XIV International CME Course
under the aegis of ERA-EDTA, ISN and KDIGO
SCIENTIFIC PROGRAM
Thursday, September 17, 2015

Adipokines as CV risk-factors in CKD

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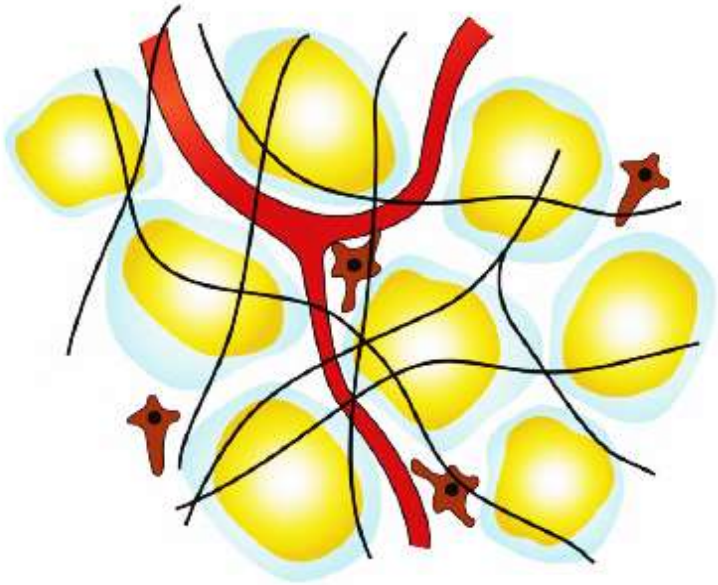
I have no relevant financial relationship to disclose

Andrzej Wiecek

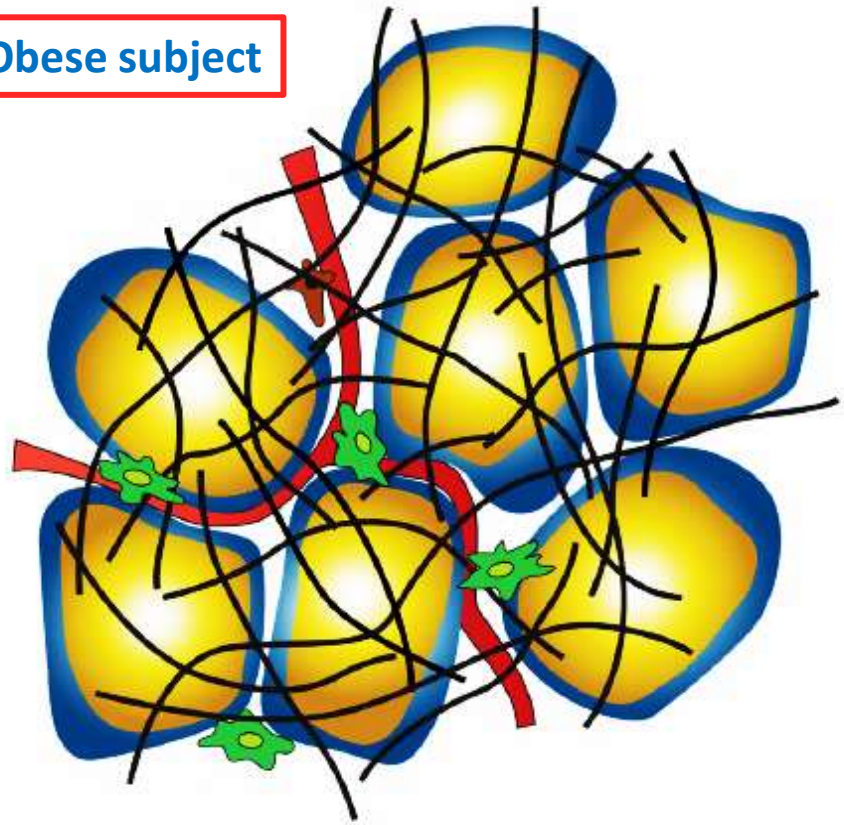
White adipose tissue in the lean *vs* obese state

Adipocytes are shown with yellow triglyceride droplets and blue cytoplasm. In the lean state the light blue cytoplasm represent a state of normoxia, whereas the dark blue in the obese state represents a hypoxic state. Pre adipocytes are shown in brown, macrophages in green, blood vessels/endothelial cells in red, and the extracellular matrix as black.

Lean subject



Obese subject



Halberg N. et al. Endocrinol. Metab. Clin. North. Am., 2008; 37: 753

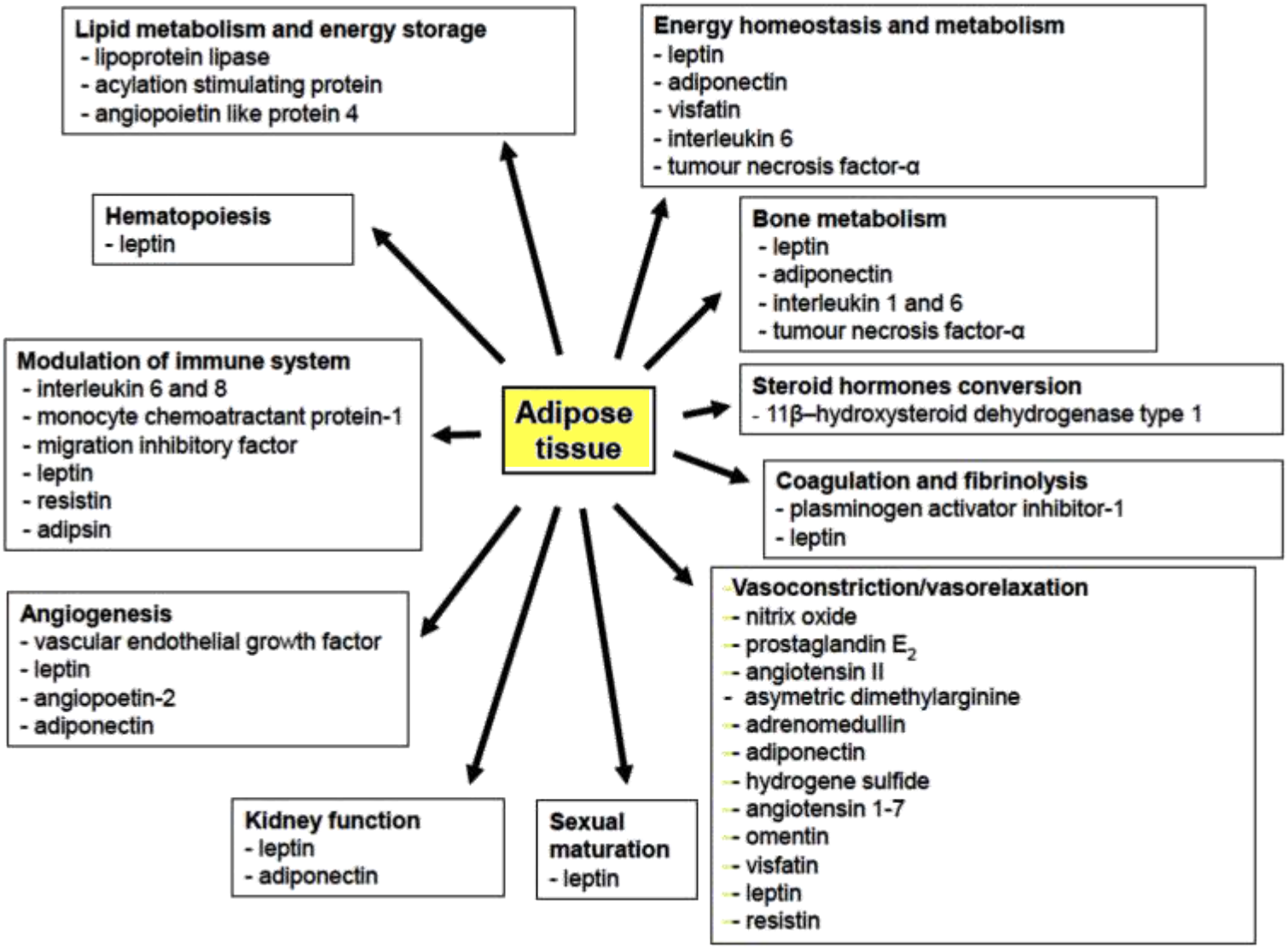
Adipokines (hormones, cytokines, chemokines, growth factors and complement factors) produced by adipose tissue (42)

- Adiponectin
- Leptin
- Visfatin
- Apelin
- Resistin
- Vaspin
- Agouti protein
- Acylation stimulating protein (ASP)
- Omentin
- Chemerin
- Zinc-α2 glycoprotein (ZAG)
- Retinol binding protein-4 (RBP-4)
- Autotaksin
- Lipokain-2
- Asymmetric dimetylarginin (ADMA)
- Nitric oxide (NO)
- Hydrogen peroxide (H_2O_2)
- Hydrogen sulfide (H_2S)
- Atrial natriuretic peptide (ANP)
- Neuropeptide Y (NPY)
- Renin
- Macrophage migration inhibitory factor (MIF)
- Prostaglandins E_2, F_2 (PGE_2, PGF_2)
- Endocannabinoids: 2-arachidonoyl glycerol (2-AG), arachidonylethanolamide (anandamide)
- Colony stimulating factor-1 (CSF-1)
- Hepatocyte growth factor (HGF)
- Vascular endothelial growth factor (VEGF)
- Nerve growth factor (NGF)
- Heparin binding epidermal growth factor–like growth factor (HB-EGF)
- Osteopontin
- Insulin-like growth factor-1 (IGF-1)
- Complement factor D (adipsin)þ
- Complement factors B, C, C3, C1q
- Plasminogen activator inhibitor-1 (PAI-1)
- TNF-α
- IL-1β, 6, 8, 10
- IFN-γ–inducible protein 10 (IP-10)
- Macrophages and monocyte chemoattractant protein 1 (MCP-1)
- Adrenomedulin
- Angiotensinogen
- Serum amyloid A3
- Lipocalin-2

