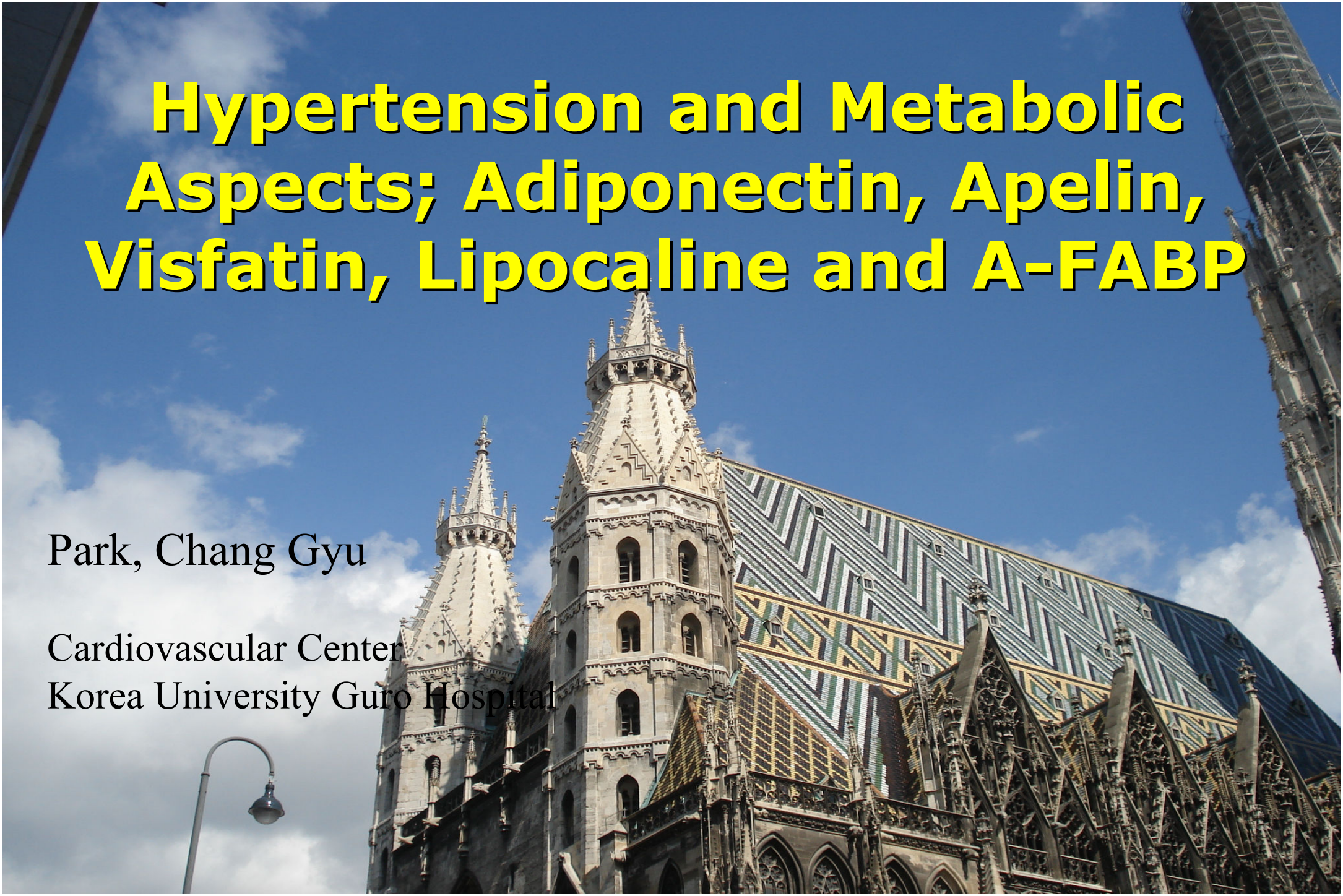


Hypertension and Metabolic Aspects; Adiponectin, Apelin, Visfatin, Lipocaline and A-FABP

