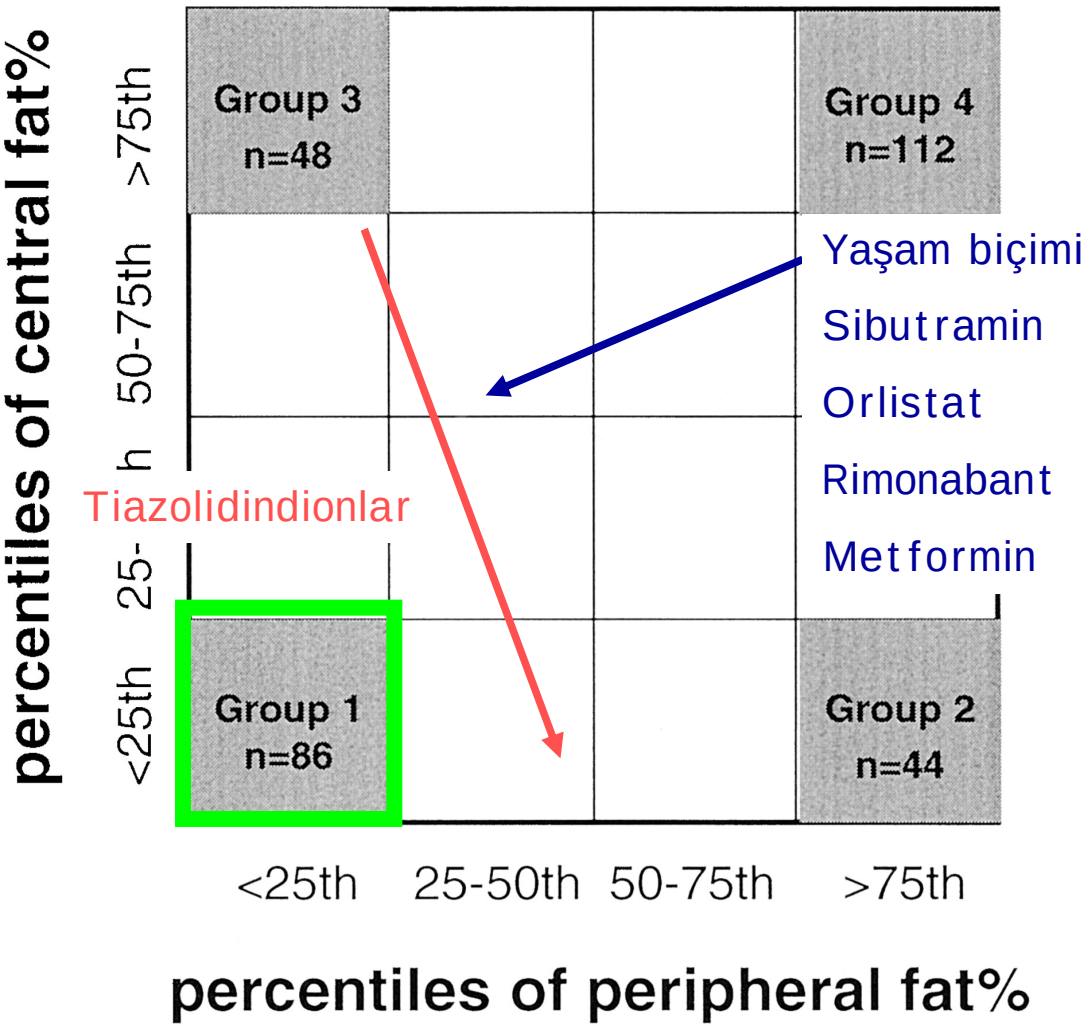
RPF in the obese group before and after weight loss.

Am Soc Nephrol 14:1480-1486, 2003

The Effects of Weight Loss on Renal Function in Patients with Severe Obesity

Kimler risk altındadır ?

- Abdominal obezler
- Organ disfonksiyonu olanlar


Group 3
n=48
Group 4
n=112
Group 1
n=86
Group 2
n=44
Yaşam biçimi
Sibutramin
Orlistat
Rimonabant
Metformin
Tiazolidindionlar
percentiles of central fat%
>75th
50-75th
25-
<25th
<25th
25-50th
50-75th
>75th
percentiles of peripheral fat%