Adamczak M., Wiecek A.,

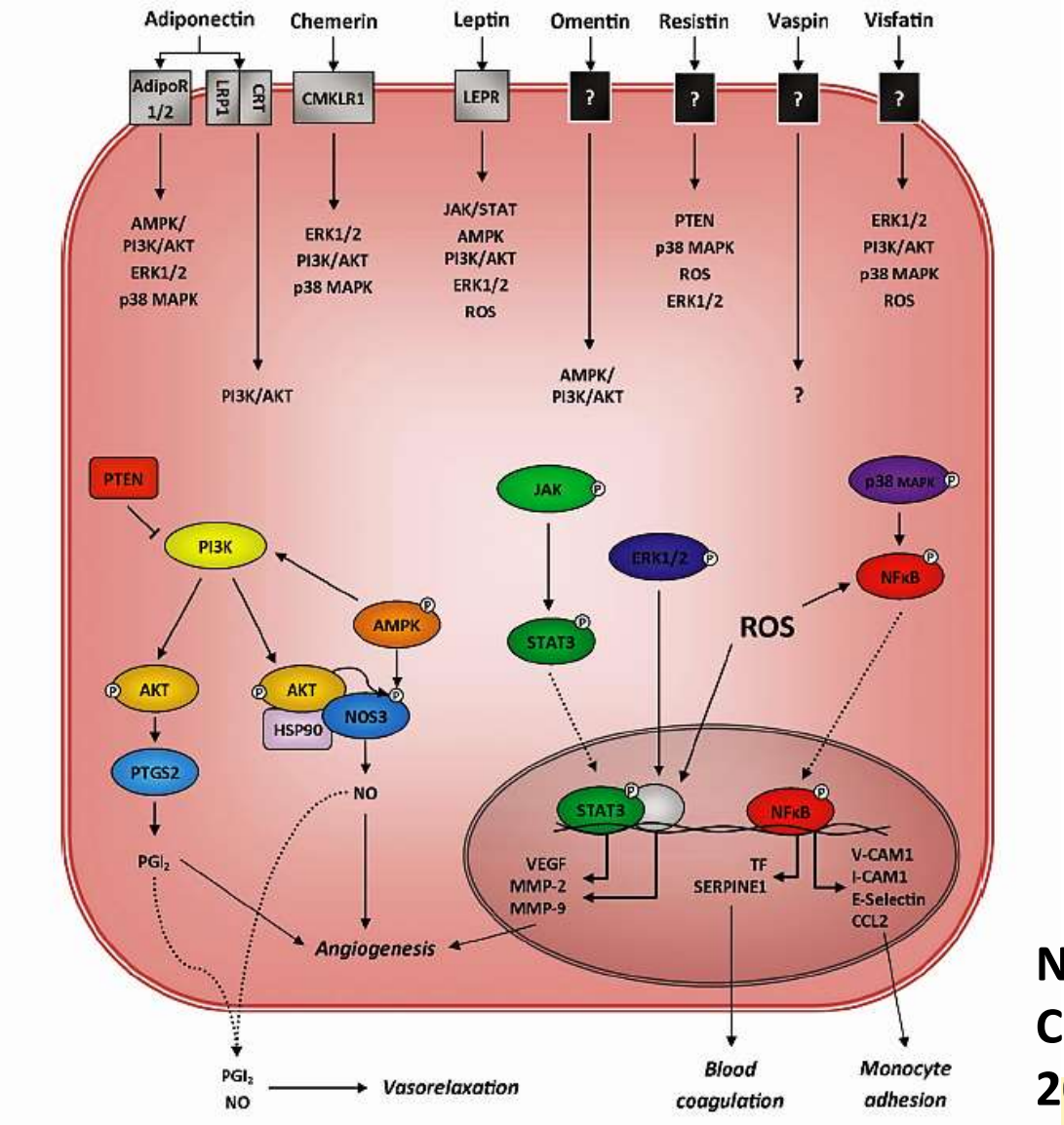
Sem. Nephrol., 2013; 33: 2-13

The major physiological functions of adipose tissue secretory products

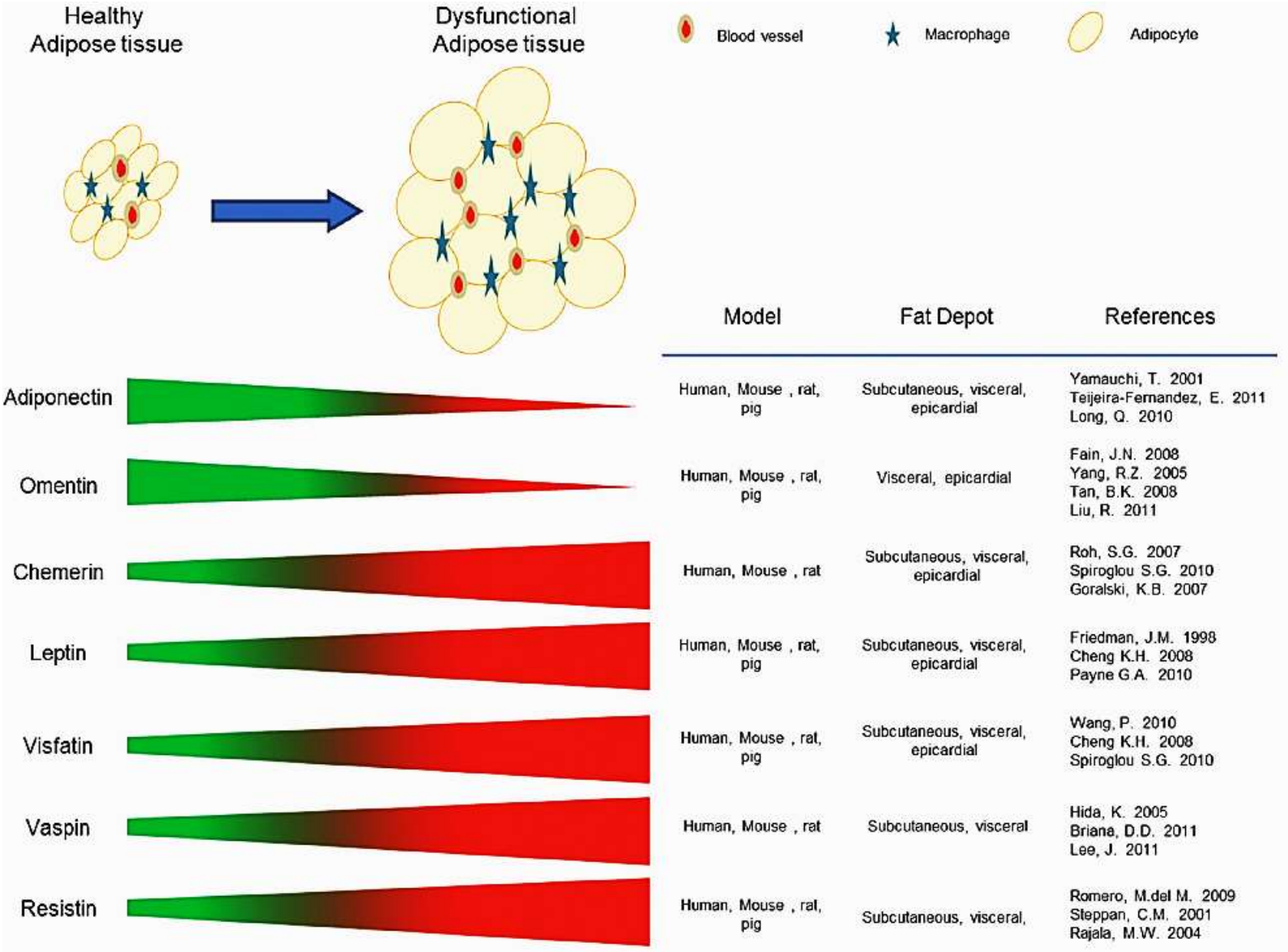


Adamczak M., Wiecek A., Sem. Nephrol., 2013, 33, 2-13

Adipokine signalling mechanisms and their effects on endothelial cell function



Northcott J.M. et al., Can. J. Physiol. Pharmacol., 2012, 90, 1029 - 1059



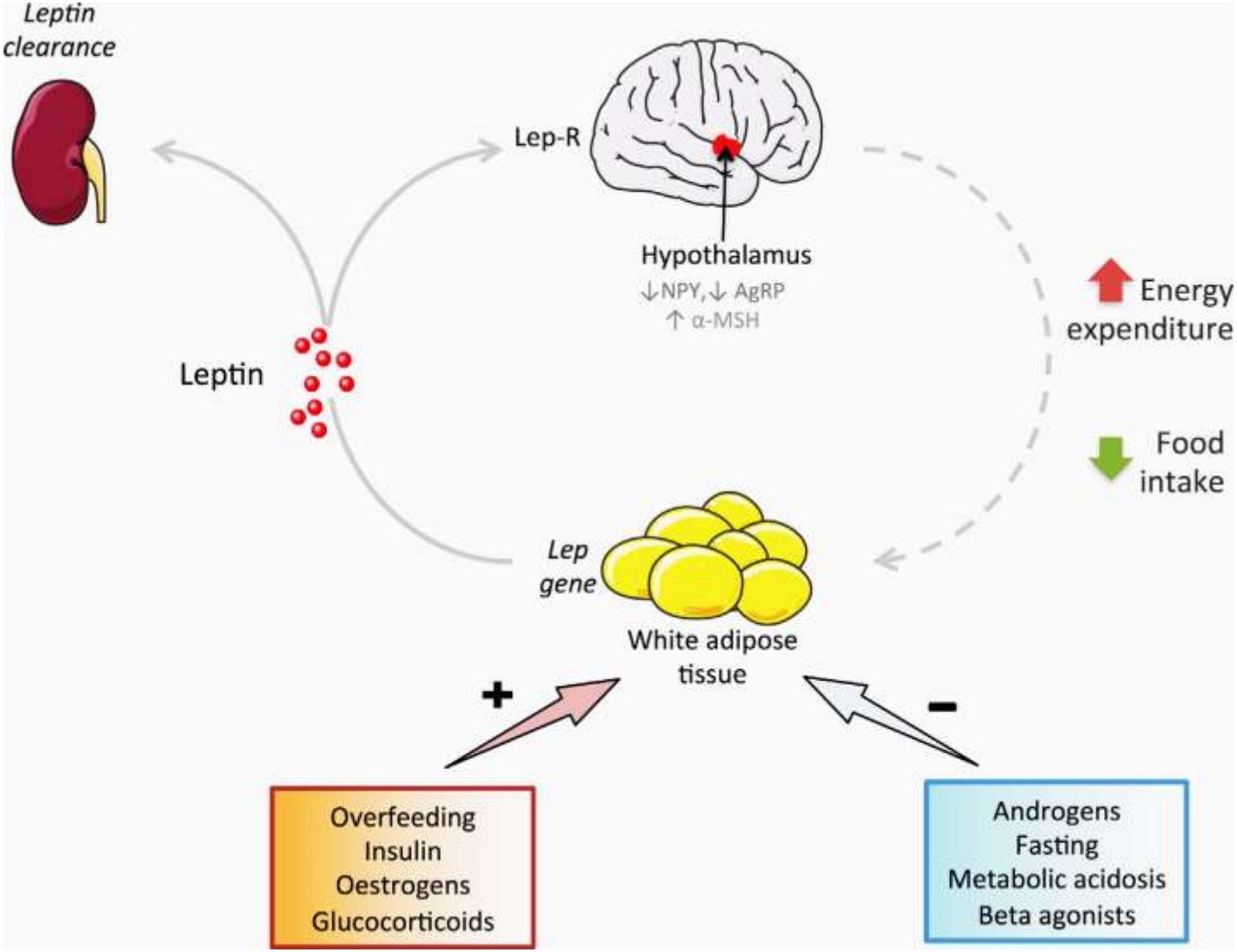
	Model	Fat Depot	References
Adiponectin	Human, Mouse , rat, pig	Subcutaneous, visceral, epicardial	Yamauchi, T. 2001 Teijeira-Fernandez, E. 2011 Long, Q. 2010
Omentin	Human, Mouse , rat, pig	Visceral, epicardial	Fain, J.N. 2008 Yang, R.Z. 2005 Tan, B.K. 2008 Liu, R. 2011
Chemerin	Human, Mouse , rat	Subcutaneous, visceral, epicardial	Roh, S.G. 2007 Spiroglou S.G. 2010 Goralski, K.B. 2007
Leptin	Human, Mouse , rat, pig	Subcutaneous, visceral, epicardial	Friedman, J.M. 1998 Cheng K.H. 2008 Payne G.A. 2010
Visfatin	Human, Mouse , rat, pig	Subcutaneous, visceral, epicardial	Wang, P. 2010 Cheng K.H. 2008 Spiroglou S.G. 2010
Vaspin	Human, Mouse , rat	Subcutaneous, visceral	Hida, K. 2005 Briana, D.D. 2011 Lee, J. 2011
Resistin	Human, Mouse , rat, pig	Subcutaneous, visceral,	Romero, M.del M. 2009 Steppan, C.M. 2001 Rajala, M.W. 2004

Northcott J.M. et al., Can. J. Physiol. Pharmacol., 2012,90, 1029 - 1059

Abnormalities in the hormones of adipose tissue in chronic kidney disease

Leptin	↑
Adiponectin	↑
Resistin	↑
Visfatin	↑

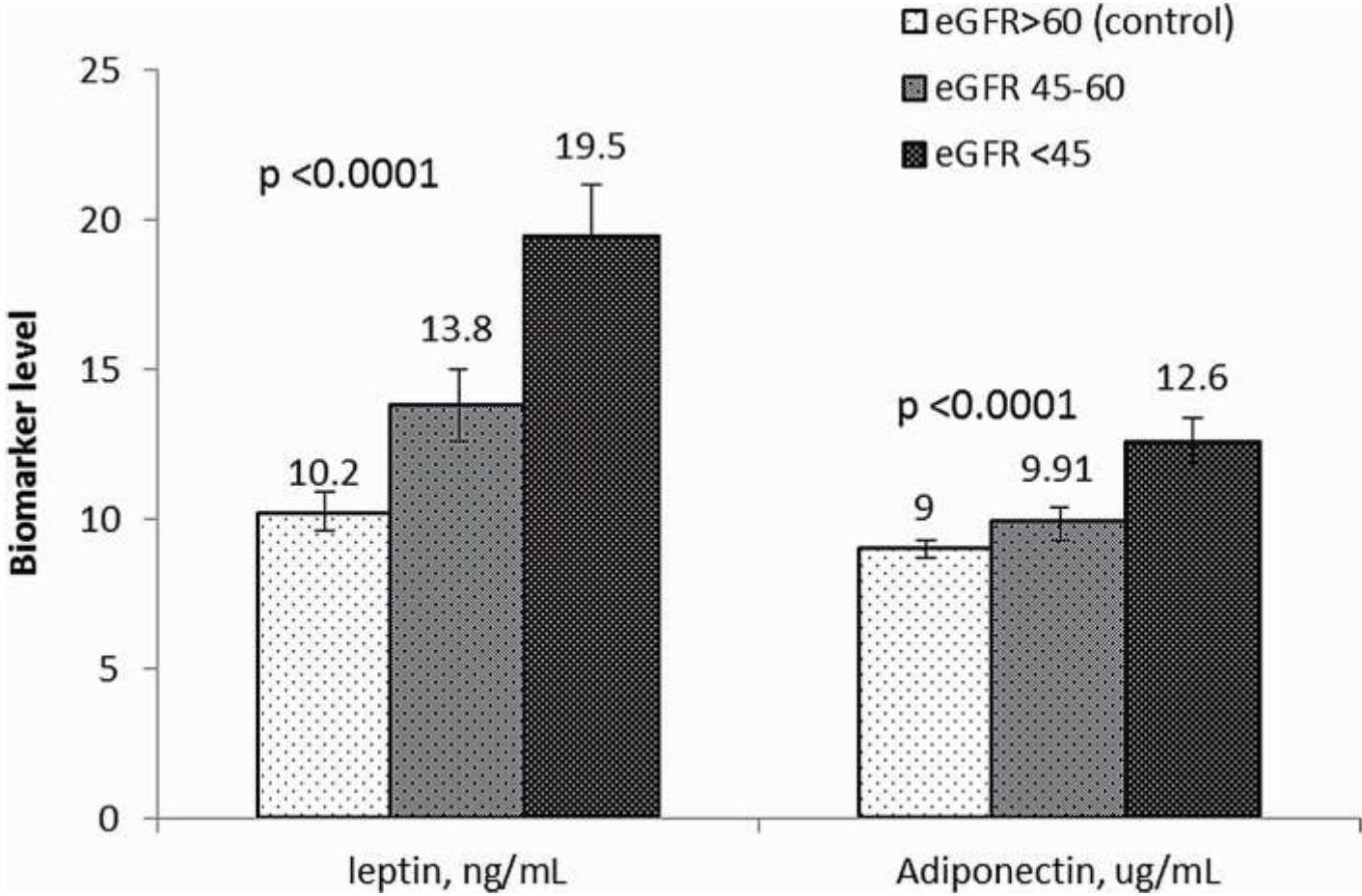
Leptin is the afferent signal of a negative feedback loop aimed at maintaining homeostatic control of white adipose tissue mass



Alix P. M. et al., Biochimie, 2014, Oct, 105C, 12-21

Adjusted mean leptin and adiponectin levels by severity of CKD defined by eGFR levels

Adjusted for age, sex, ethnicity, primary/below education, diabetes, CVD, BMI, systolic BP, current smoking, ever drinker, total and HDL cholesterol

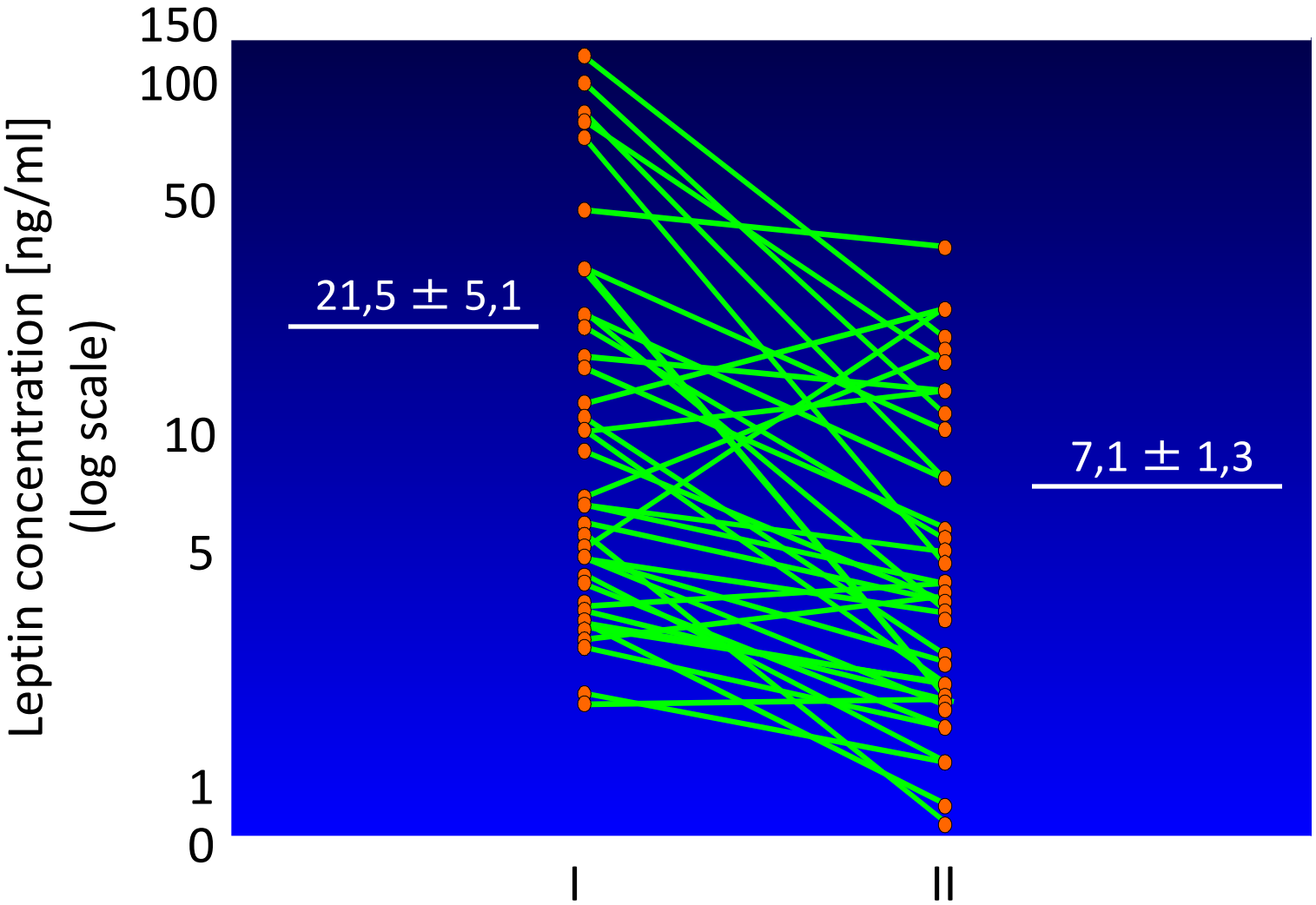


Lim C.C.et al., PLOS ONE | DOI:10.1371/journal.pone.0122009 March 20, 2015

Pathogenesis of hyperleptinaemia in patients with CKD

- Decreased renal elimination and biodegradation of leptin
- Hyperinsulinaemia
- Stimulation by cytokines (IL-1; TNF- α)

Plasma leptin levels 2-4 days after transplantation (I) and 1 day before hospital discharge (II)



Kokot F., Adamczak M., Więcek A., Nephrol. Dial. Transplant., 1998, 13, 2276

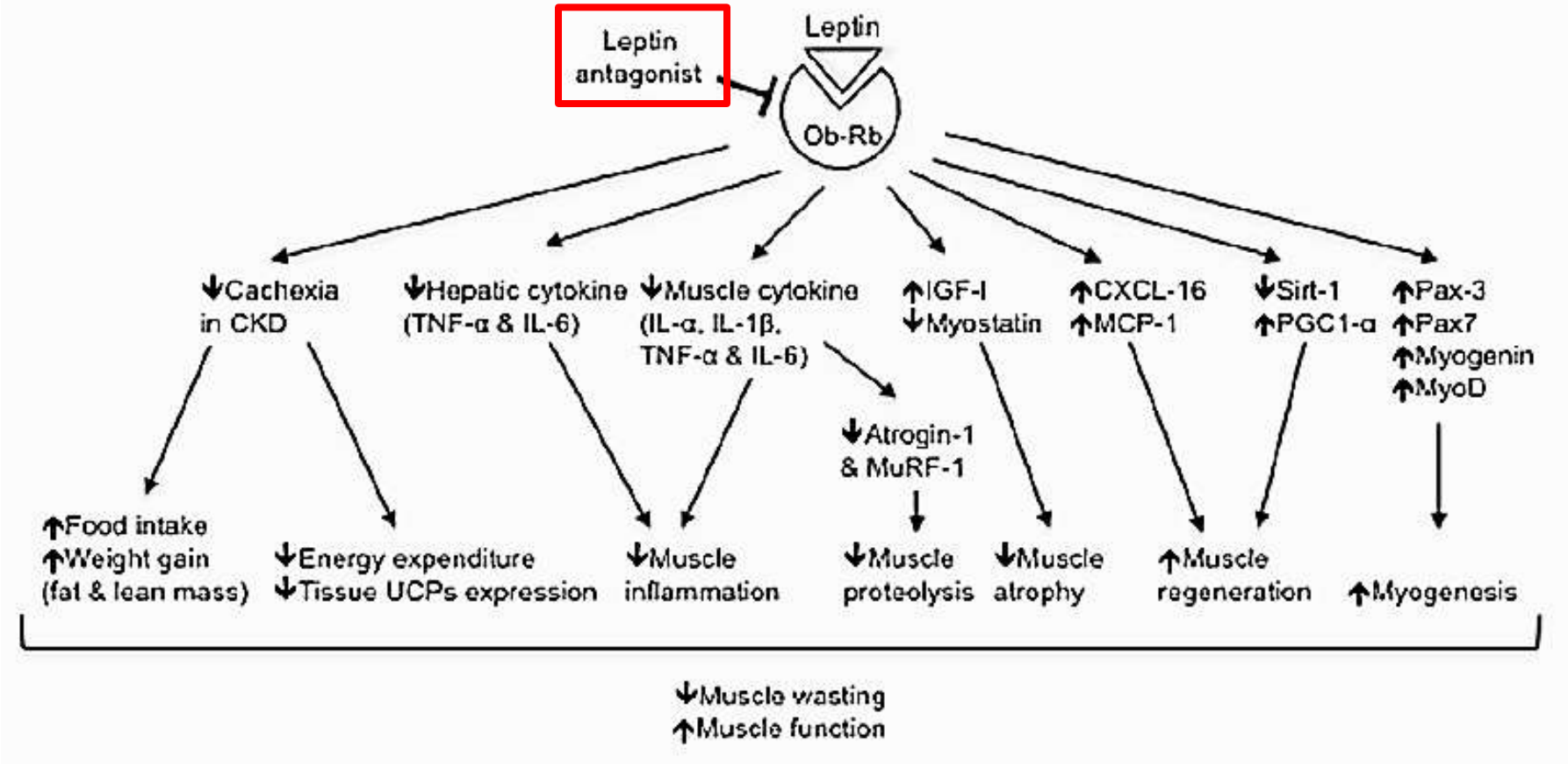
Leptin in patients with CKD

Leptin – a new uraemic toxin?