Park, Chang Gyu

Cardiovascular Center
Korea University Guro Hospital

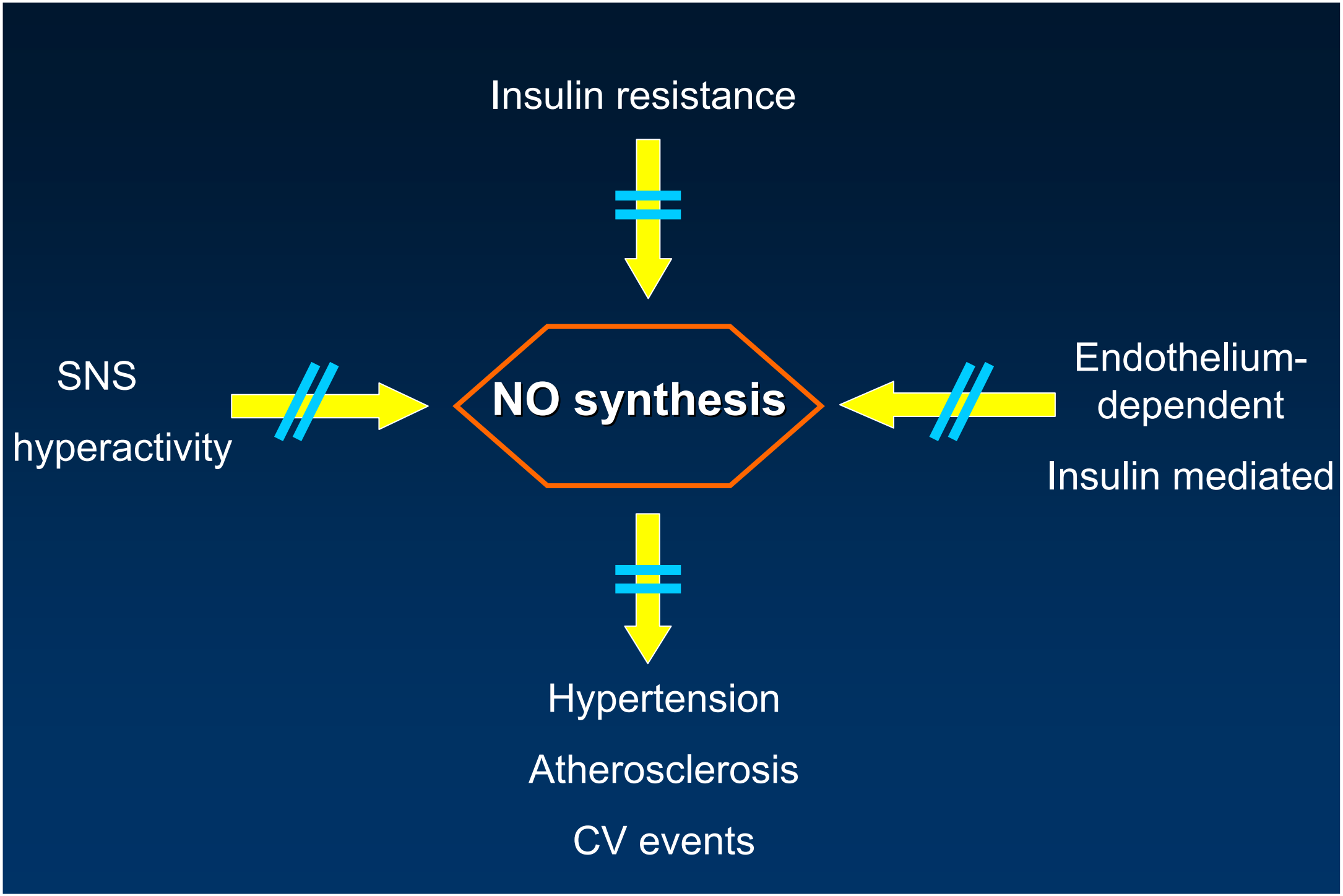
Hypertension: pathophysiology

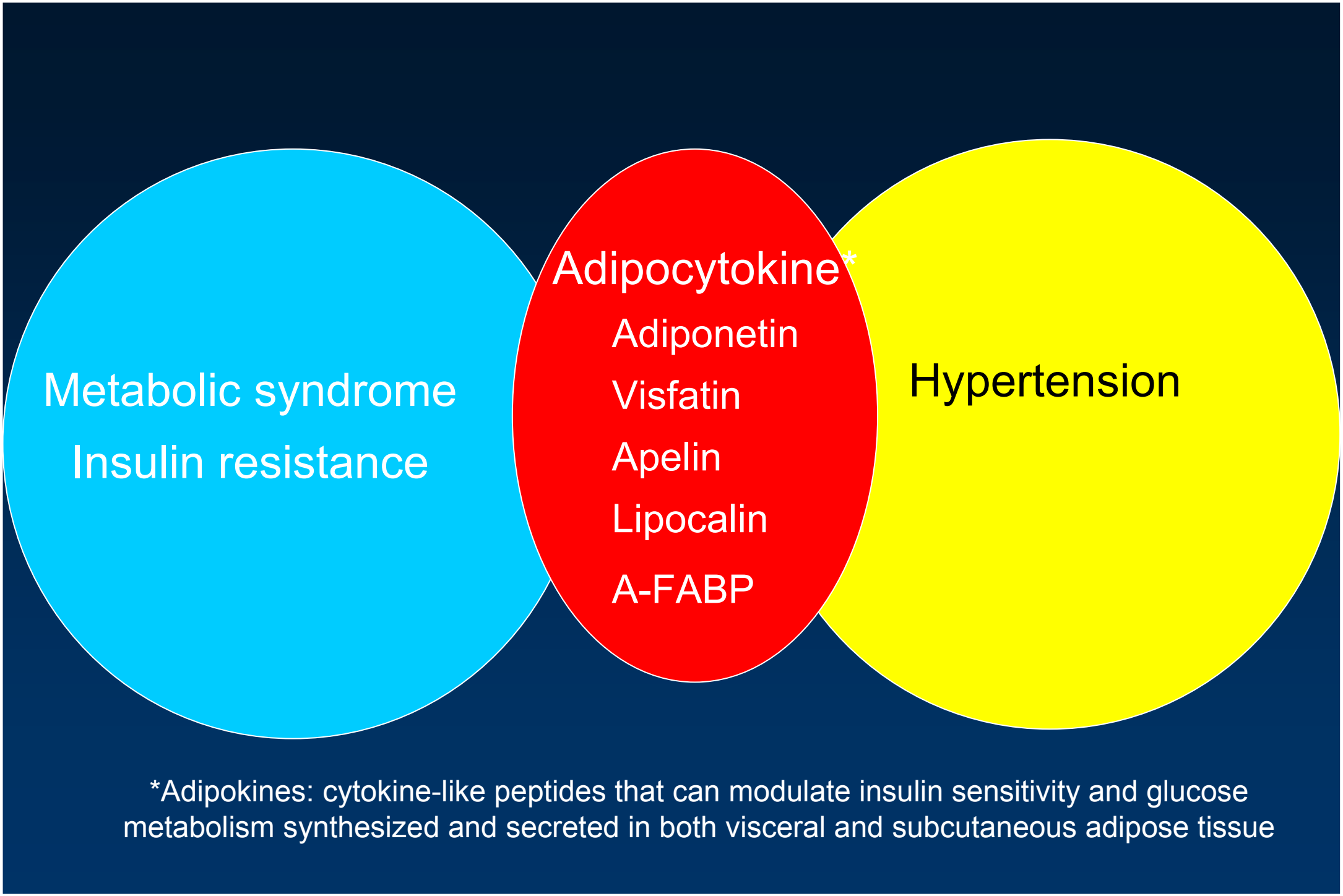
- Systemic and local renin-angiotensin system
- Sympathetic nervous system
- Insulin resistance

50% of Hypertensive patients are associated with Insulin resistance

- Endothelial function
- Kallikrein-kinin system
- Natriuretic peptides

Beevers et al. *BMJ* 2001;322:912–916


Insulin resistance
SNS
hyperactivity
NO synthesis
Endothelium-
dependent
Insulin mediated
Hypertension
Atherosclerosis
CV events

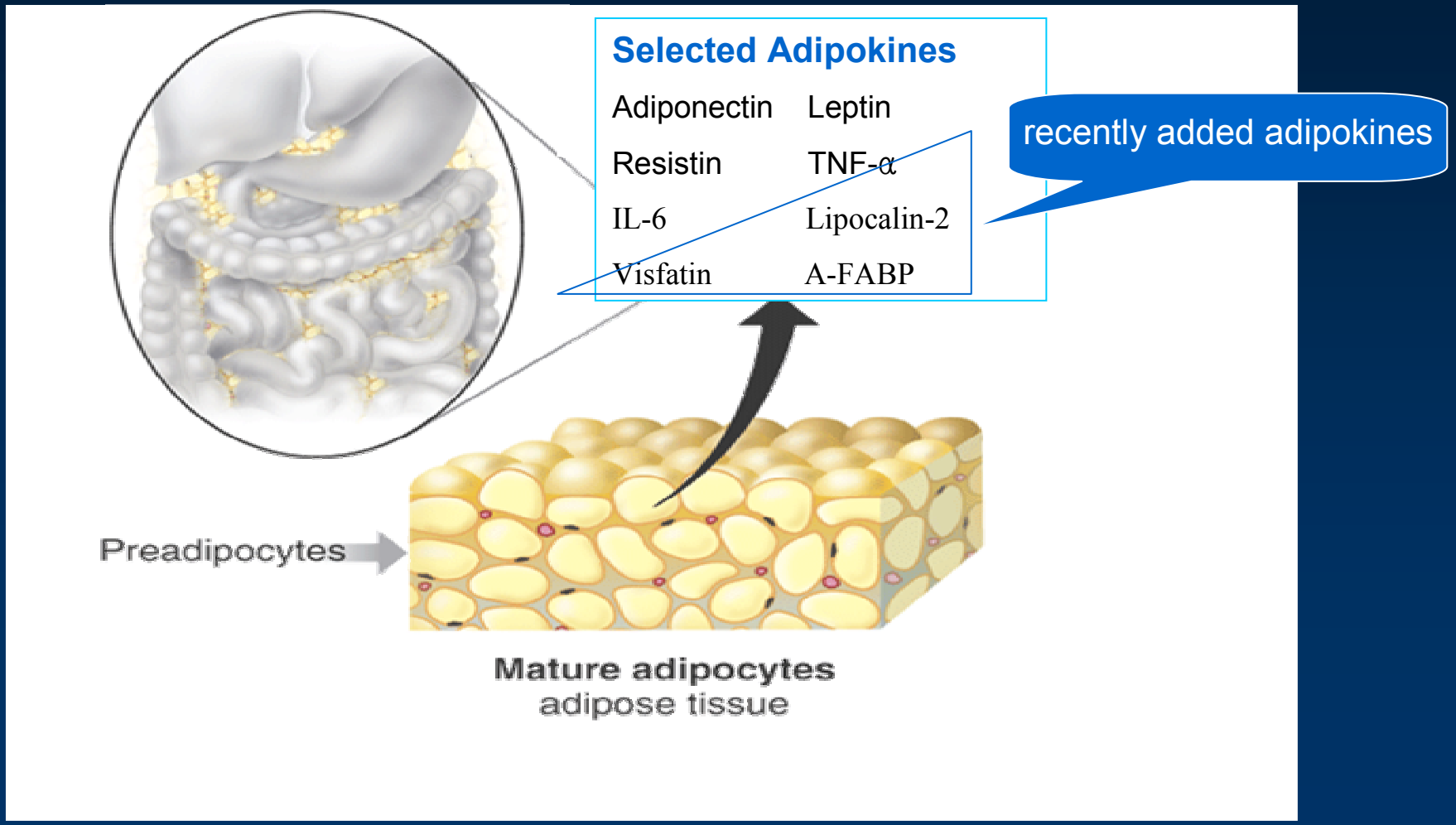


*Adipokines: cytokine-like peptides that can modulate insulin sensitivity and glucose metabolism synthesized and secreted in both visceral and subcutaneous adipose tissue

Metabolic Aspects of Hypertension ;

Clinical Implications of Adipocytokines

Adipose Tissue as an Important Endocrine Organ



Adiponectin

- ✓ insulin sensitizing, antidiabetic
- ✓ anti-atherogenic
- ✓ anti-inflammatory properties

The Journal of clinical endocrinology and metabolism. 2004;89:2548-56.

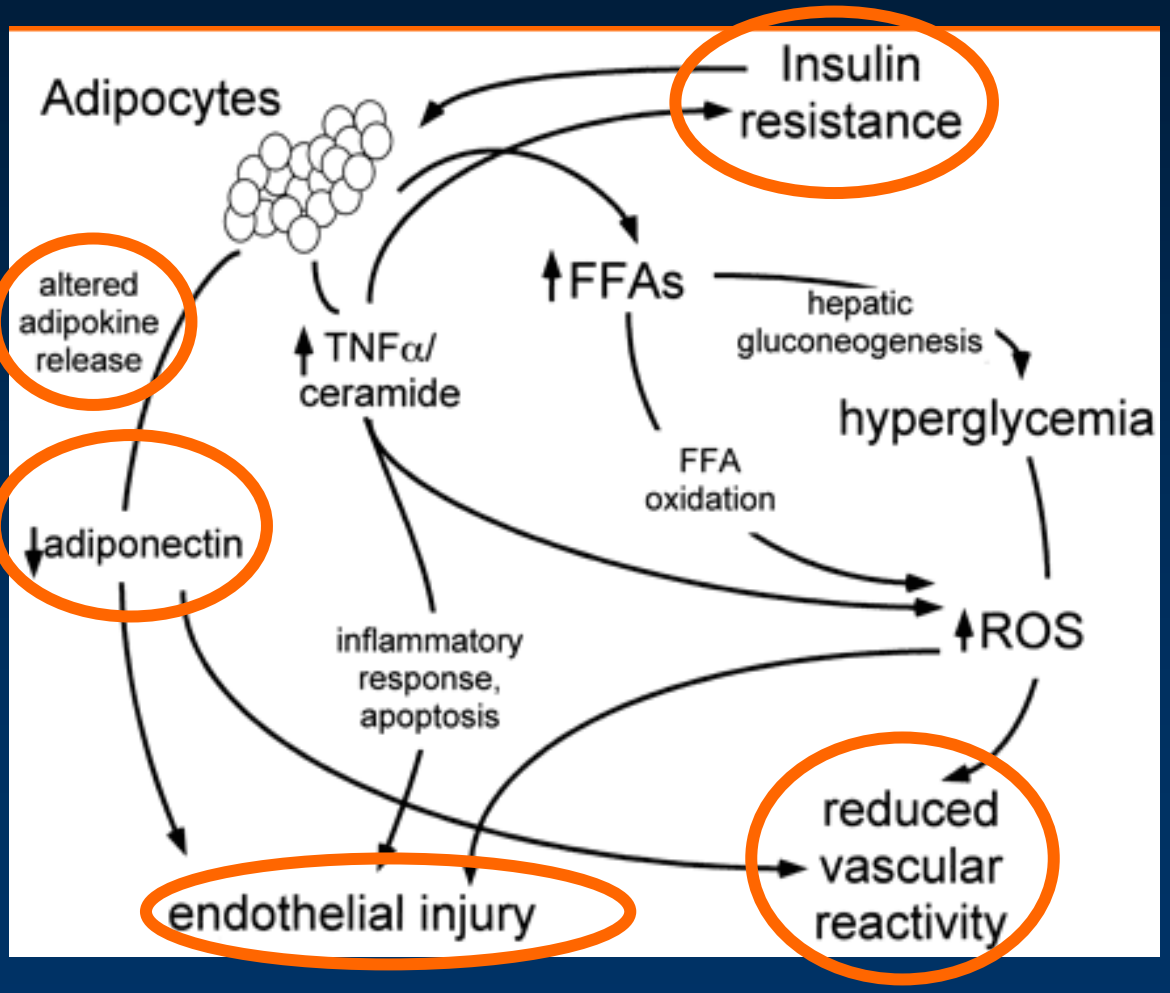
Nature medicine. 2002;8:1288-95.