or

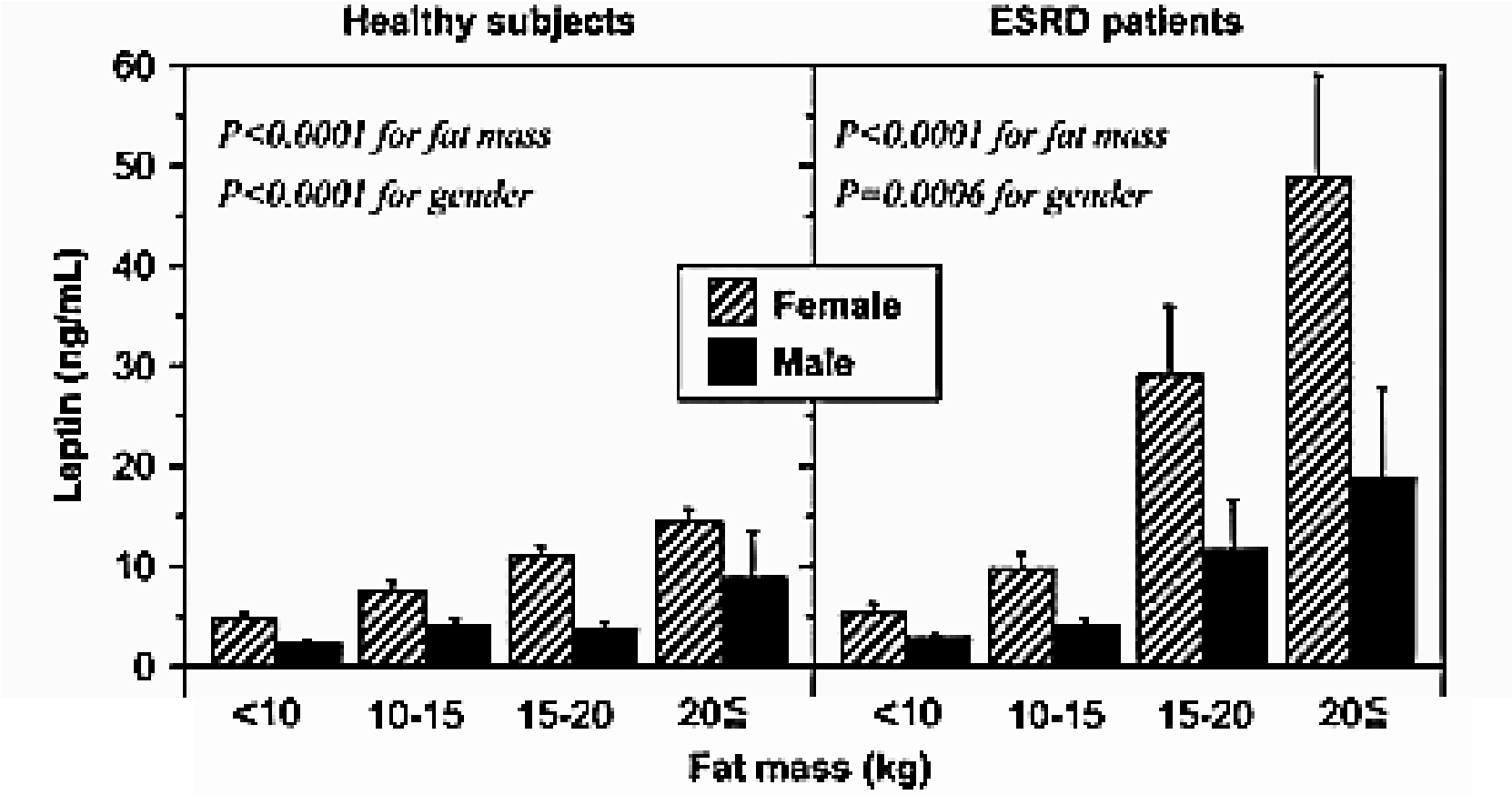
Leptin – marker of nutrition?

Beneficial effects of pegylated leptin antagonists treatment on food intake, energy expenditure and muscle wasting in CKD mice



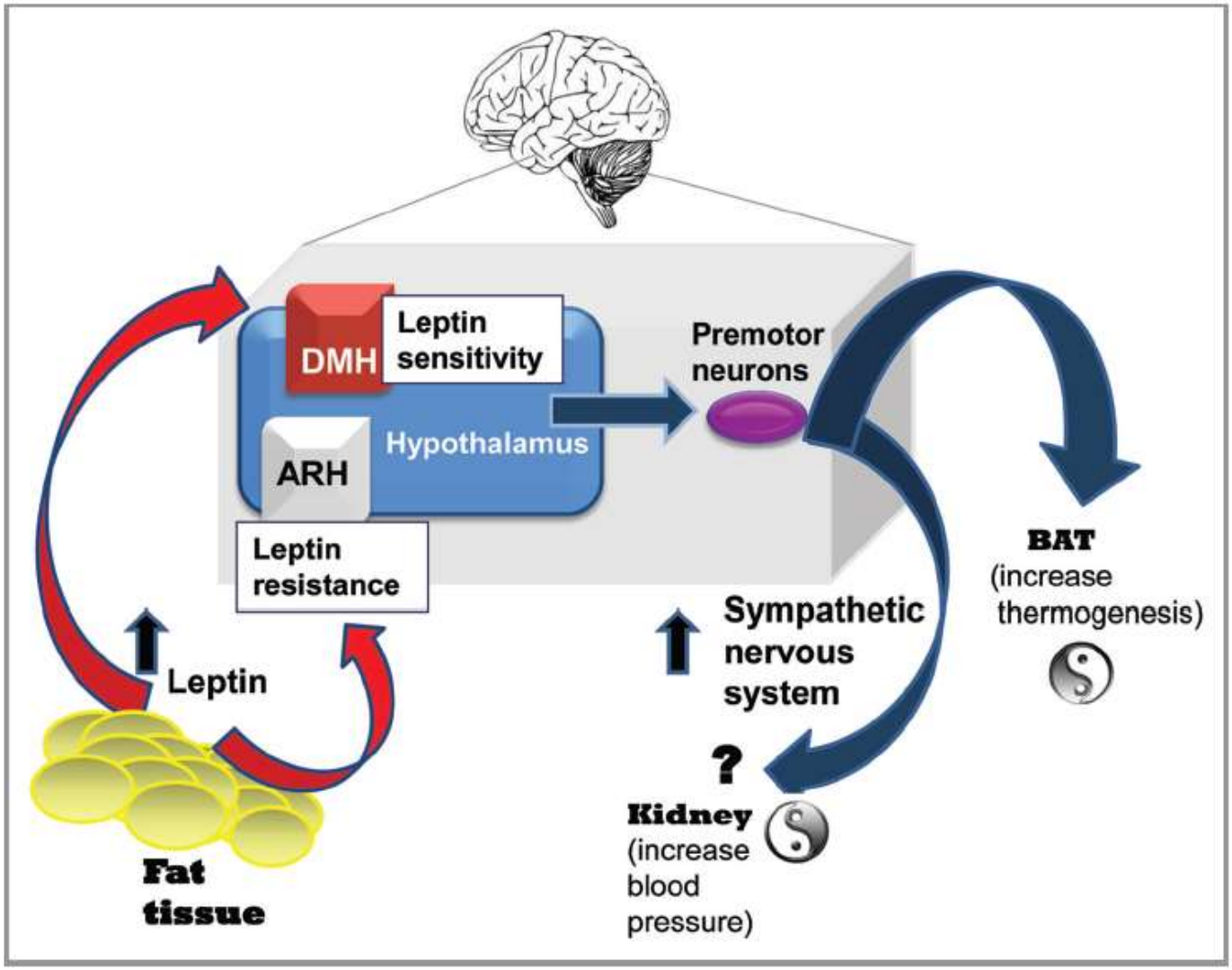
Cheung W.W. et al., J. Am. Soc. Nephrol., 2014, 25, 119–128

Relationship between body fat mass and plasma leptin concentration in healthy subjects and CKD patients



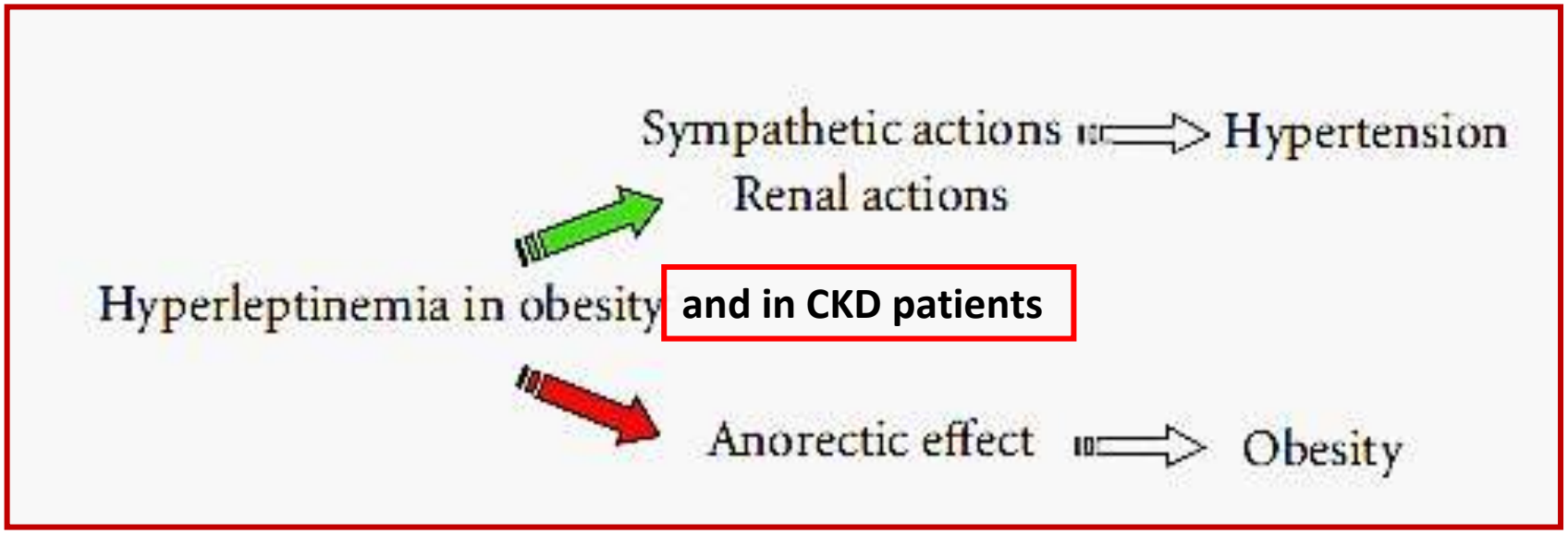
Shoji T. et al.: Metabolism 2005; 54: 330-334

Effects of hyperleptinemia in obese subjects



Simonds S. et al., Adipocyte, 2012, 1, 177-181

Role of hyperleptinemia in the pathogenesis of hypertension in obesity and in CKD patients



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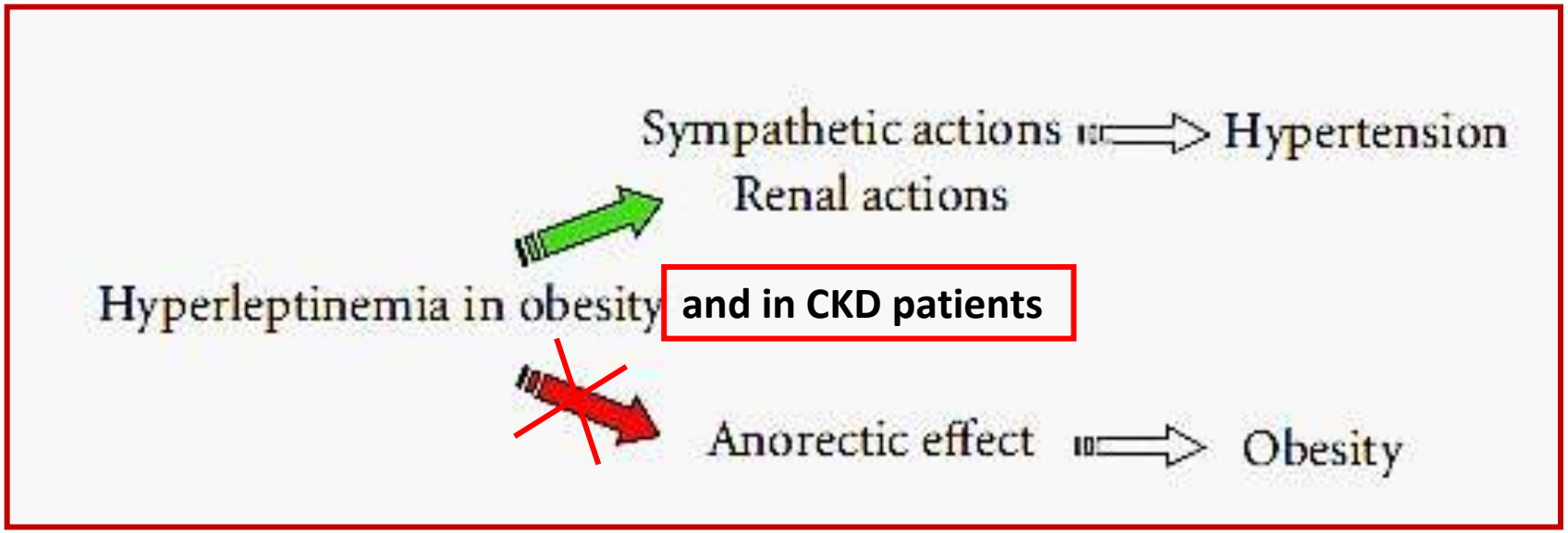
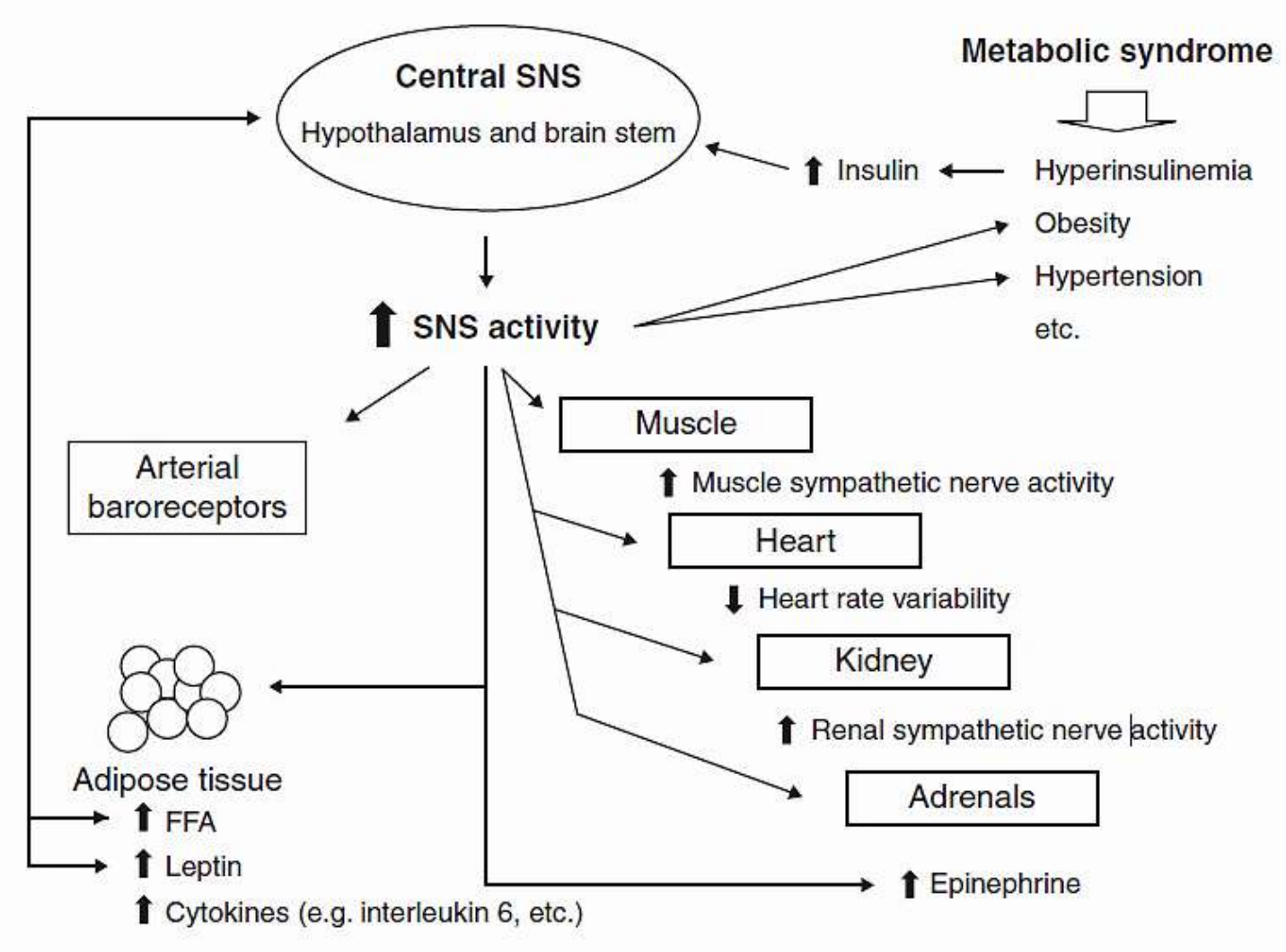
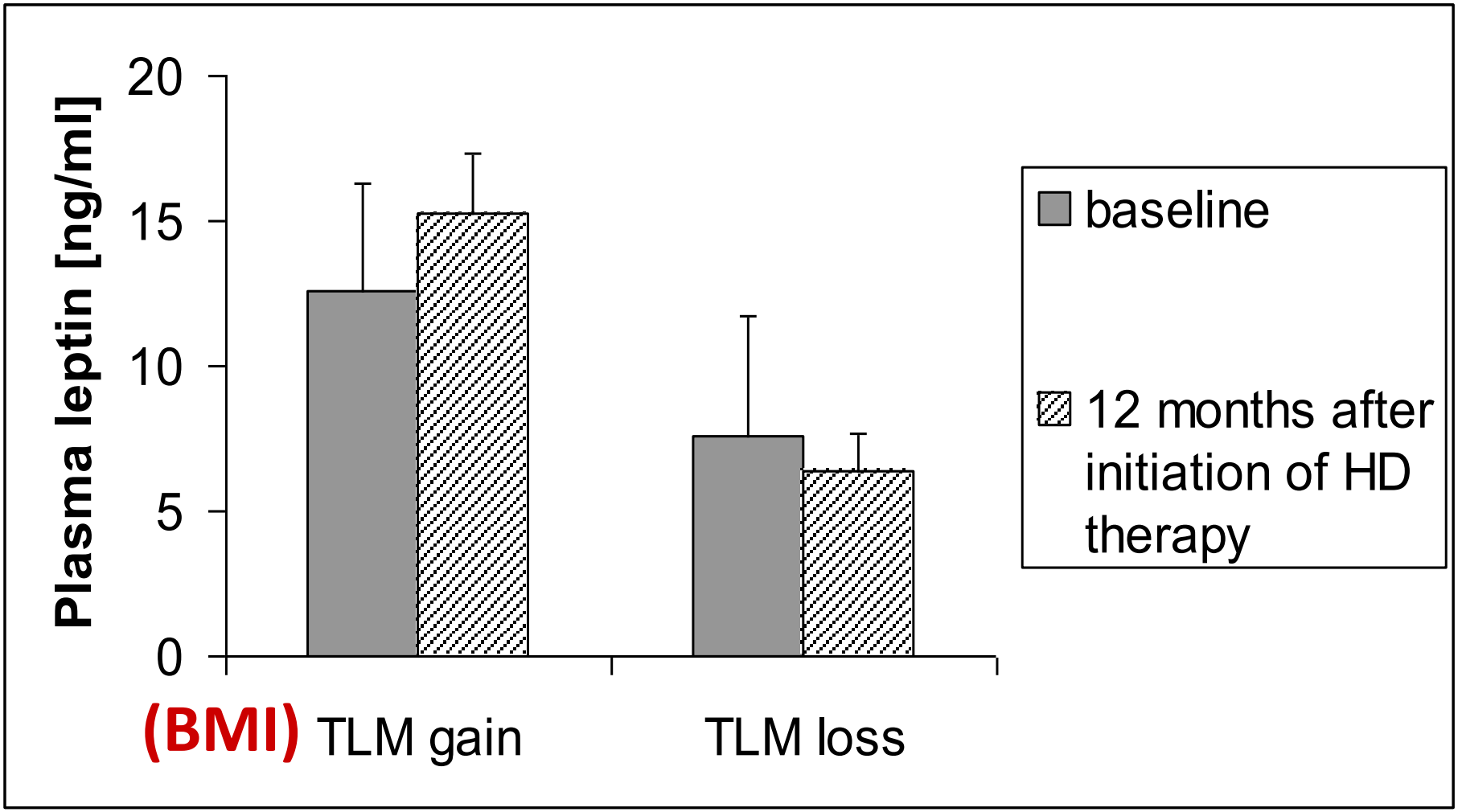


Particular metabolic and other effects of SNS activation in obese subjects and CKD patients



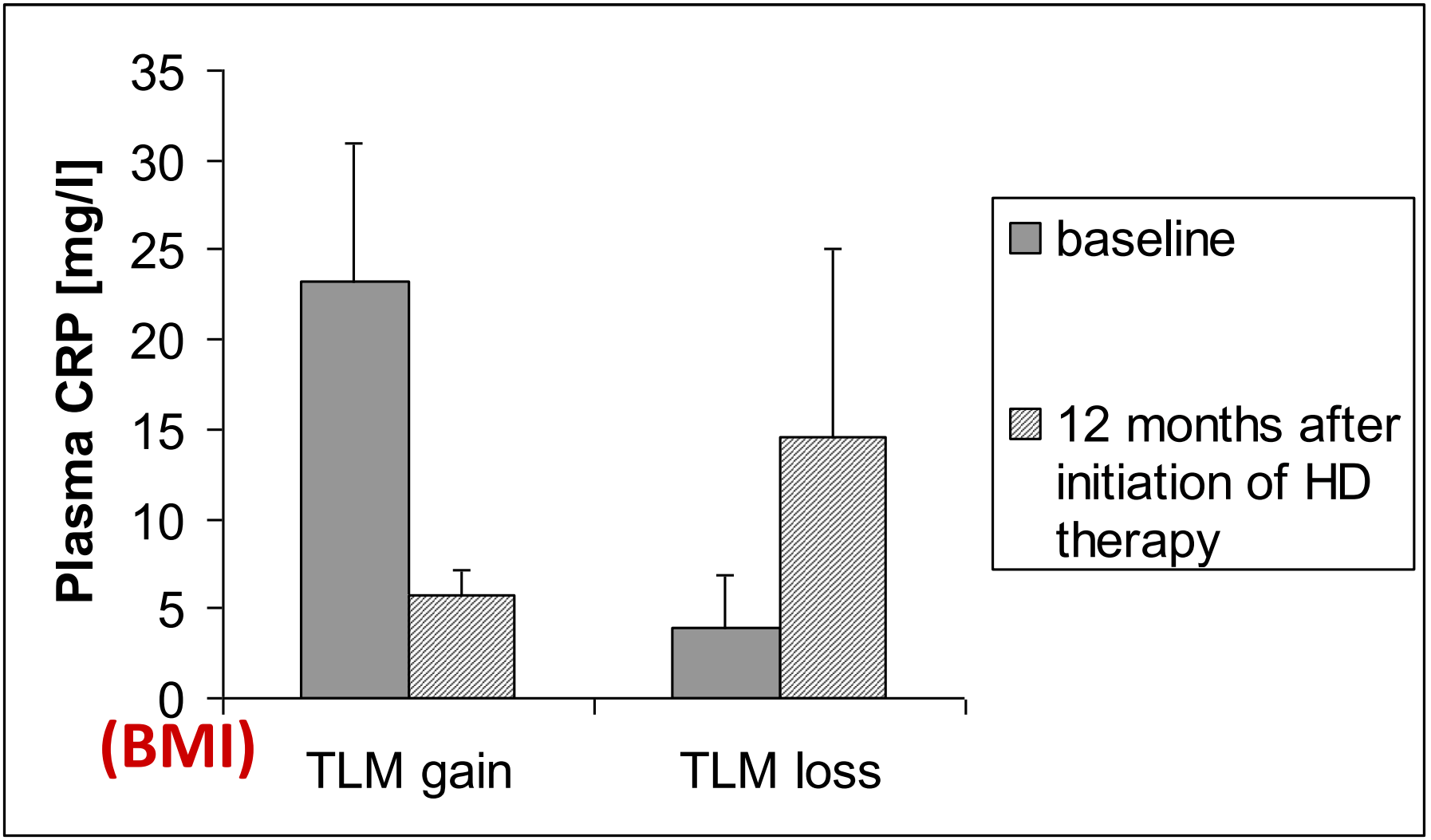
Vaneckova I. et al., J. Endocrinol., 2014, 223, R63–R78

Plasma leptin concentration in patients who gained or lost weight 12 month after initiation of HD therapy



Chudek J. Wiecek A. et al., Med. Sci. Monit., 2003, 9, CR377-CR382

Plasma leptin concentration in patients who gained or lost weight 12 month after initiation of HD therapy



Chudek J. Wiecek A. et al., Med. Sci. Monit., 2003, 9, CR377-CR382

Nephrol Dial Transplant (2005) 20: 2620–2622
doi:10.1093/ndt/gfi192
Advance Access publication 11 October 2005

Translational Nephrology

Nephrology Dialysis Transplantation

How does leptin contribute to uraemic cachexia?

Andrzej Więcek

Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia, Katowice Poland

Leptin is a marker of nutrition:

1. Postive correlation with fat tissue:

a) low BMI = low serum leptin concentation

b) caloric suplemenation increases body fat mass and median serum leptin concentration

2. Markedly elevated serum leptin concentration does not suppress appetite in uraemic patients (leptin resistance). Uraemia is characterised by relative resistance to many hormones (PTH, HGH, Insulin) and cytokines:

a) Serum leptin increses and serum CRP decreases in those HD patiens who gain weight after 12 months after initiation of HD treatment

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Leptin in CKD patients

Low Serum Leptin Predicts Mortality in Patients with Chronic Kidney Disease Stage 5

Alexandra Scholze, Dirk Rattensperger, Walter Zidek, and Martin Tepel

Abstract

SCHOLZE, ALEXANDRA, DIRK RATTENSPERGER, WALTER ZIDEK, AND MARTIN TEPEL. Low serum leptin predicts mortality in patients with chronic kidney disease stage 5. *Obesity*. 2007;15:1617–1622.

Objective: Leptin, secreted from adipose tissue, regulates food intake, energy expenditure, and immune function. It is unknown whether leptin predicts mortality in patients with centrations were above the median (all-cause mortality, $\chi^2 = 5.05$; $p = 0.02$).

Discussion: Low serum leptin concentration is an independent predictor of mortality in patients with chronic kidney disease stage 5 on hemodialysis therapy.

Key word: leptin

Scholze A. et al., Obesity, 2007, 15, 1617-1622

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Low Serum Leptin Predicts Mortality in Patients with Chronic Kidney Disease Stage 5

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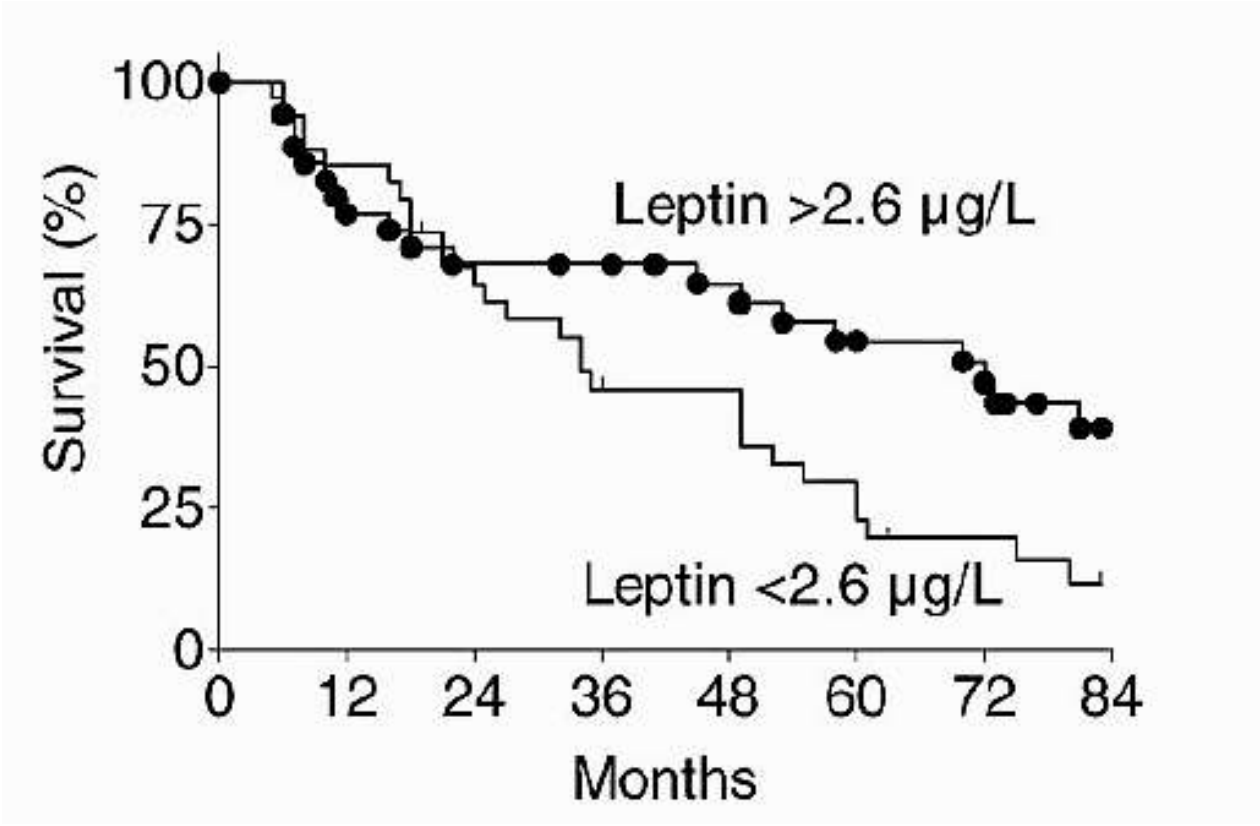
Kaplan-Meier survival curves for death in 71 patients with CKD stage 5



Survival was worse in patients with leptin concentrations below the median (2.6 g/L) than in those with leptin concentrations above the median (2.6 g/L; log rank test, 2 5.05; *p* <0.02)

Scholze A. et al., Obesity, 2007, 15, 1617-1622

Leptin in CKD patients

So, Is Leptin Good or Bad in Chronic Kidney Disease?