European Journal of Endocrinology 2003; 148; 293-300

- Potent inhibitory effect on the expression of adhesion molecules in endothelial cells and an inhibitory effect on the expression in macrophages.
- Adiponectin knockout mice showed severe insulin resistance and impaired glucose metabolism when fed a high-fat, high-sucrose diet

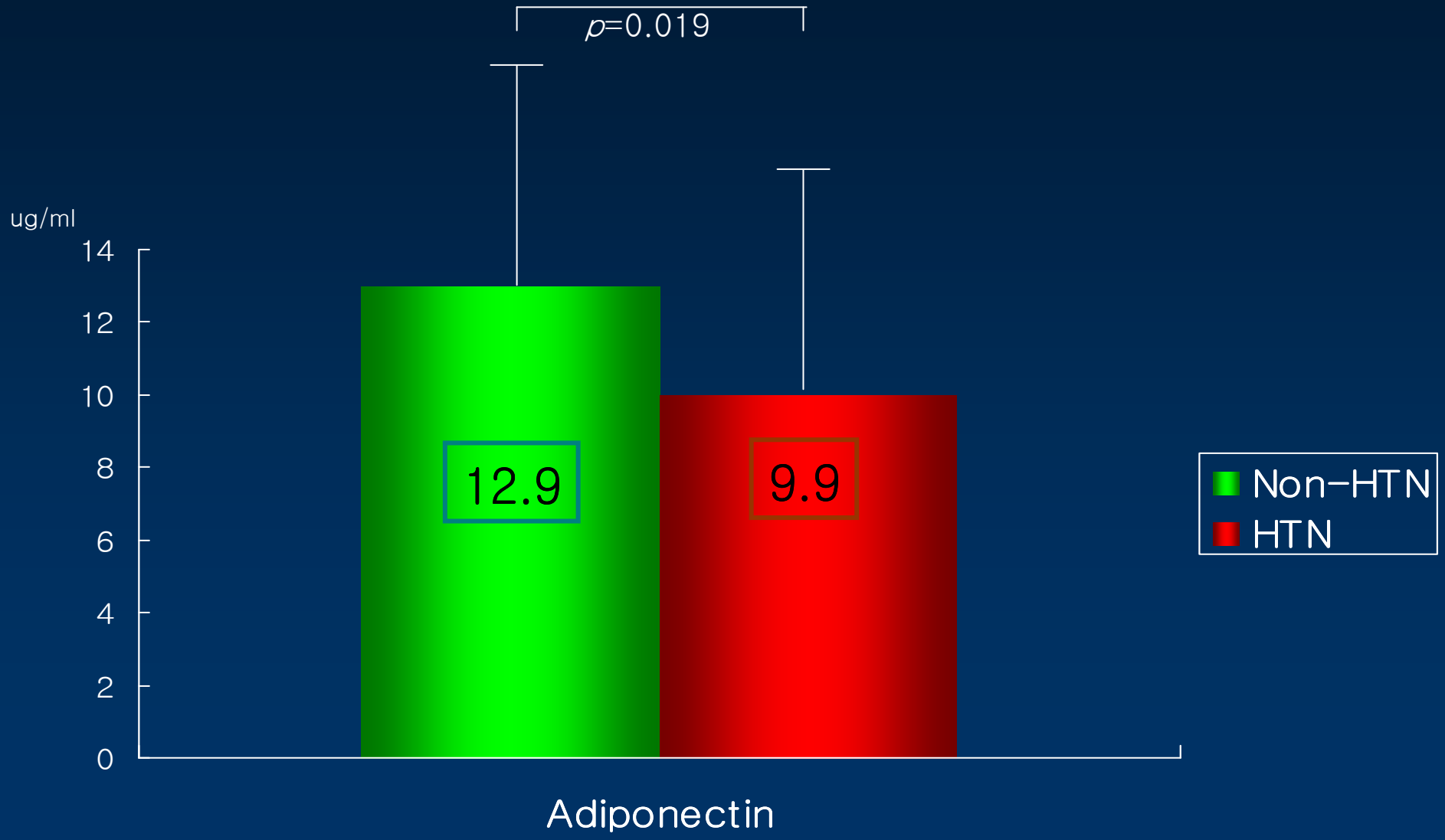
Horm Res. 2003;60 Suppl 3:56-9

Changes in Adipocytokines in Response in States of Insulin Resistance and Obesity