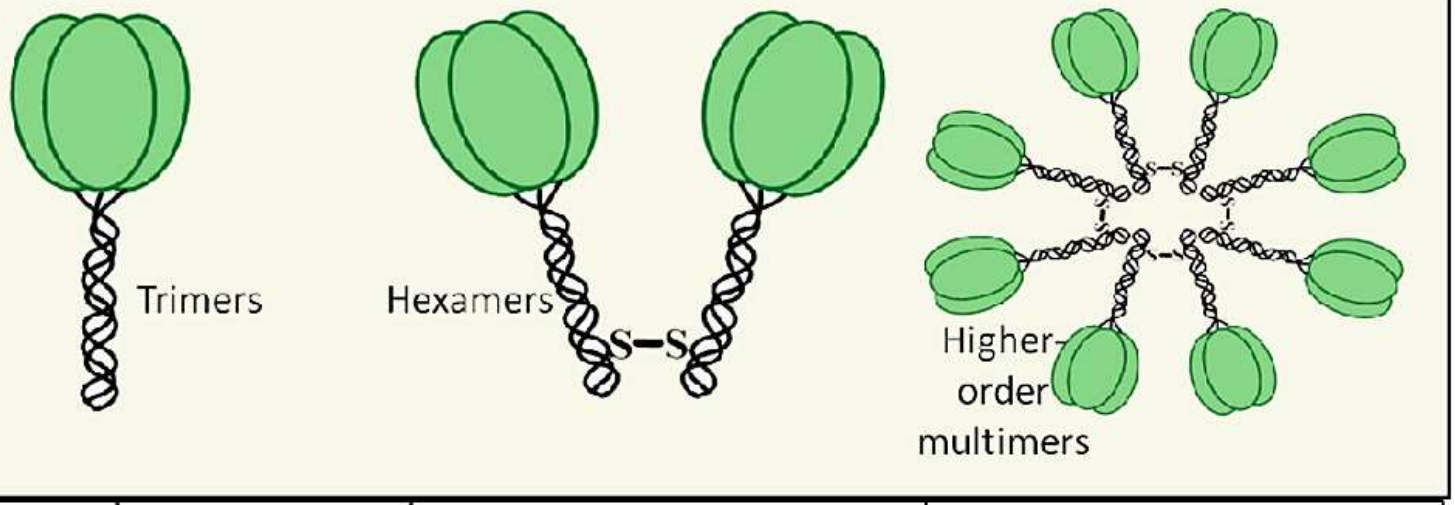
Kamyar Kalantar-Zadeh

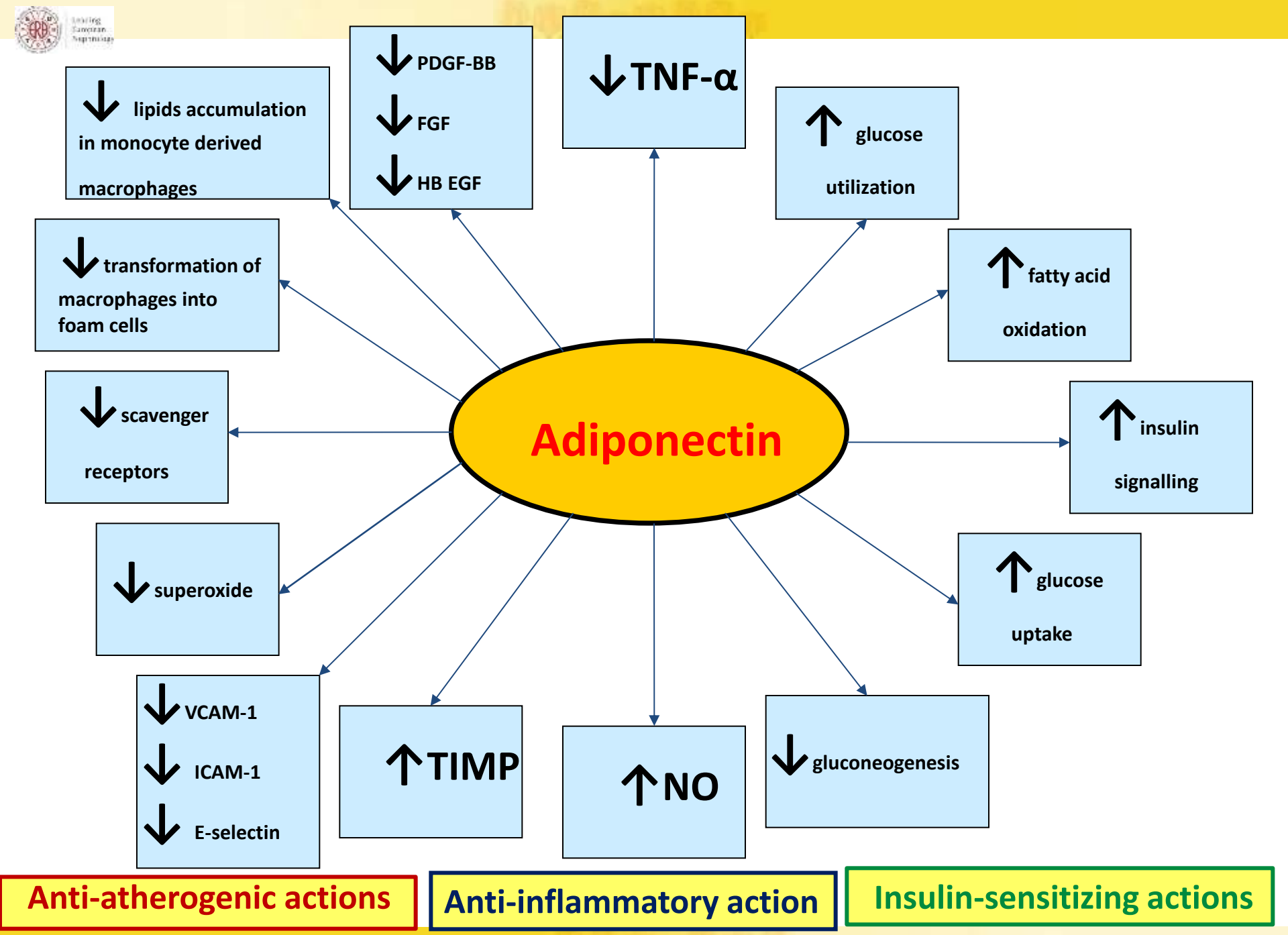
There are, increasing number of studies that suggest a paradoxically inverse association between higher serum leptin and improved markers of nutritional status and outcome in CKD

These counterintuitive constellations, together also known as "reverse epidemiology"

Obesity, 2007, 15, 1343 - 1344

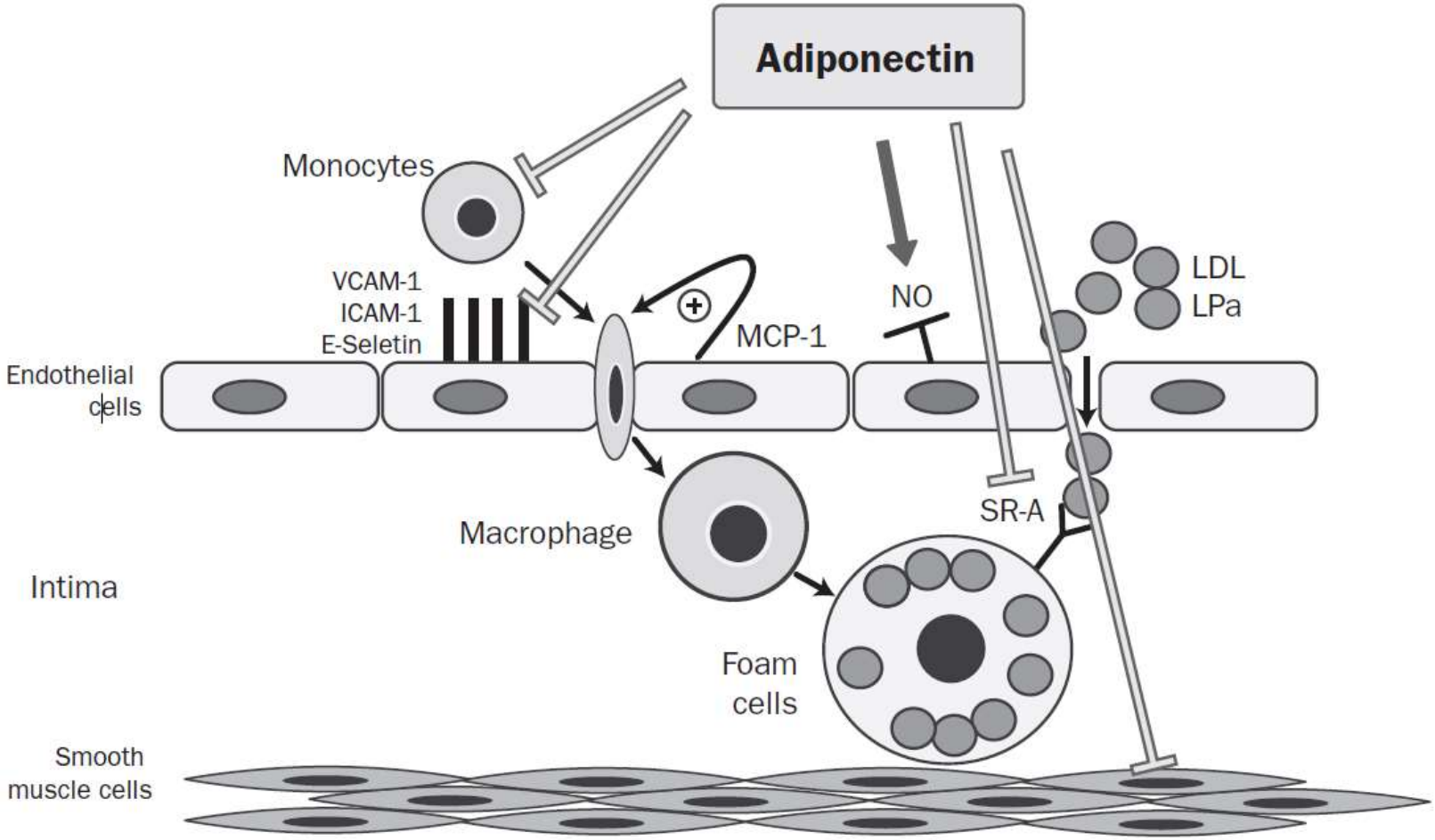
Circulating adiponectin isoforms

Low-molecular wt.	Medium-molecular wt.	High-molecular wt.
		
Women	++	+++	+++
Men	++	+	+



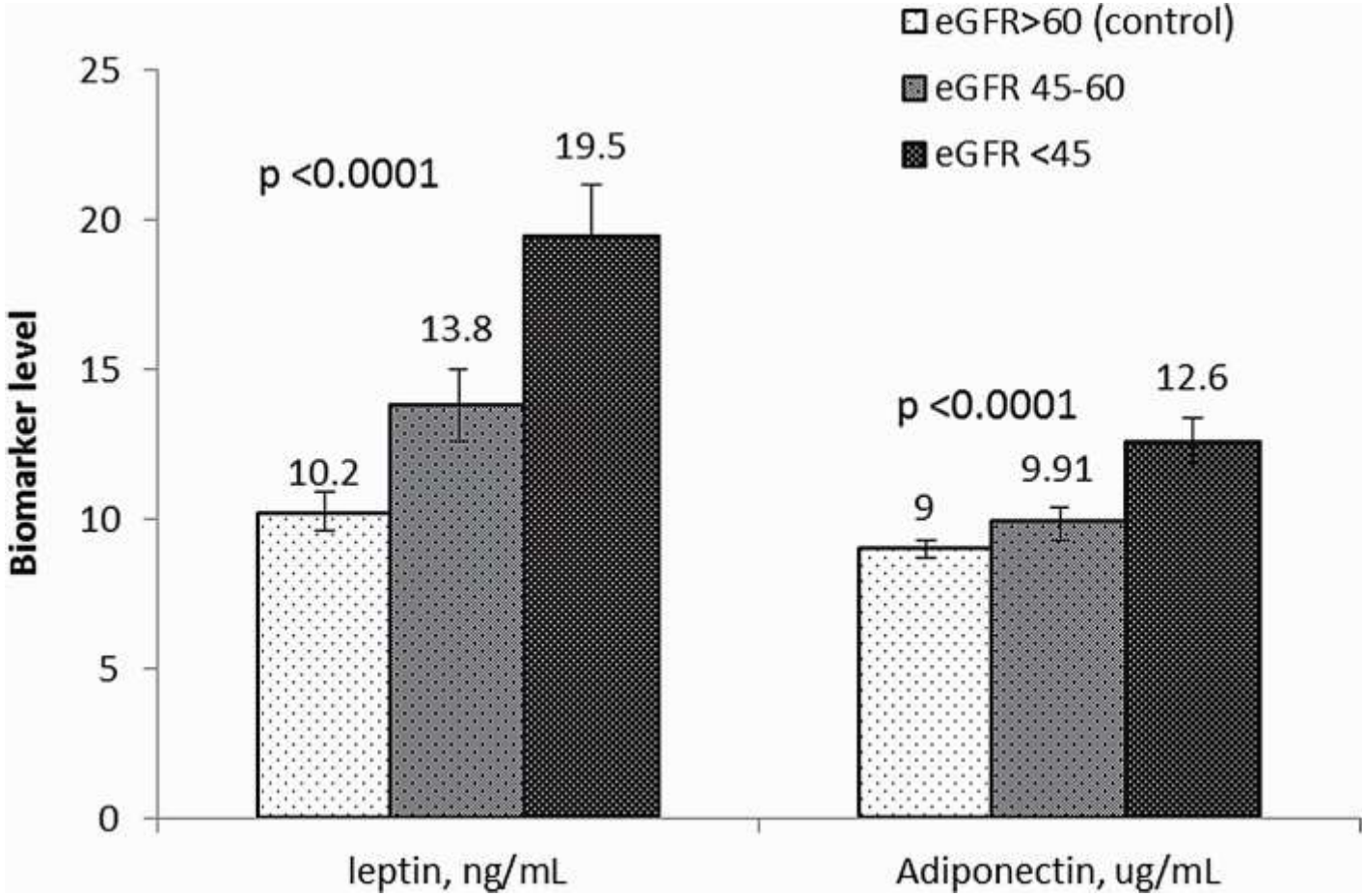
Wiecek A., Adamczak M., Chudek J.: Nephrol. Dial. Transplant., 2007

Adiponectin inhibits the up-regulation of adhesion molecules, the binding of monocytes to endothelial cells, the transformation of macrophages into foam cells and the proliferation and migration of vascular smooth muscle cells. In addition, the production of nitric oxide from endothelial cells is stimulated by adiponectin



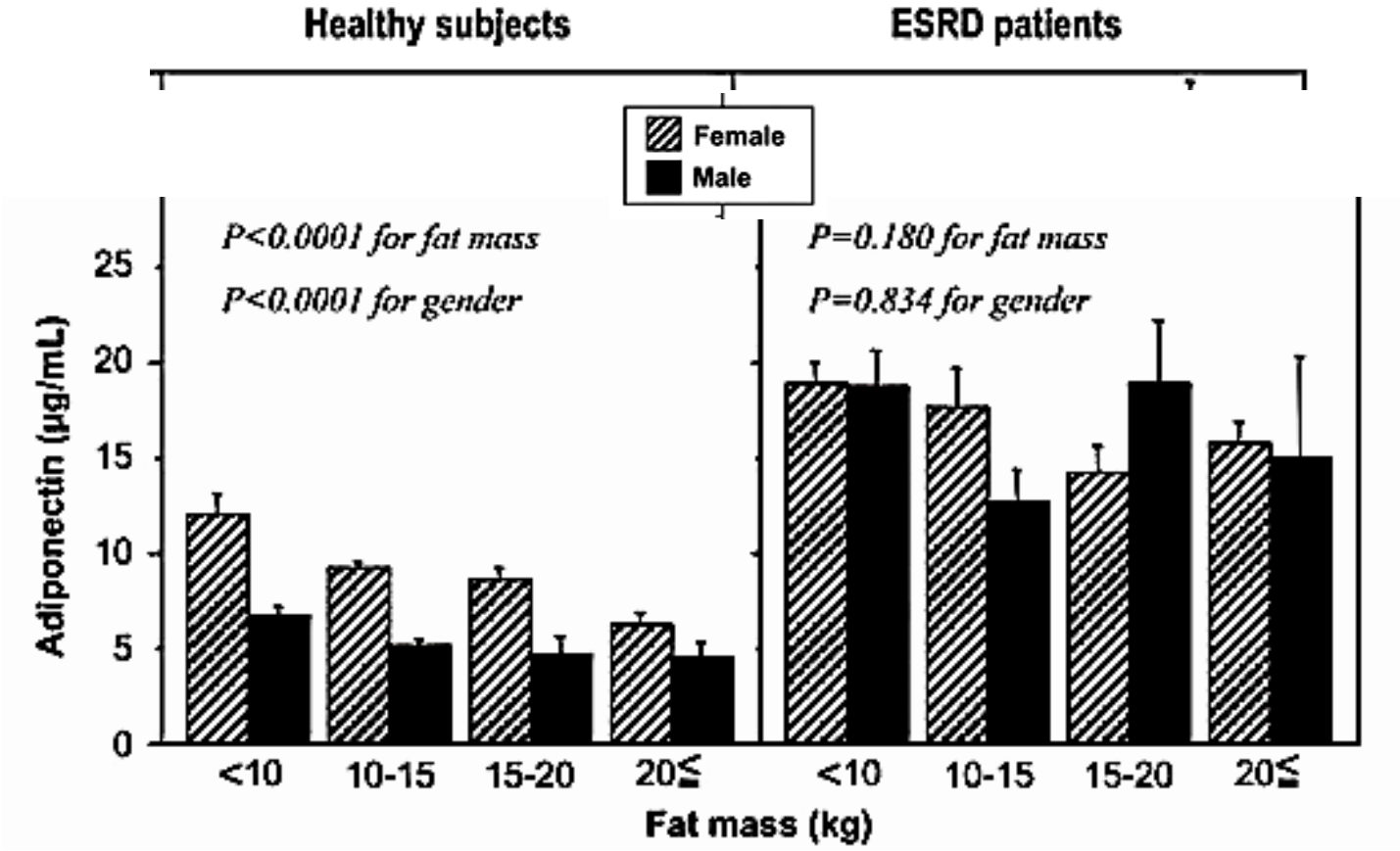
Adjusted mean leptin and adiponectin levels by severity of CKD defined by eGFR levels

Adjusted for age, sex, ethnicity, primary/below education, diabetes, CVD, BMI, systolic BP, current smoking, ever drinker, total and HDL cholesterol



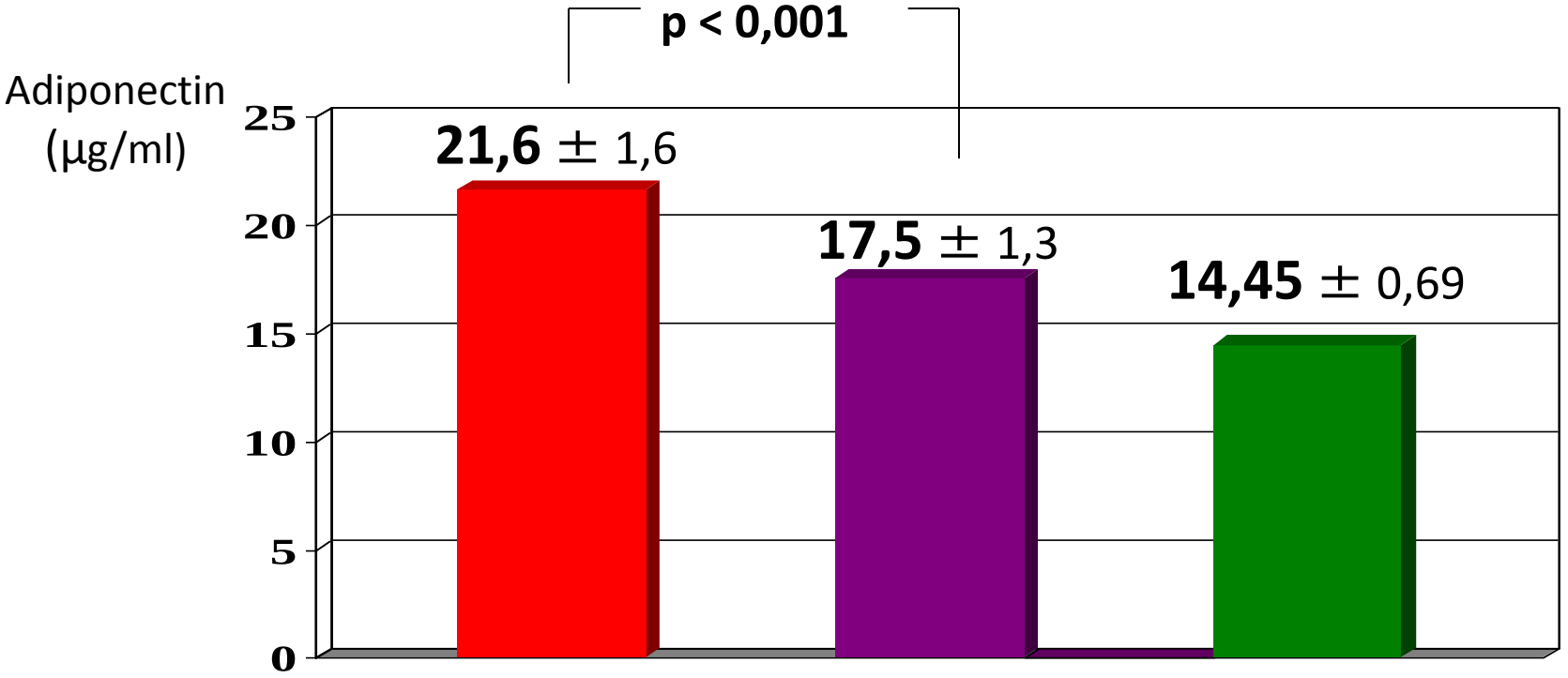
Lim C.C.et al., PLOS ONE | DOI:10.1371/journal.pone.0122009 March 20, 2015

Relationship between body fat mass and plasma adiponectin concentration



Shoji T et al.: Metabolism 2005; 54: 330-334

Plasma adiponectin concentration in uraemic patients before and after kidney transplantation



	Before Tx	After tx	Healthy subjects
n	23	23	55
Creatinine (µmol/l)	835 ± 63	210 ± 29	79,5 ± 2,8
BMI (kg/m^2)	24,1 ± 0,9	-	26,0 ± 0,48

Chudek J, Adamczak M, Karkoszka H, Budzinski G, Ignacy W, Funahashi T, Matsuzawa Y, Cierpka L, Kokot F, Wiecek A. Transplant . Proc., 2003; 35:2186-9.

Adiponectin and arteriosclerosis in CKD patients

American Journal of Nephrology

Original Report: Patient-Oriented, Translational Research

Am J Nephrol 2011;34:249–255
DOI: 10.1159/000330178

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Association of Adiponectin with Carotid Arteriosclerosis in Predialysis Chronic Kidney Disease

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Toru Aoyama[e] Hirotake Kasuga[f] Shigeki Yamada[f] Koji Ohashi[d]
Syoichi Maruyama[a] Seiichi Matsuo[a] Noriyuki Ouchi[d] Toyoaki Murohara[b]
Takanobu Toriyama[e]

Departments of [a]Nephrology and [b]Cardiology, [c]CKD Initiatives Internal Medicine and [d]Molecular Cardiology, Nagoya University Graduate School of Medicine, and Departments of [e]Cardiology and [f]Nephrology, Nagoya Kyoritsu Hospital, Nagoya, Japan

Adiponectin and arteriosclerosis in CKD patients

Table 2. Incidence of carotid arteriosclerosis

	Control (n = 81)	CKD (n = 95)	p
Carotid arteriosclerosis	3 (3.7)	21 (22.1)	0.0004
IMT, mm	0.69 ± 0.17	0.81 ± 0.19	0.0010
PS, mm	1.19 ± 2.54	2.53 ± 4.02	0.0072

Carotid arteriosclerosis is defined as IMT >1.2 mm and/or PS >5.0 mm

Hayashi M. et al.,
Am. J. Nephrol., 2011, 34, 249-255

Adiponectin and arteriosclerosis in CKD patients

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Table 5. Incidence of carotid arteriosclerosis according to adiponectin levels in patients with CKD

	High-adiponectin group (n = 50)	Low-adiponectin group (n = 45)	p
Carotid arteriosclerosis	6 (12.0%)	15 (33.3%)	0.012
IMT, mm	0.76 ± 0.14	0.86 ± 0.23	0.015
PS, mm	1.59 ± 2.66	3.35 ± 4.76	0.030

Hayashi M. et al.,
Am. J. Nephrol., 2011, 34, 249-255

Association of clinical characteristics with carotid arteriosclerosisin CKD patients by logistic regression analysis

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Male	1.95 (0.64–5.90)	0.24		
Age	1.06 (0.99–1.12)	0.061		
BMI	1.10 (0.96–1.26)	0.17	1.01 (0.84–1.18)	0.90
Hemoglobin A1C	1.67 (1.06–2.63)	0.025	1.60 (1.01–2.54)	0.046
Hematocrit	0.98 (0.90–1.08)	0.67		
Albumin	0.43 (0.14–1.28)	0.13		
C-reactive protein	1.29 (0.53–3.14)	0.57		
Smoking	1.26 (0.38–4.27)	0.70	1.49 (0.60–5.30)	0.40
Hypertension	2.88 (0.77–10.73)	0.12		
Hyperlipidemia	1.29 (0.46–3.57)	0.62		
eGFR	0.98 (0.95–1.01)	0.15		
Low adiponectin	3.67 (1.28–10.52)	0.015	3.97 (1.20–10.13)	0.023

Multivariate model includes BMI, smoking status and all variables at baseline with $p < 0.05$ by univariate analysis.

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Multivariate model includes BMI, smoking status and all variables at baseline with $p < 0.05$ by univariate analysis.

Adiponectin and atherosclerosis in CKD patients

- In conclusion, relatively lower adiponectin levels are associated with an increased risk of atherosclerosis in patients with predialysis CKD. Our findings provide the clinical value of adiponectin as a potential surrogate marker of atherosclerotic status at the early stages of renal dysfunction

- Therapeutic approaches aimed at increasing adiponectin production, such as pharmacological treatment and caloric restriction, could have direct benefits on vascular disorders at the initial stage of CKD

Adiponectin in haemodialysis CKD patients

Original Paper

nephron Clinical Practice

Nephron Clin Pract 2005;101:c18–c24
DOI: 10.1159/000085707

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Reciprocal Association of Plasma Adiponectin and Serum C-Reactive Protein Concentration in Haemodialysis Patients with End-Stage Kidney Disease – A Follow-Up Study

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Yuji Matsuzawa[b] Franciszek Kokot[a] Andrzej Więcek[a]

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Plasma adiponectin and CRP in HD patients

Table 1. Clinical and biochemical characteristics of HD patients and healthy controls (means ± SEM or medians and 95% CI; for abbreviations see text)

	HD (n = 80)	Control (n = 22)	p
Age, years	47.0 ± 2.0	44.6 ± 2.0	NS
BMI, kg/m^2	24.0 ± 0.5	24.5 ± 0.9	NS
TFM, kg	15.8 ± 1.0	18.8 ± 1.9	NS
TLM, kg	46.2 ± 1.0	52.4 ± 2.4	0.02
Fat content, %	24.4 ± 1.2	25.5 ± 2.0	NS
IMT, mm	0.77 ± 0.01	0.64 ± 0.01	<0.001
Serum creatinine, µmol/l	893 ± 4	83 ± 3	<0.001
Kt/V	1.29 ± 0.04	–	–
Serum glucose, mmol/l	5.5 ± 0.1	4.7 ± 0.2	<0.001
Serum total cholesterol, mmol/l	5.0 ± 0.1	5.5 ± 0.1	NS
Serum triglycerides, mmol/l	1.8 ± 0.1	1.4 ± 0.2	0.01
Plasma adiponectin, µg/ml	29.0 ± 2.1	8.7 ± 2.6	<0.001
Serum CRP, mg/l	10.7 ± 2.8 11.0 (5.4–16.6)	2.9 ± 1.1 2.0 (2.0–4.0)	<0.001
Serum albumin, g/l	38.0 ± 0.5	42.5 ± 0.5	<0.001

Ignacy W. et al., Nephron Clin. Pract., 2005, 101, c18 – c24

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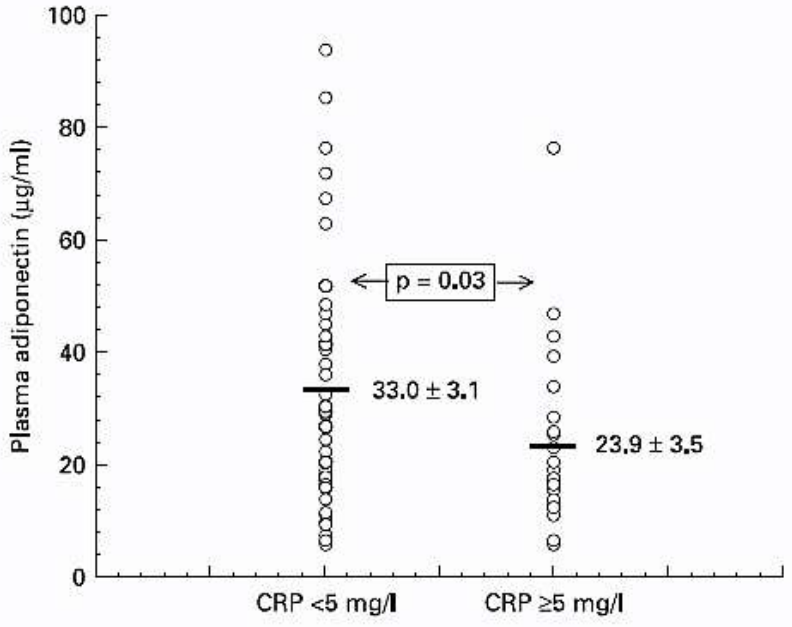


Fig. 1. Plasma adiponectin concentration in HD patients with serum CRP concentrations ≥ 5 and <5 mg/l.

Ignacy W. et al., Nephron Clin. Pract., 2005, 101, c18 – c24

Plasma adiponectin or CRP and survival in HD patients

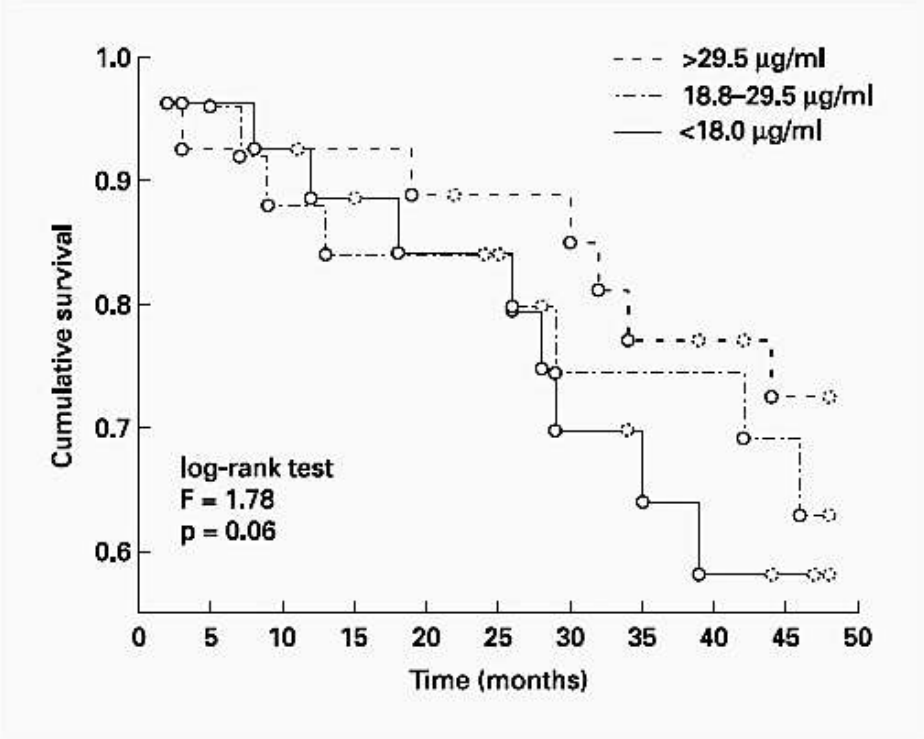
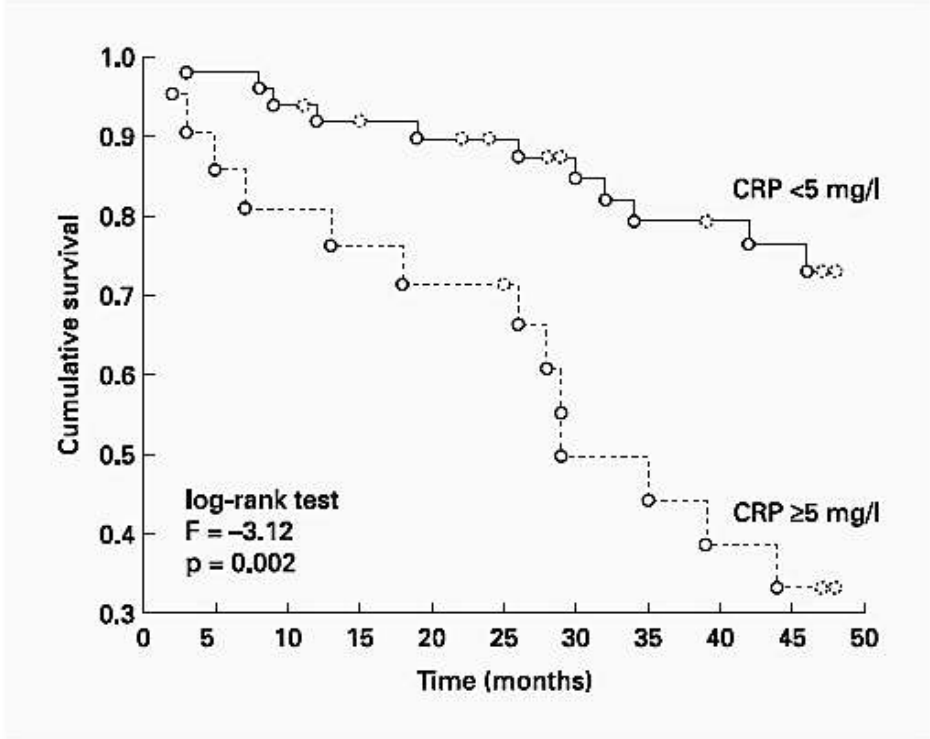


Fig. 2. Kaplan-Meier estimation of survival in HD patients with plasma adiponectin concentration in the highest, middle and the lowest tertile.