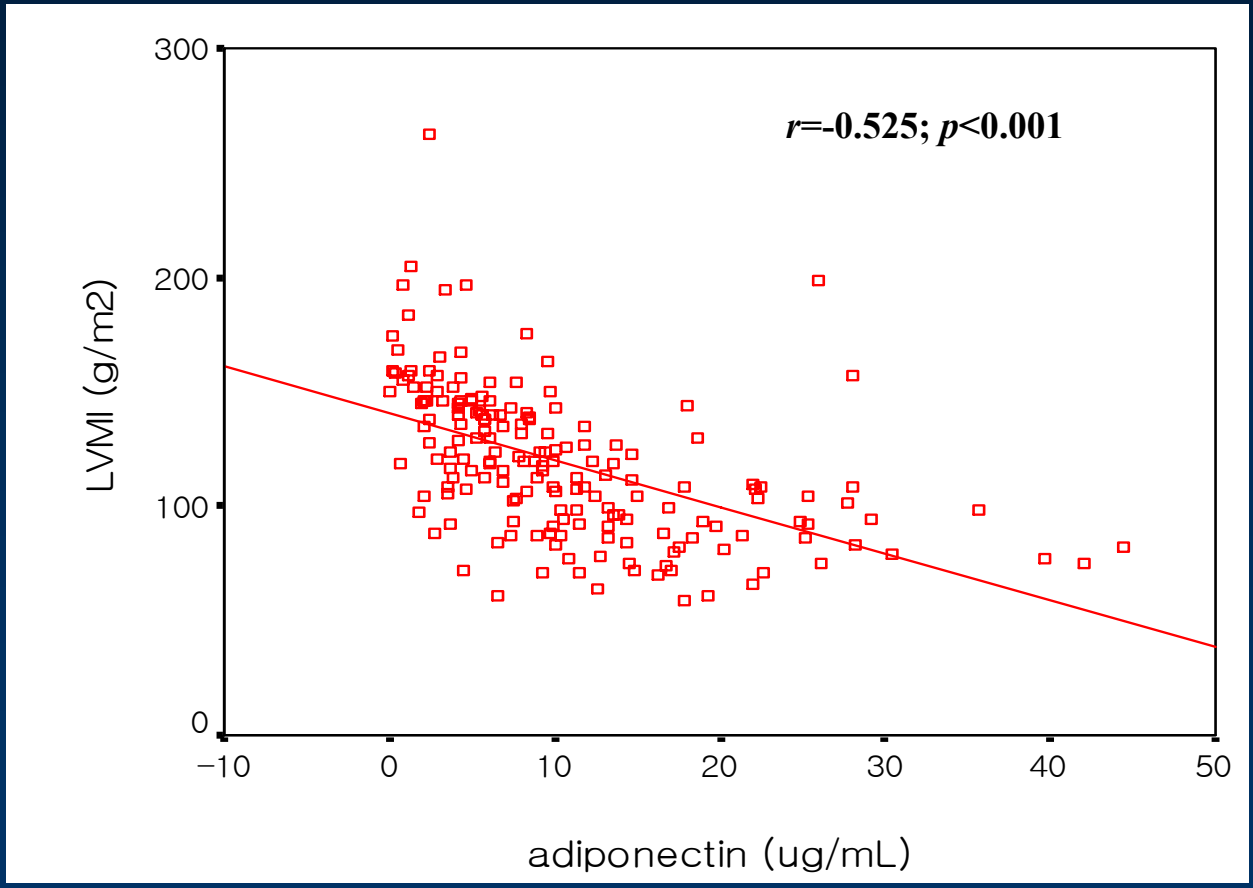
Diabetes 2003; 52:2867-73

Comparison of Adiponectin Between Normotensive and Hypertensive group



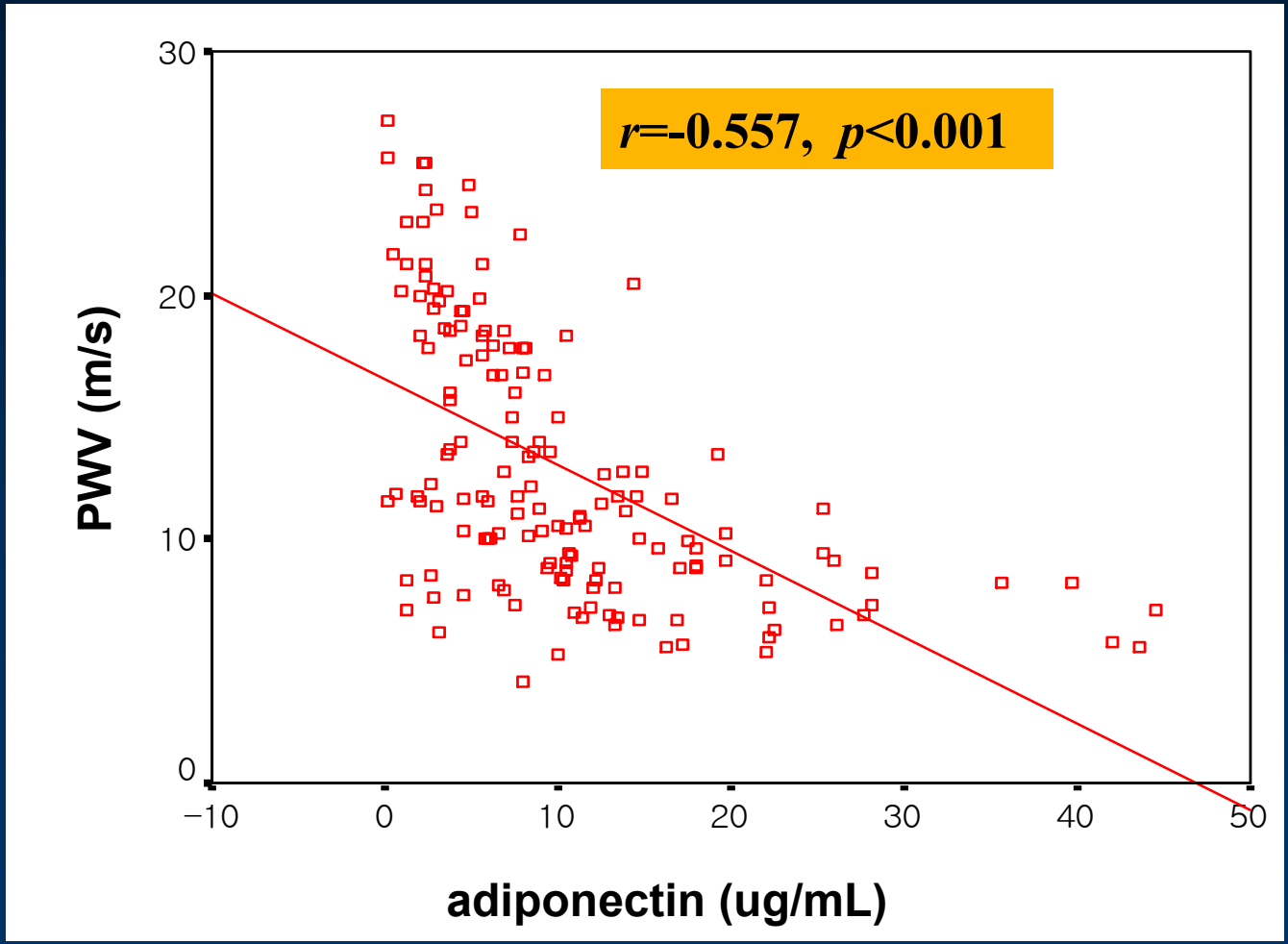
Hong SJ, Park CG et al Blood Pressure 2004; 13:236-42

Correlation Between Adiponectin and Left Ventricular Mass Index (LVMI)



Hong SJ, Park CG et al Blood Pressure 2004; 13:236-42

Plasma Adiponectin vs. Aortic Stiffness



Hong SJ, Park CG et al Blood Pressure 2004; 13:236-42

Multiple Regression Analysis

Intercept	***B*0 = 99.012**	***t* = 6.583**	***p* = 0.001**
PWV (m/s)	***B*1 = 1.934**	***t* = 2.634**	***p* = 0.021**
Adiponectin (ug/mL)	***B*2 = -1.006**	***t* = -2.266**	***p* = 0.041**

LVMI = 99.012 + 1.934 · [PWV] – 1.006 · [Adiponectin].

Analysis of variance from regression: F=17.827; p<0.001.
Multiple correlation coefficient: R = 0.856, $R2$ = 73.3%, $Ra2$ = 69.2%.
PWV, pulse wave velocity; LVMI, left ventricular mass index.

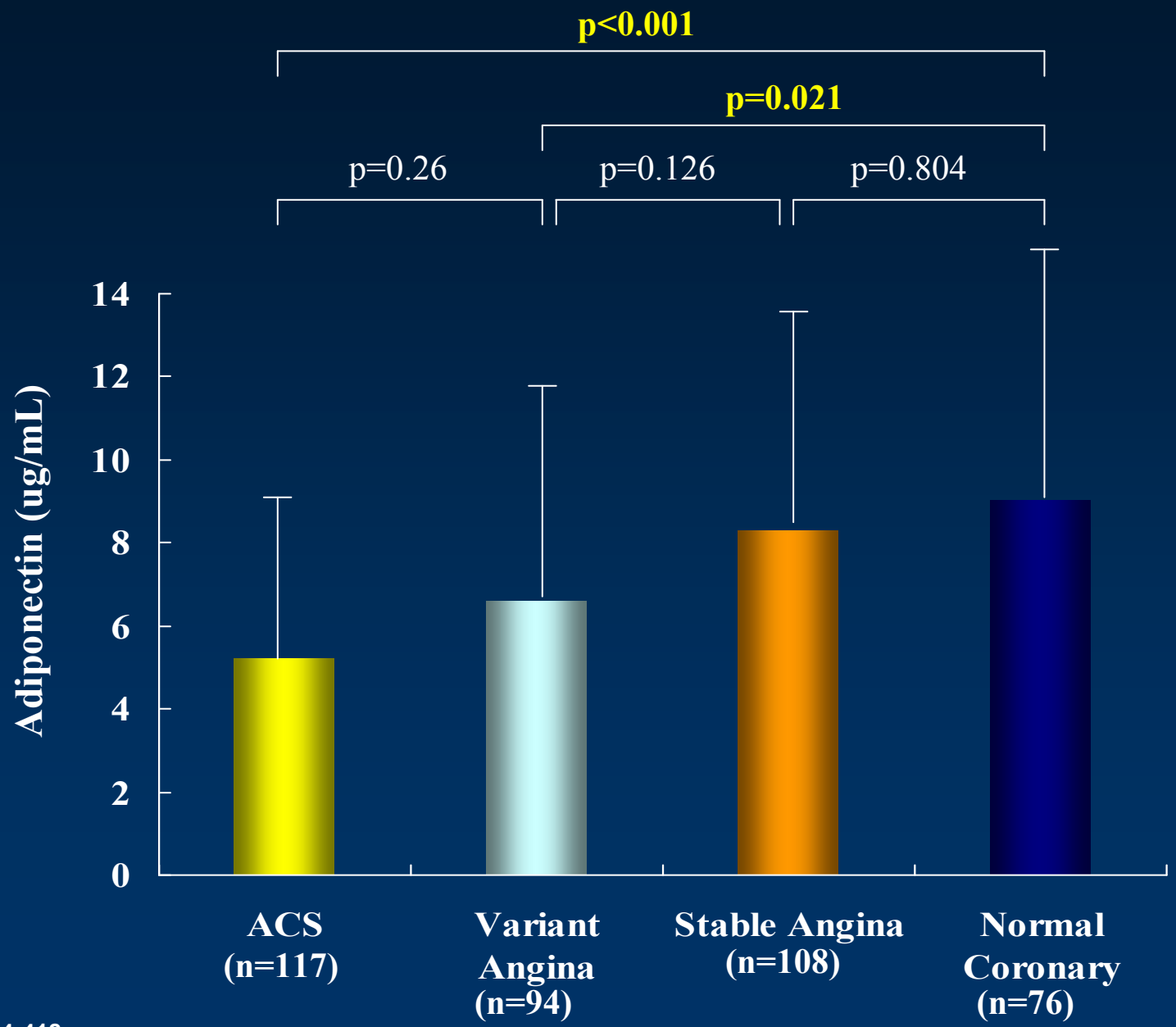
Hong SJ, Park CG et al Blood Pressure 2004; 13:236-42

Correlation of Plasma Adiponectin Concentration With Other Various Parameters

	Pearson correlation coefficient	p Value
Age (yrs)	**0.069**	**NS**
Total cholesterol (mg/dl)	**- 0.008**	**NS**
HDL-cholesterol (mg/dl)	0.243	**< 0.001**
Triglyceride (mg/dl)	- 0.224	**< 0.001**
LDL-cholesterol (mg/dl)	**- 0.016**	**NS**
Lipoprotein(a) (mg/dl)	**0.026**	**NS**
Uric acid (mg/dl)	- 0.208	**< 0.001**
CRP (mg/L)	- 0.241	**< 0.001**
Fasting blood sugar (mg/dl)	- 0.188	**0.006**
HbA1c (%)	- 0.181	**0.011**
Body mass index (kg/m^2)	**- 0.070**	**NS**

Hong SJ, Park CG et al Blood Pressure 2004; 13:236-42

Decreased Adiponectin in Variant Angina and ACS



Hong SJ, Park CG. Circ J 2006; 70:414-418

Logistic Regression Analysis for Variant Angina

Parameters	Multivariate		
	p Value	OR	95% CI
Age (yrs)	**0.019**	**0.967**	**0.940-0.995**
Women	–	–	–
Adiponectin (μ g/mL)	**0.005**	**0.724**	**0.660-0.793**
Diabetes mellitus	**NS**	**2.397**	**0.936-6.140**
Hypertension	**NS**	**1.450**	**0.783-2.683**
Smoking	**0.022**	**2.033**	**1.110-3.725**
Hyperlipidemia	**NS**	**1.160**	**0.438-3.071**
CRP (mg/L)	**NS**	**0.980**	**0.911-1.053**
FBS (mg/dl)	**NS**	**0.994**	**0.986-1.001**
Total cholesterol (mg/dl)	–	–	–
HDL cholesterol (mg/dl)	**NS**	**1.016**	**0.991-1.042**
Triglyceride (mg/dl)	–	–	–
LDL cholesterol (mg/dl)	–	–	–
Lipoprotein(a) (mg/dl)	–	–	–
Uric acid (mg/mL)	–	–	–
Body mass index (kg/m^2)	–	–	–