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Ignacy W. et al., Nephron Clin. Pract., 2005, 101, c18 – c24

Relationship between survival and plasma adiponectin concentration in hemodialysed patients with ESRD

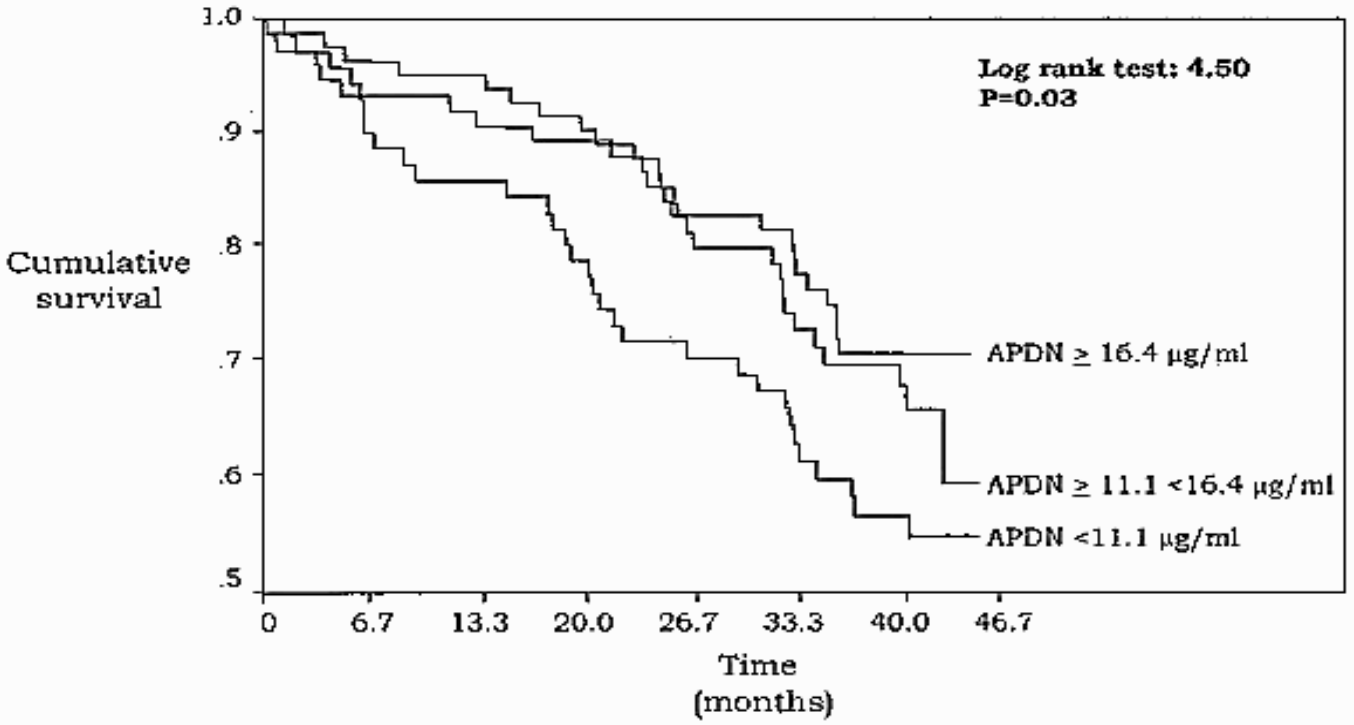


Figure 4. Kaplan-Meier survival curves for cardiovascular events (fatal and nonfatal) in the study cohort. Patients were stratified into three tertiles according to plasma ADPN concentrations (first tertile, ADPN levels of <11.1 µg/ml; second tertile, >11.1 to <16.4 µg/ml; third tertile, ≥16.4 µg/ml).

Zoccali C. et al., J. Am. Soc. Nephrol., 2002, 13, 134-141

Adiponectin and CV complications in CKD patients

Therapeutic Apheresis and Dialysis

Therapeutic Apheresis and Dialysis 2014; 18(2):185–192
doi: 10.1111/1744-9987.12065

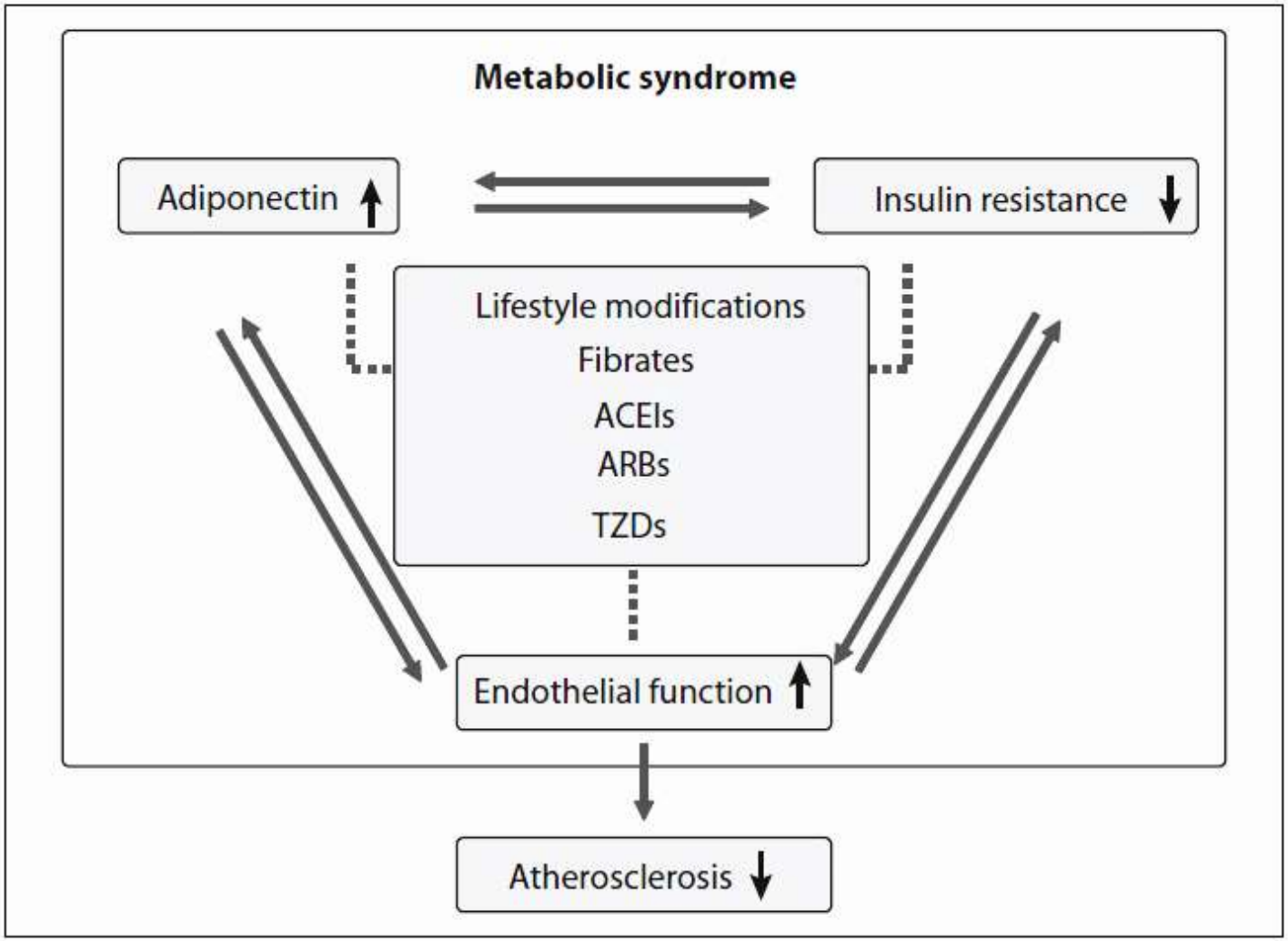
Plasma Adiponectin Levels for Prediction of Cardiovascular Risk Among Hemodialysis Patients

Eid M El-Shafey,[1] and Mohamed Shalan[2]

[1]Nephrology Unit, Internal Medicine Department, [2]Clinical Pathology Department, Faculty of Medicine, Tanta University, Tanta, Egypt

- **Plasma ADPN levels were lower (*P* = 0.000) among patients who experienced new CV events (11.13 +/- 2.15 mg/mL) than among event-free patients (16.82 +/- 2.45 mg/mL), and seem to predict cardiovascular outcomes.**
- **The inverse relationships between ADPN and several cardiovascular risk factors indicate that ADPN may have a protective role in the prevention of CV events.**

Influence of therapeutic interventions on adiponectin, insulin resistance and endothelial function



Balsan G.A., et al., Rev. Assoc. Med. Bras., 2015; 61: 72-80

Adiponectin agonist – orally active compound

ARTICLE

doi:10.1038/nature12656

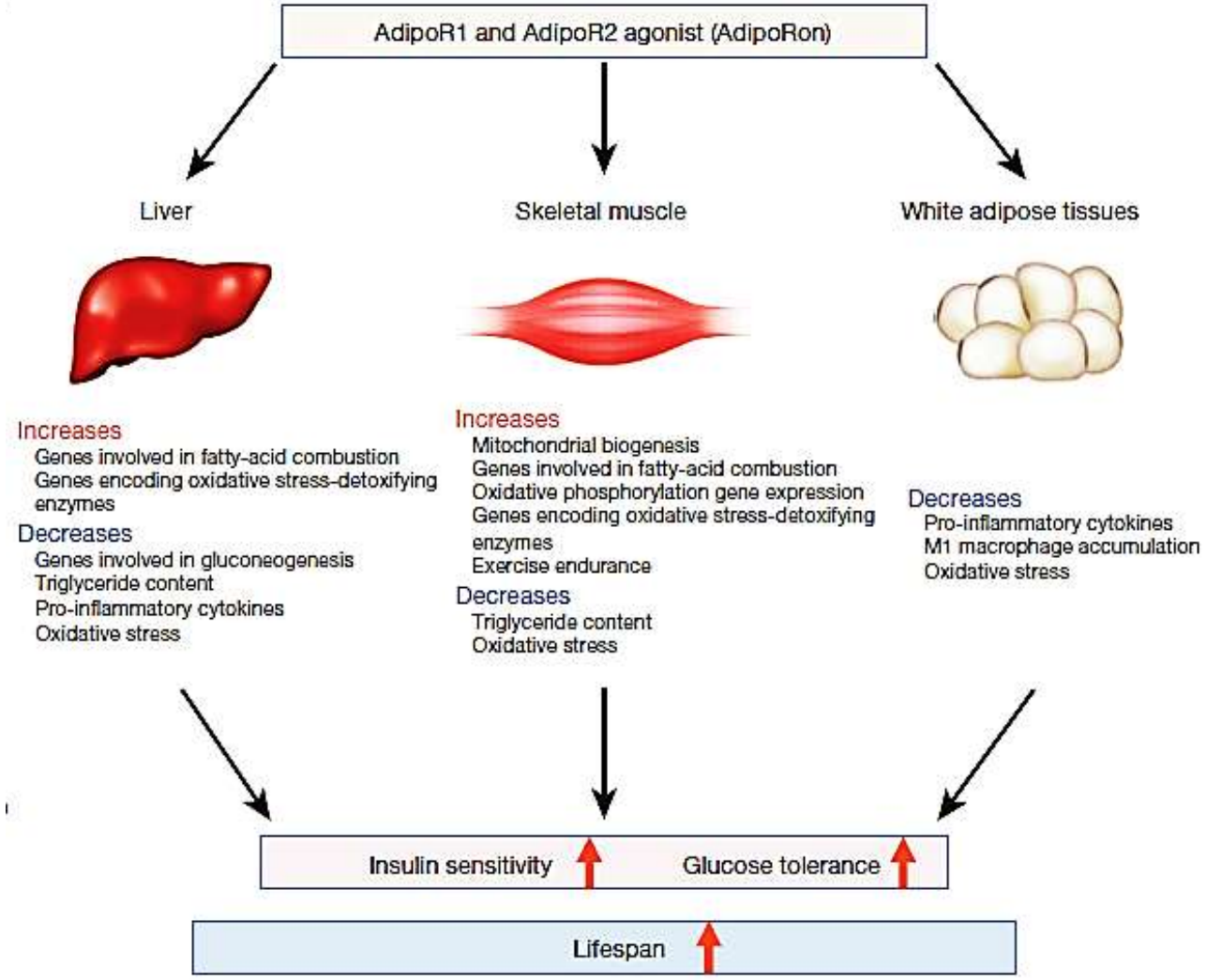
A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity

Miki Okada-Iwabu[1,2,3]*, Toshimasa Yamauchi[1,2,3]*, Masato Iwabu[1,2]*, Teruki Honma[4], Ken-ichi Hamagami[1], Koichi Matsuda[1], Mamiko Yamaguchi[1], Hiroaki Tanabe[4], Tomomi Kimura-Someya[4], Mikako Shirouzu[4], Hitomi Ogata[5], Kumpei Tokuyama[5], Kohjiro Ueki[1], Tetsuo Nagano[6], Akiko Tanaka[4,6], Shigeyuki Yokoyama[4,7] & Takashi Kadowaki[1,2,3]

Adiponectin secreted from adipocytes binds to adiponectin receptors AdipoR1 and AdipoR2, and exerts antidiabetic effects via activation of AMPK and PPAR-α pathways, respectively. Levels of adiponectin in plasma are reduced in obesity, which causes insulin resistance and type 2 diabetes. Thus, orally active small molecules that bind to and activate AdipoR1 and AdipoR2 could ameliorate obesity-related diseases such as type 2 diabetes. Here we report the identification of orally active synthetic small-molecule AdipoR agonists. One of these compounds, AdipoR agonist (AdipoRon), bound to both AdipoR1 and AdipoR2 ***in vitro***. AdipoRon showed very similar effects to adiponectin in muscle and liver, such as activation of AMPK and PPAR-α pathways, and ameliorated insulin resistance and glucose intolerance in mice fed a high-fat diet, which was completely obliterated in AdipoR1 and AdipoR2 double-knockout mice. Moreover, AdipoRon ameliorated diabetes of genetically obese rodent model ***db/db*** mice, and prolonged the shortened lifespan of ***db/db*** mice on a high-fat diet. Thus, orally active AdipoR agonists such as AdipoRon are a promising therapeutic approach for the treatment of obesity-related diseases such as type 2 diabetes.