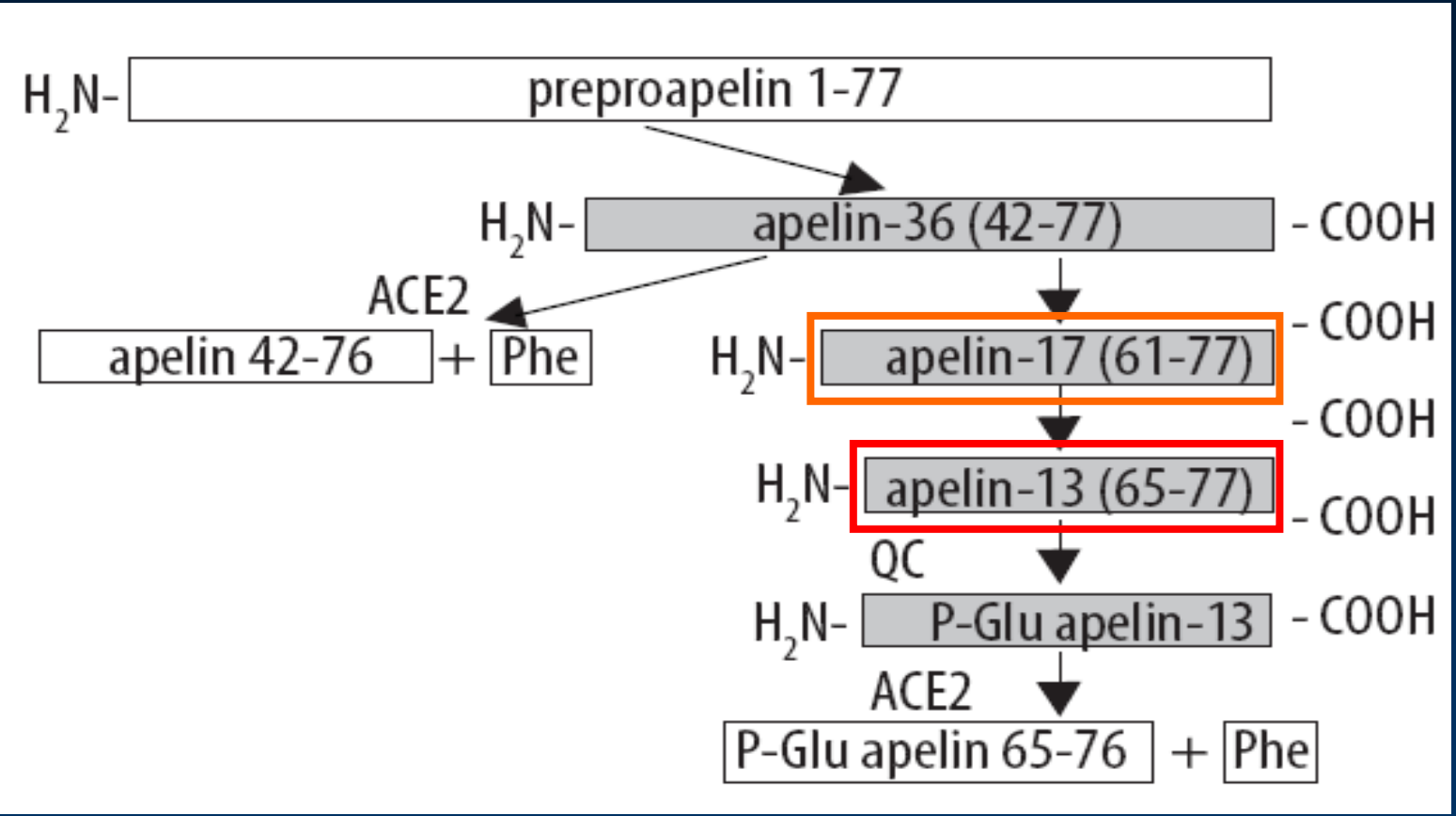
Hong SJ, Park CG. Circ J 2006; 70:414-418

Apelin

Apelin

- In 1993, O'Dowd and coworkers cloned a gene displaying considerable sequence similarity with the angiotensin receptor type 1 (AT-1) gene, despite high sequence homology to AT-1, did not bind angiotensin II.
- In 1998, Tatemoto isolated a 36-amino-acid peptide which was named apelin (from APJ endogenous ligand) in bovine stomach homogenates
- Apelin immunoreactivity are expressed in the central nervous system and in various peripheral tissues, including the heart, lung, and mammary gland

Synthesis and metabolism of apelin peptides.



Biologically active peptides are marked in gray.

QC – glutaminyl cyclase, ACE2 – angiotensin-converting enzyme-2,

P-Glu –pyroglutamyl residue, Phe – phenylalanine

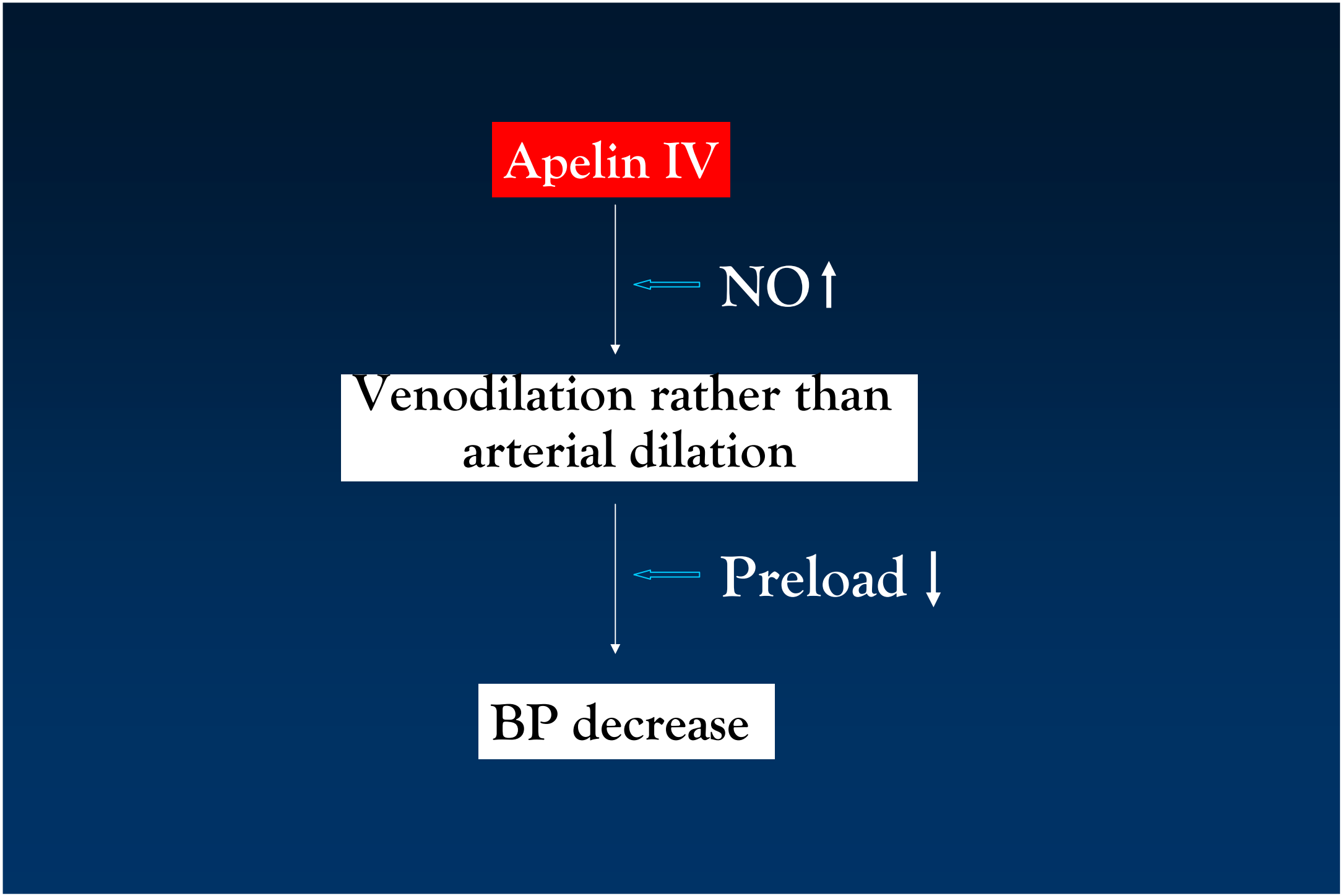
CARDIOVASCULAR EFFECTS of APELIN

- Effects on BP and vascular tone
- Angiogenesis
- Myocardial contractility
- Effect of myocardial overload, hypertrophy

Apelin

Effects on blood pressure and vascular tone

- *In vivo* studies revealed that apelin is a very potent venodilator
  - more efficacious than Ca2+-antagonists, hydralazine, isoprenaline, or nitroglycerin.
- Apelin could reduce BP predominantly by dilating peripheral veins and reducing preload rather than by dilating arterioles and reducing peripheral resistance.
- The hypotensive effect of apelin is mediated by endothelium- derived NO.
- Apelin increases plasma concentration of NO metabolites, nitrites+nitrates.


Apelin IV
NO↑
Venodilation rather than arterial dilation
Preload ↓
BP decrease

Apelin

Angiogenesis

- Apelin is abundantly expressed in the endothelium of embryonic vessels.
- APJ expression is upregulated during formation of new vessels and down-regulated after vessel stabilization.
- Apelin-13 potently stimulates the proliferation of cultured human umbilical vein endothelial cells

Myocardial contractility

- Apelin significantly increase in contractility similar to that of the potent inotropic mediators endothelin-1 and adrenomedullin.
- Apelin that it does not induce myocardial hypertrophy, distinguishes it from other mediators which exert chronic positive inotropic effect.

Effect of myocardial overload, hypertrophy

- Plasma apelin concentration is increased in patients with early stages of heart failure (NYHA class I and II)
- Whereas in those with severe disease (NYHA class III and IV) it decreases to a level similar to that in healthy individuals.

Myocardial apelin synthesis is up-regulated in early stages of heart failure,

Possibly in an attempt to improve myocardial contractility

Visfatin

Visfatin (pre–B-cell colony-enhancing factor)

- A putative adipokine predominantly produced in visceral fat that mimics the effects of insulin

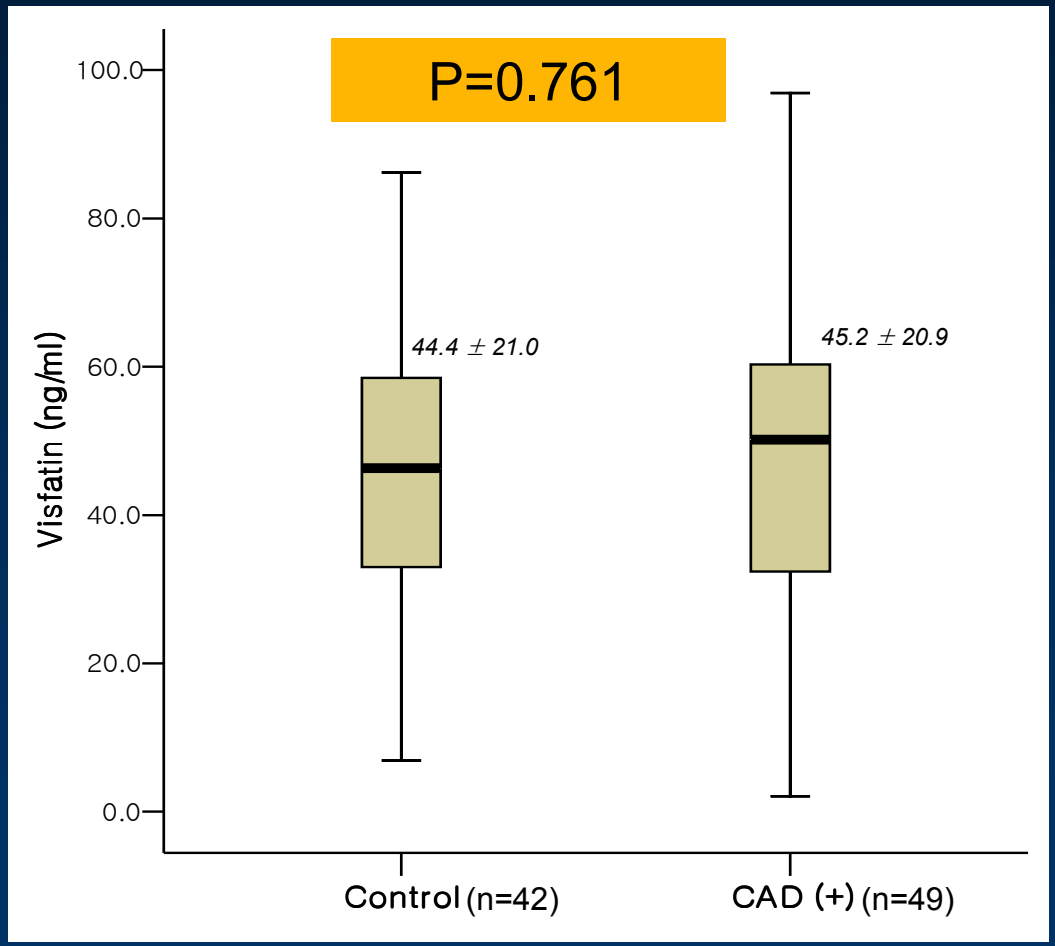
However, recent study failed to detect any difference in visfatin gene expression between visceral and subcutaneous fat in humans and were also unable to find any correlations between visceral fat mass and plasma visfatin concentrations

Diabetes 2005; 54 : 2911–2916

- [illegible] independent of obesity in nondiabetic healthy Korean women

Korea Univer. Diabetes Res Clin Pract. 2007 Sep 26

Comparison of Visfatin between CHD and Control



Park CG, Kim EJ. submitted at J Endocrinology 2007

Adipose Fatty Acid Binding Protein (A-FABP)

Adipose Fatty Acid Binding Protein (A-FABP)

- A-FABPs **is expressed in adipocytes and macrophages**.
- A-FABPs are involved in the formation of atherosclerosis predominantly through the direct modification of macrophage cholesterol trafficking and inflammatory responses.
- A-FABPs also exert a dramatic impact on obesity, dyslipidemia, insulin resistance, type 2 diabetes and fatty liver disease.

Clin Chem. 2006;52:405-413

Lipocalin family

- Lipocalin-2
- Retinol Binding Protein-4 (RBP4)

Lipocalin-2

- ✓ Associated with obesity and insulin resistance
- ✓ Positively correlated with body mass index (BMI), hyperTG, hyperglycemia, and insulin resistance, but negatively correlated with HDL cholesterol

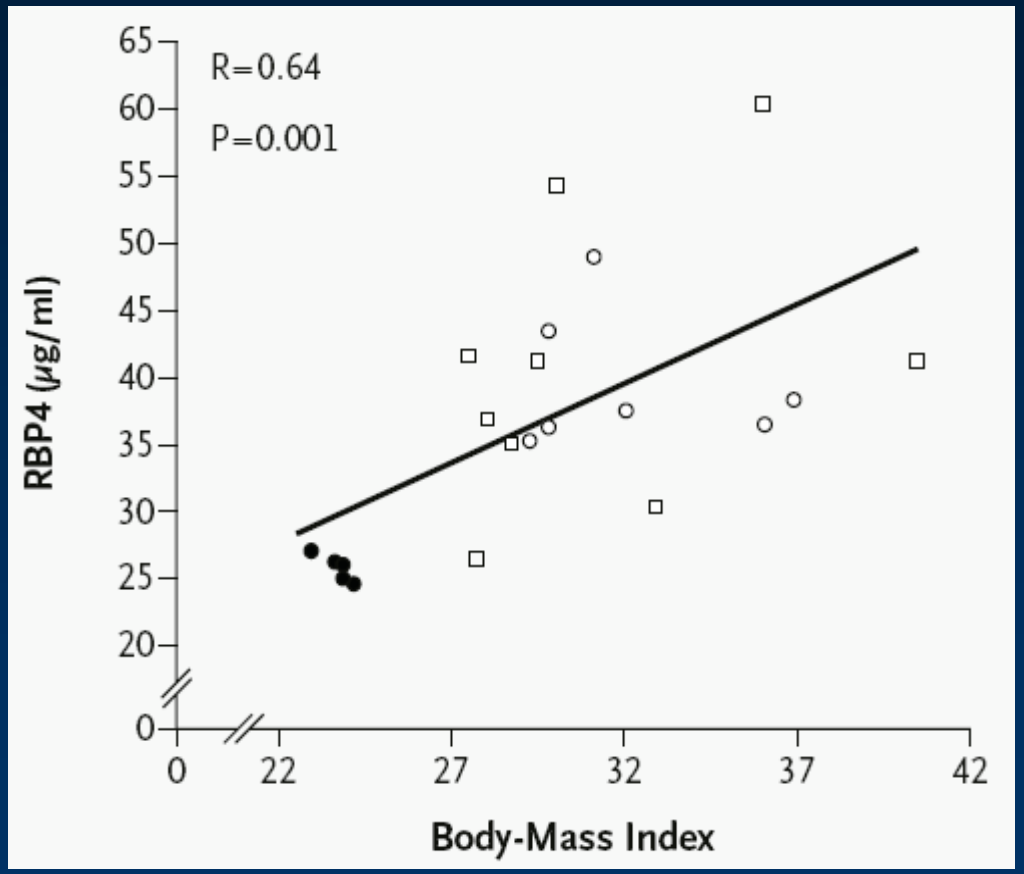
Clinical chemistry 2007;53:34-41.

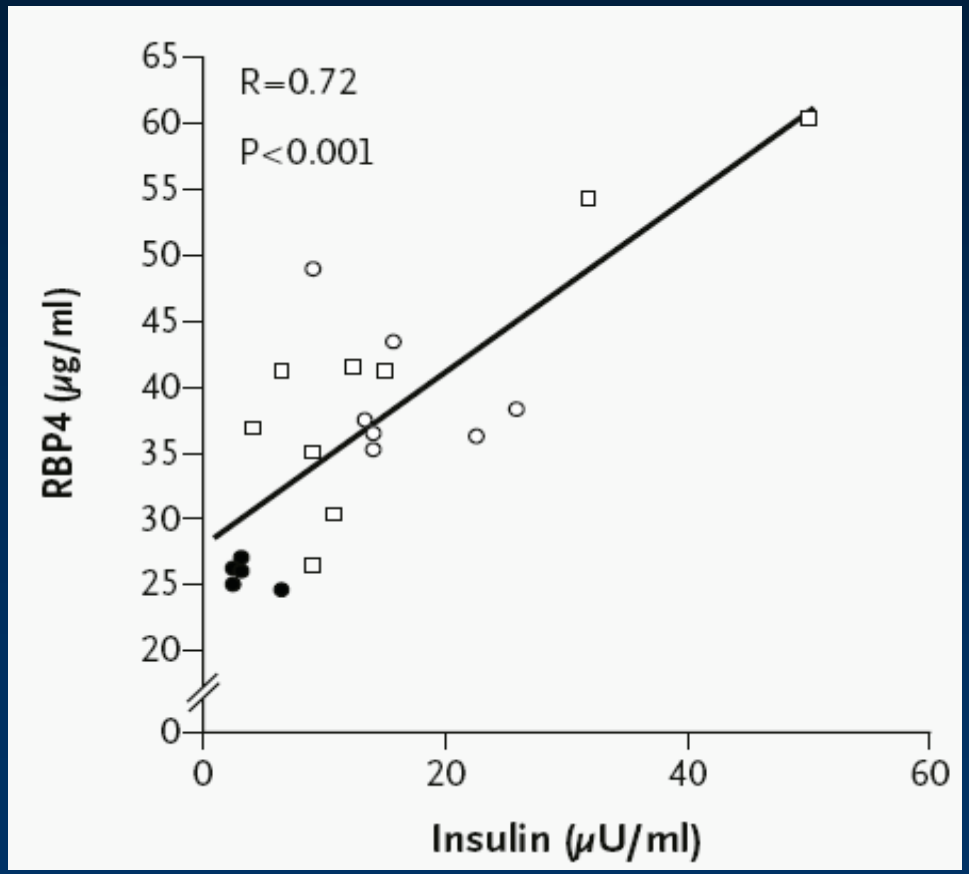
Retinol Binding Protein-4 (RBP4)

- Serum RBP4 levels are elevated in insulin-resistant mice and humans with obesity and type 2 diabetes.
- RBP4 levels are normalized by rosiglitazone, an insulin-sensitizing drug.
- Transgenic overexpression of human RBP4 or injection of recombinant RBP4 in normal mice causes insulin resistance.
- Conversely, genetic deletion of RBP4 enhances insulin sensitivity.

Yang Q et al. Nature 2005;436:356-362

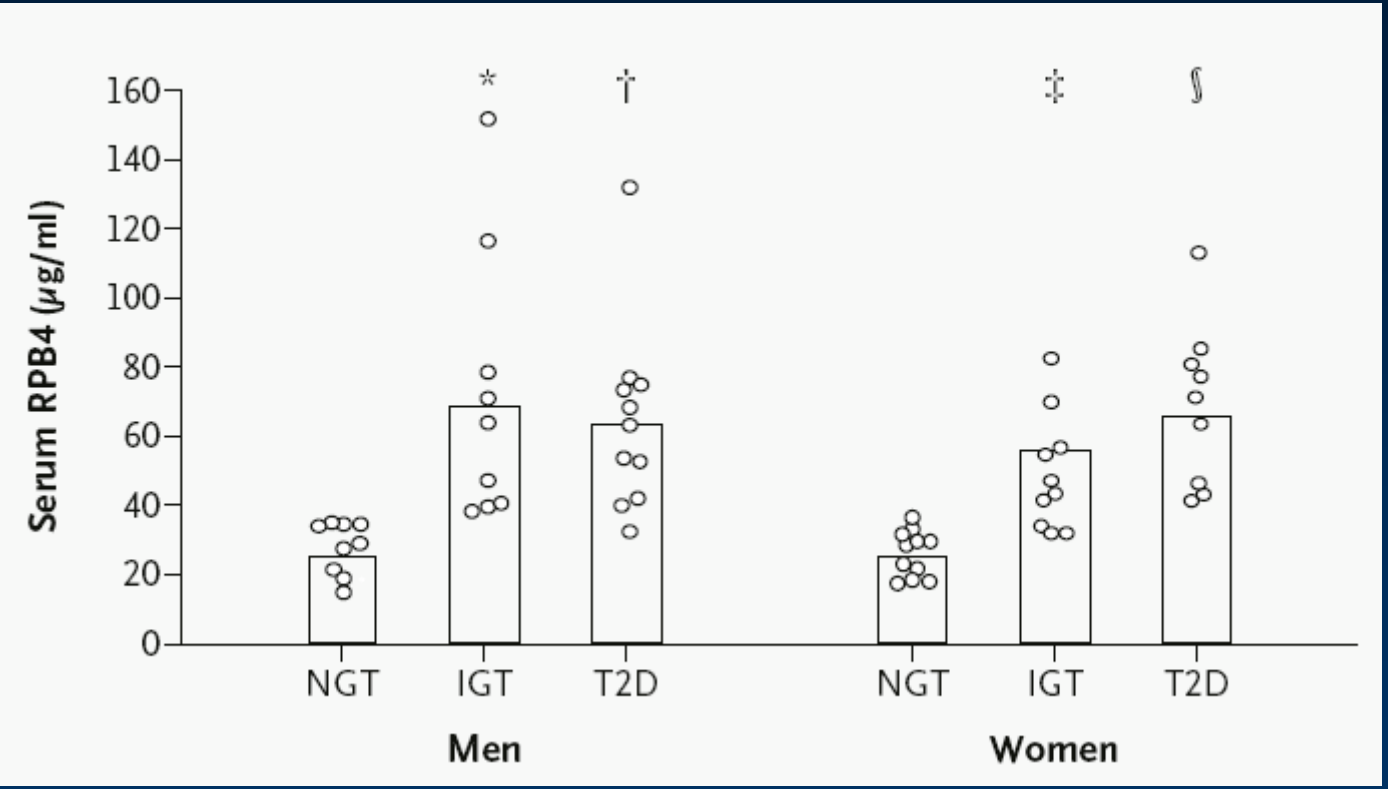
Relationship of Serum RBP4 Levels with Body-Mass Index and Fasting Plasma Insulin Levels





Graham TE et al. N Engl J Med 2006;354:2552-63

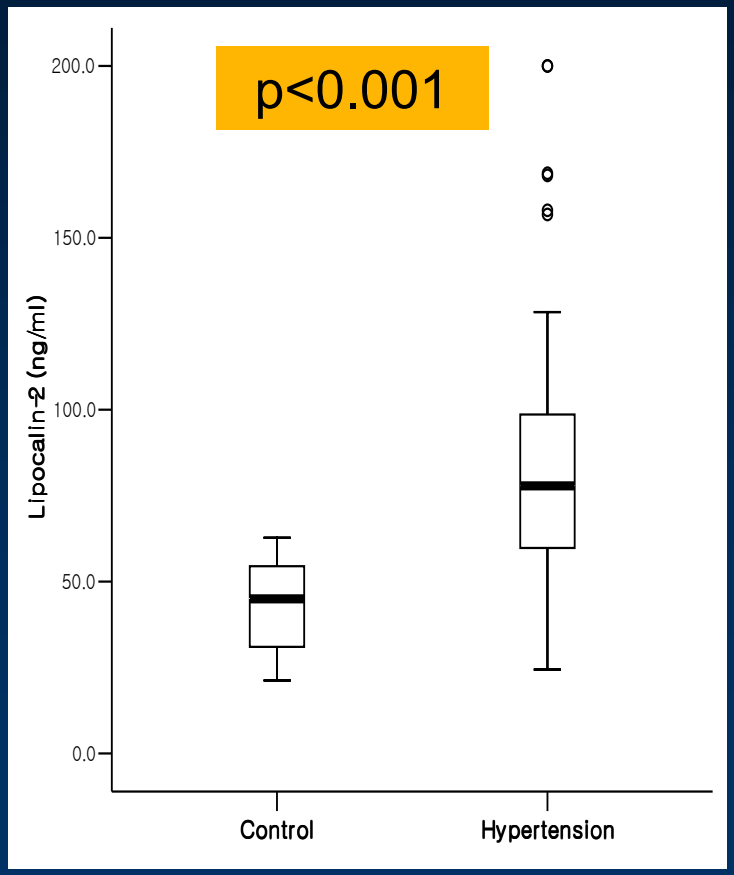
Serum RBP4 Levels and Insulin Sensitivity

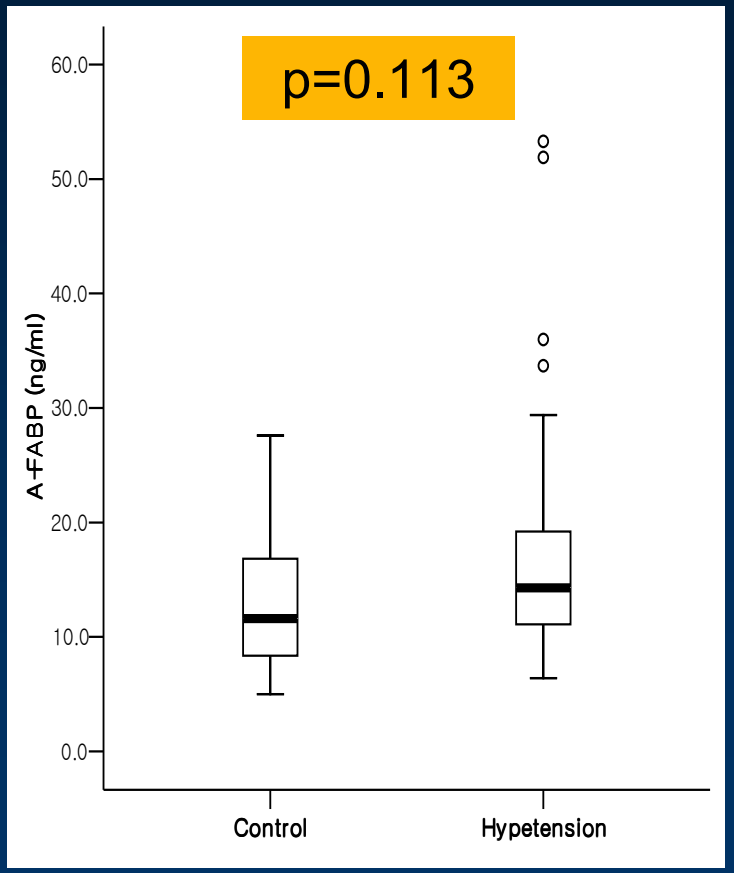


NGT; Normal Glucose Tolerance
IGT; Newly Diagnosed Impaired Glucose Tolerance
T2D; Type 2 Diabetes

Graham TE et al. N Engl J Med 2006;354:2552-63

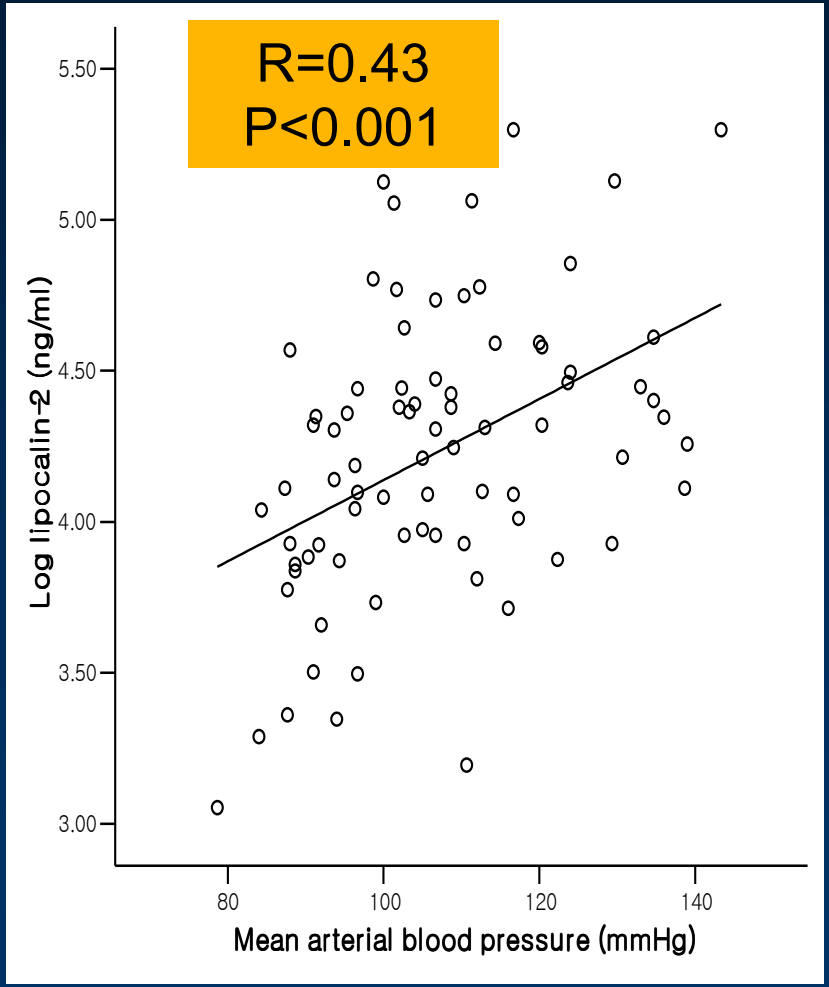
Comparison of Lipocalin-2 & A-FABP Between Normotensive and Hypertensive Group





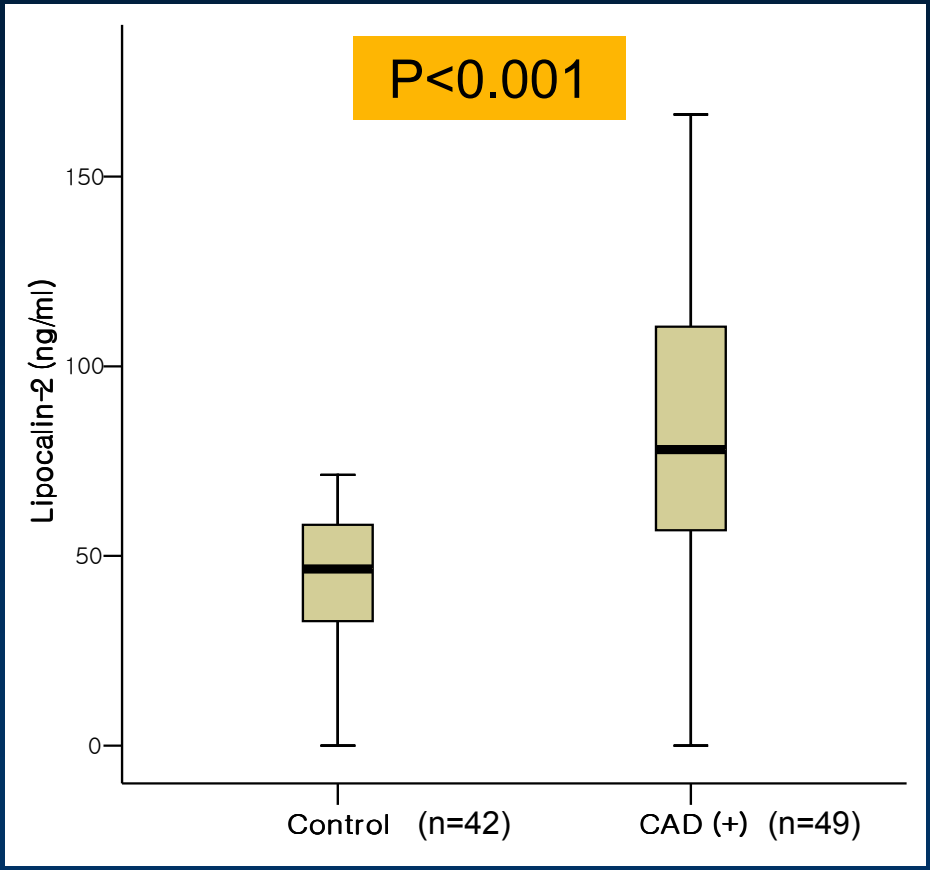
Park CG, Kim EJ. submitted at J Hypertension 2007

Correlation Between log lipocalin-2 levels and Mean Arterial Pressure



Park CG, Kim EJ. submitted at J Hypertension 2007

Lipocalin-2 in Coronary Artery Diseases



Multivariate Logistic Regression Analysis with CAD

	B	S.E.	Wald	*P*	Exp(B)
SBP	0.091	0.059	2.364	0.124	1.095
HOMA-IR	5.293	1.965	7.253	**0.007**	199.025
Lipocalin-2	0.045	0.023	3.835	**0.050**	1.046
Constant	-28.635	11.737	5.952	0.015	0.000

Park CG, Kim EJ. submitted at J Endocrinology 2007

Effects of Exercise Training on Metabolic Values and Serum Adipokine Levels in Newly Diagnosed IGF or Type 2 DM

Measurement	Marginal Response (N=14)†			Improved Insulin Sensitivity (N=26)‡		
	Baseline	Post–Exercise Training	Wilcoxon P Value	Baseline	Post–Exercise Training	Wilcoxon P Value
GDR (mg/kg/min)§	4.1±2.0	4.7±2.1	0.005	3.4±1.0	7.1±1.7¶	<0.001
BMI	31.2±3.7	30.5±3.4	0.04	30.3±2.3	29.4±0.7	<0.001
Waist-to-hip ratio	1.29±0.14	1.25±0.10	0.005	1.22±0.10	1.18±0.11	<0.001
Fasting glucose (mg/dl)‖	108±13	106±10	0.18	106±7	99±6	0.007
2-hr OGTT glucose (mg/dl)‖	218±9	205±17	0.08	194±27	176.4±31	0.02
Fasting insulin (μU/ml)**	64.1±30.6	39.6±18.4	0.002	74.3±46.2	44.4±29.2	<0.001
RBP4 (μg/ml)	55.5±19.7	65.9±22.8	0.002	69.8±26.5	40.1±10.5¶	<0.001
Leptin (pmol/liter)	19.9±12.4	17.8±17.3	0.30	18.8±11.9	17.9±10.5	0.41
Adiponectin (μg/ml)	3.6±1.7	5.8±2.0	<0.001	3.4±1.0	6.1±1.7	<0.001
Interleukin-6 (pg/ml)	6.5±3.4	5.9±3.1	0.07	4.8±2.4	5.1±2.4	0.08
C-reactive protein (μg/dl)	0.7±0.4	0.4±0.3	0.005	0.5±0.2	0.2±0.1¶	<0.001
Free fatty acids (mmol/liter)	0.49±0.24	0.44±0.17	0.17	0.58±0.17	0.52±0.25	0.07
HDL cholesterol (mg/dl)††	34±5	39±6	0.004	36±4	42±4	<0.001

Graham TE et al. N Engl J Med 2006;354:2552-63

Summary and Conclusion

- Adipokines could be used as markers for the prediction of cardiovascular diseases.
- Adiponectin has a protective effect for IR anf CVD.
- RBP4, lipocalin-2, and A-FABP can contribute to obesity and insulin resistance.
- Increased physical activity, a prudent diet, and modest weight loss improve adipokine status and insulin sensitivity, and substantially decrease risk of type 2 diabetes and CVD.


Thank you for your attention !