Okada-Iwabu M. et al., 2013, Nature, 503, 495-499

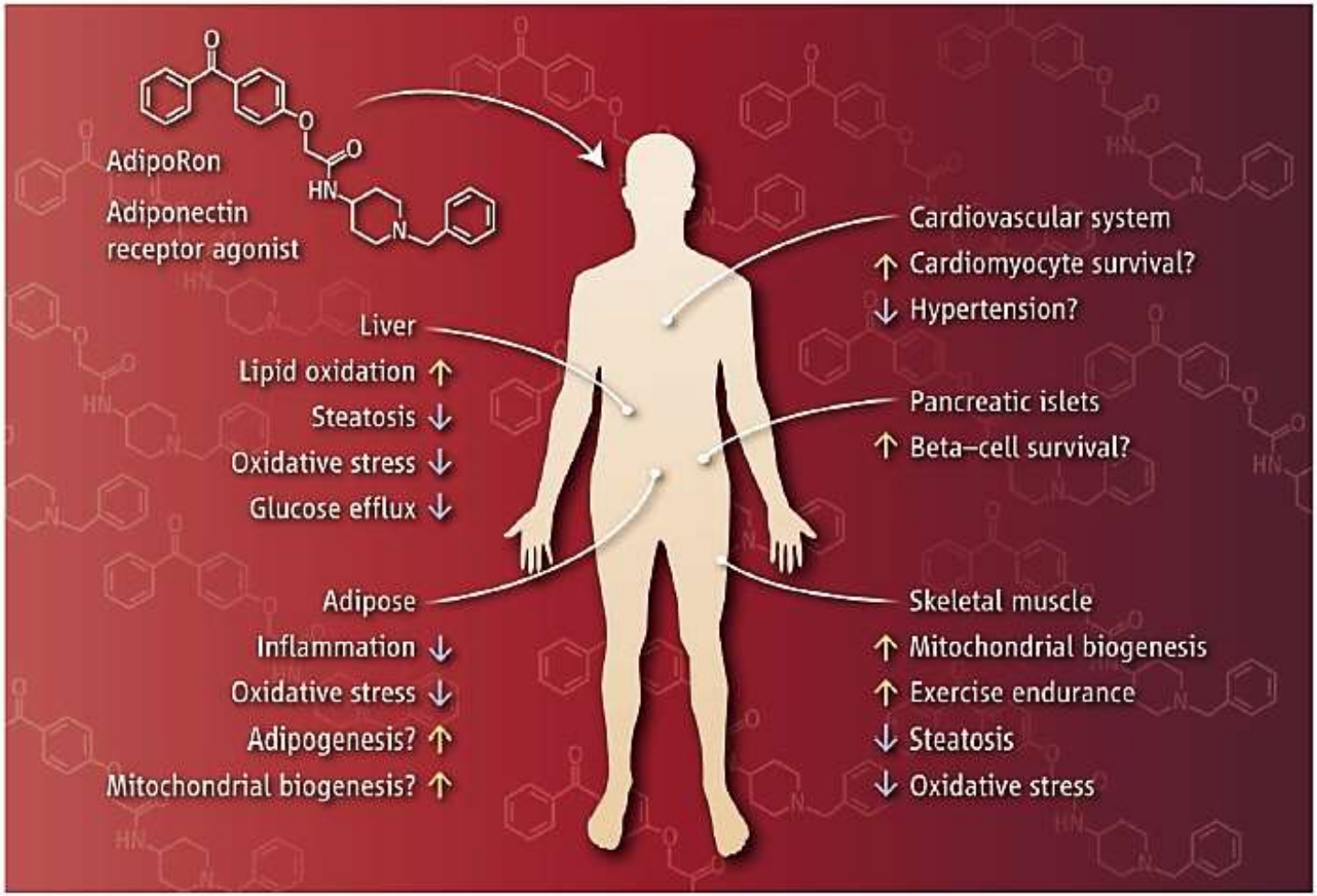
AdipoRon increased insulin sensitivity and glucose tolerance, and at the same time contributed to longevity of obese diabetic mice



Okada-Iwabu M., Nature, 2013, 503, 495-499

Adiponectin mimetic

Muscle, heart, pancreas, liver, and adipocytes are key target tissues for adiponectin receptor activation



Holland W. L., Scherer Ph. E., Science, 2013, 342, 1460-1461

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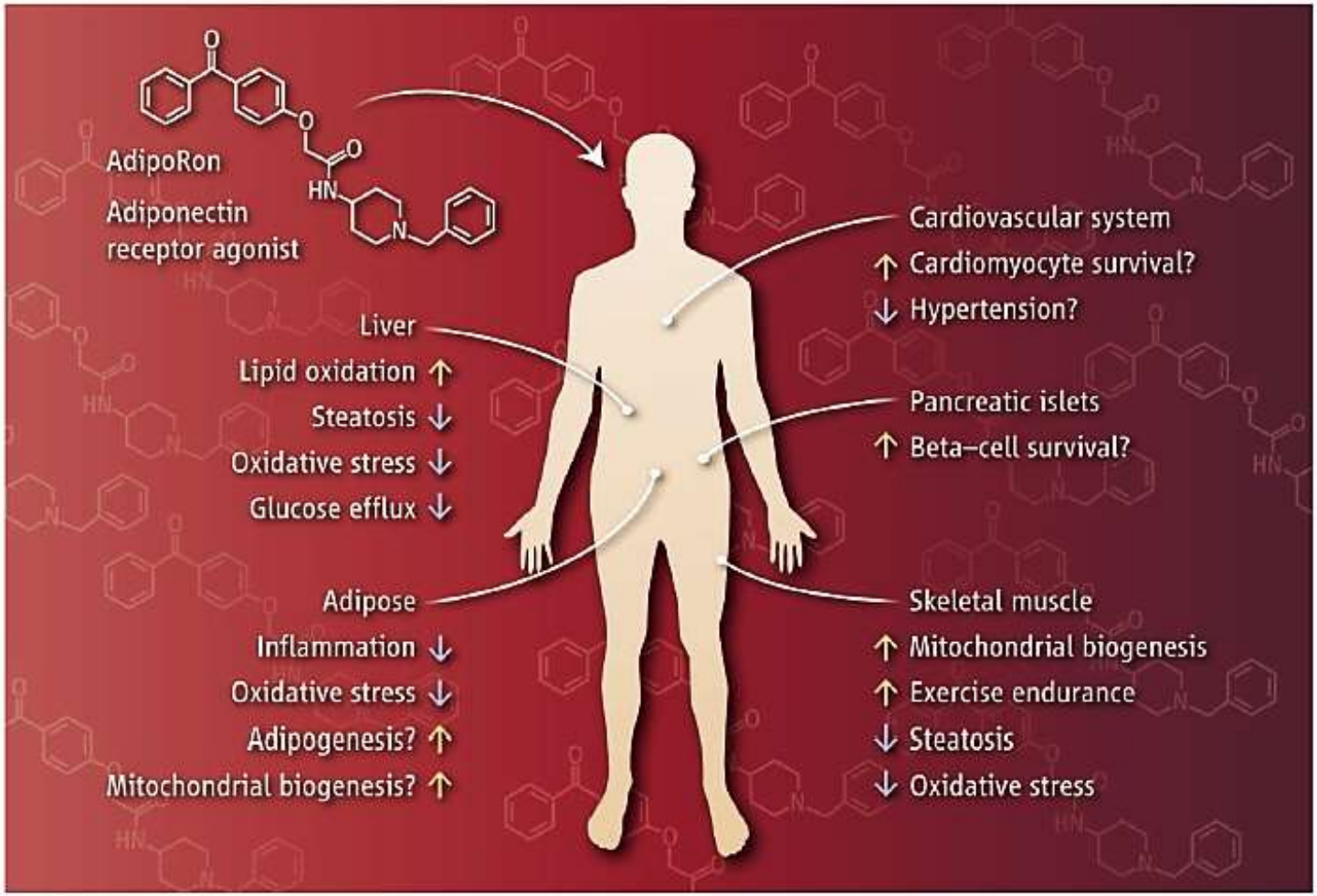
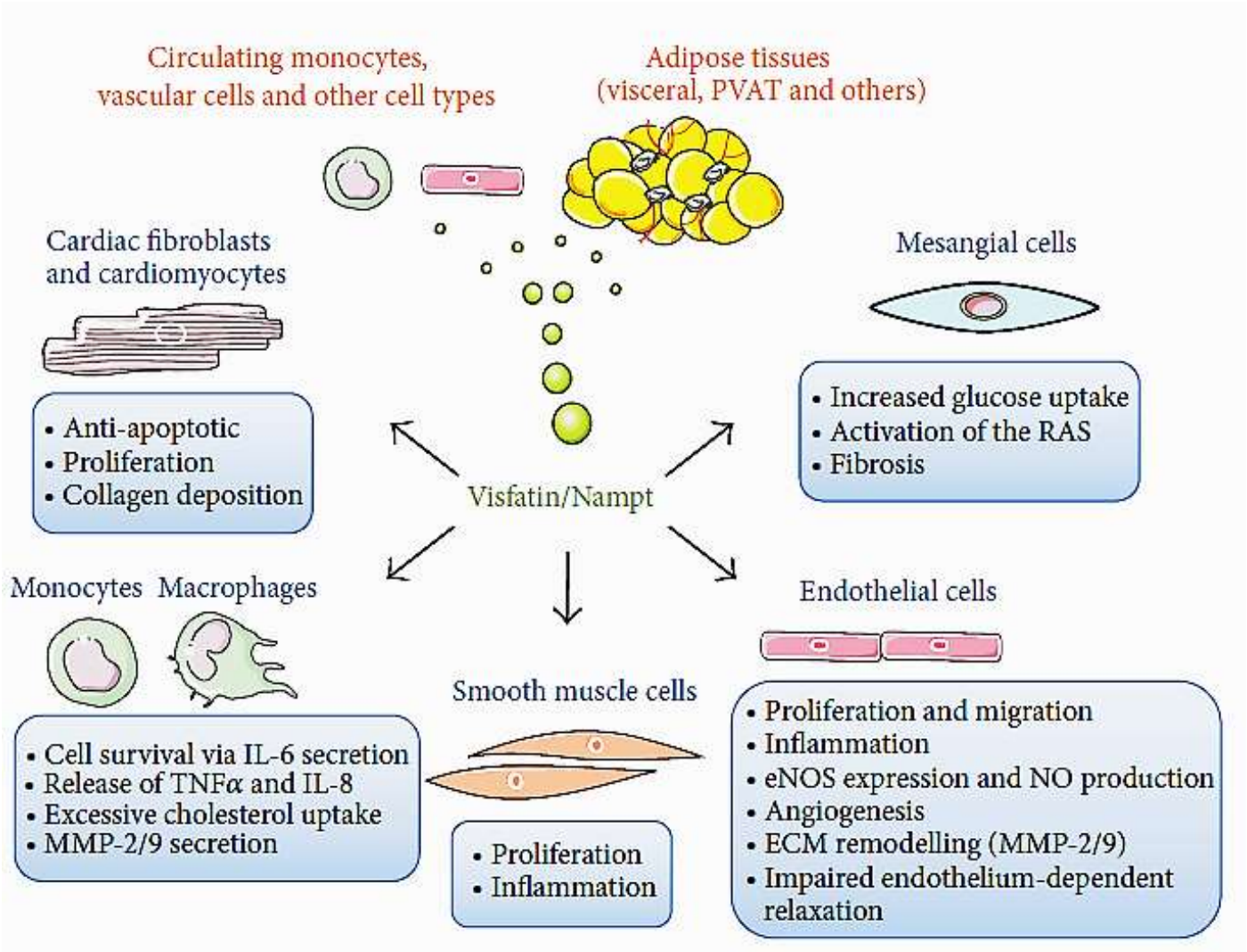


…….will reduce CV complications in CKD patients???!!!

Holland W. L., Scherer Ph. E., Science, 2013, 342, 1460-1461

The main reported direct actions of visfatin/Nampt in the cardiovascular system



Romacho T. et al., Med. Inflam., 2013, ID 946427

Visfatin in CKD patients with or without atherosclerotic plaque in the carotid artery

Table 3 Clinical characteristics of CKD patients with or without carotid artery atherosclerotic plaque

Parameters	No plaque	With plaque
n	118	62
Age/years	48.1±12.4	55.6±13.7*
Males/*n*(%)	62(52.5%)	34(54.8%)
Smoking/*n*(%)	12(10.2%)	8(12.9%)
BMI/(kg/m^2)	23.2±2.12	24.3±1.98
Serum parameters		
Visfatin/(ng/mL)	28.24±6.18	34.22±7.96*
Insulin/ (μU/mL)	169.3±22.8	145.5±23.4
HOMA-R index	5.01±1.15	8.23±1.96*
CRP/(mg/L)	2.1(0.2–27.2)	10.3(0.2–67.2)*
IL-6/(ng/mL)	3.01±0.34	4.78±0.42*
Glucose/(mmol/L)	5.01±1.02	5.32±1.19
Total cholesterol/(mmol/L)	4.82±1.41	5.04±1.31
Total triglyceride/(mmol/L)	2.06±0.41	1.87±0.56
HDL cholesterol/(mmol/L)	1.45±0.27	1.41±0.35
LDL cholesterol/(mmol/L)	2.6±1.0	2.8±0.6
VLDL cholesterol/(mmol/L)	0.96±0.26	1.02±0.34
Albumin/(g/dL)	37.1±6.5	35.2±6.0

Data were expressed as $\bar{x}\pm s$ or median (inter-quartile range), as ppropriate. *P<0.05 vs patients with no plaque.

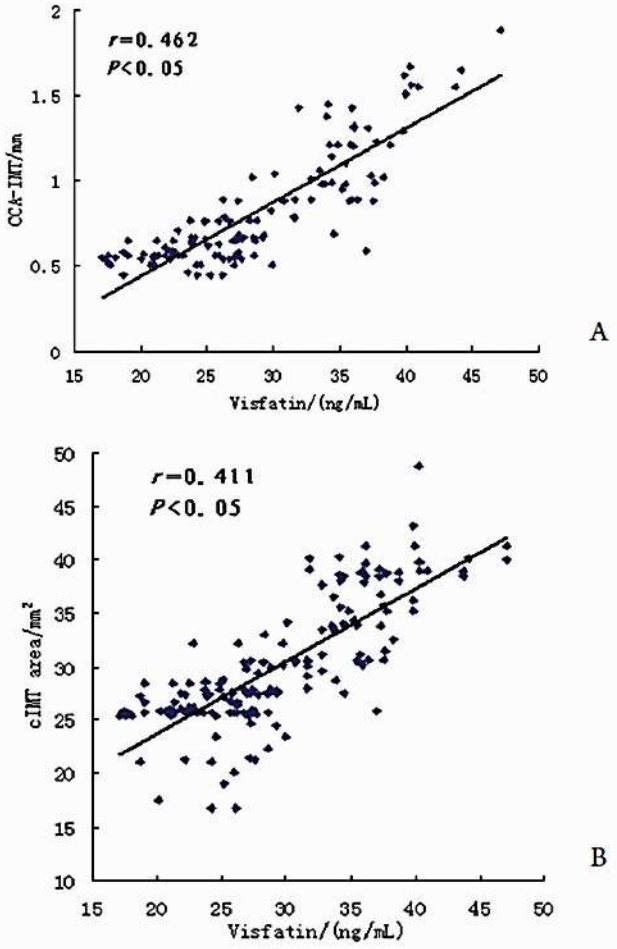


Figure 2 Correlation between Visfatin and CCA-IMT (A) and c IMT area (B).

Visfatin in patients with chronic kidney disease

Nephrol Dial Transplant (2008) 23: 959–965
doi: 10.1093/ndt/gfm727
Advance Access publication 4 November 2007

Original Article

NDT
Nephrology Dialysis Transplantation

Serum visfatin concentration and endothelial dysfunction in chronic kidney disease

Mahmut Ilker Yilmaz[1,2], Mutlu Saglam[3], Juan Jesus Carrero[2], Abdul Rashid Qureshi[2], Kayser Caglar[1], Tayfun Eyileten[1], Alper Sonmez[4], Erdinc Cakir[5], Mujdat Yenicesu[1], Bengt Lindholm[2], Peter Stenvinkel[2] and Jonas Axelsson[2]

[1]Departments of Nephrology, Gülhane School of Medicine, 06018 Etlik-Ankara, Turkey, [2]Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, K 56 Karolinska University Hospital at Huddinge, Stockholm, Sweden, [3]Departments of Radiology, [4]Departments of Internal Medicine and [5]Departments of Biochemistry, Gülhane School of Medicine, 06018 Etlik-Ankara, Turkey

Visfatin in patients with chronic kidney disease

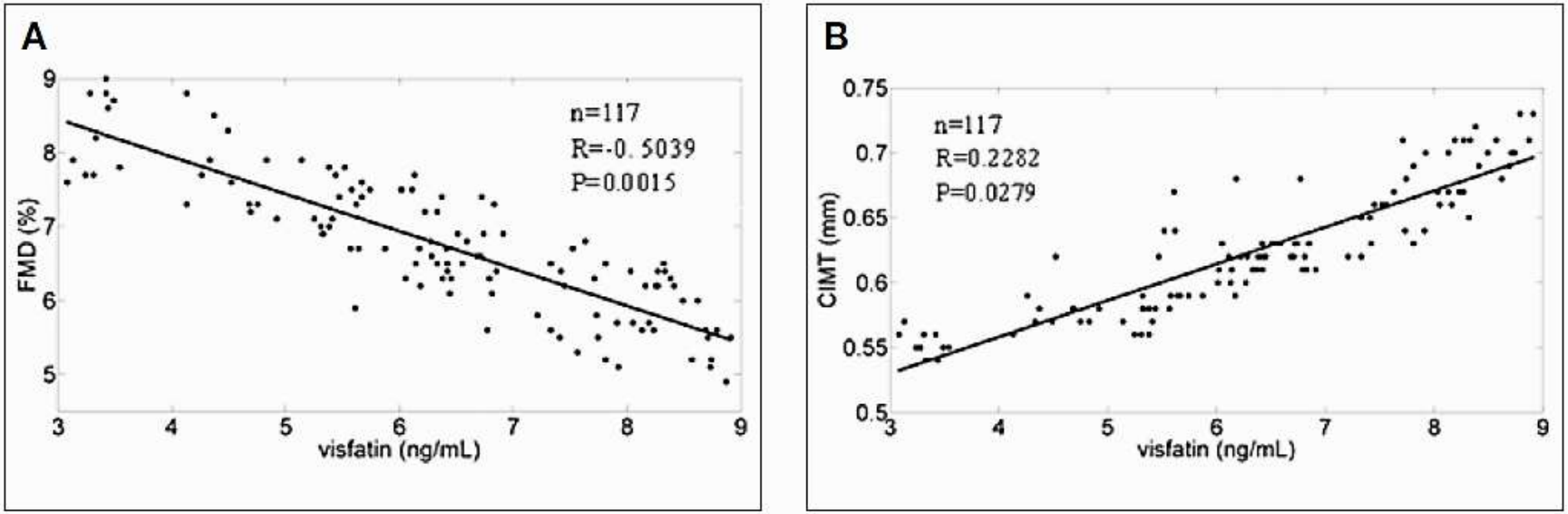
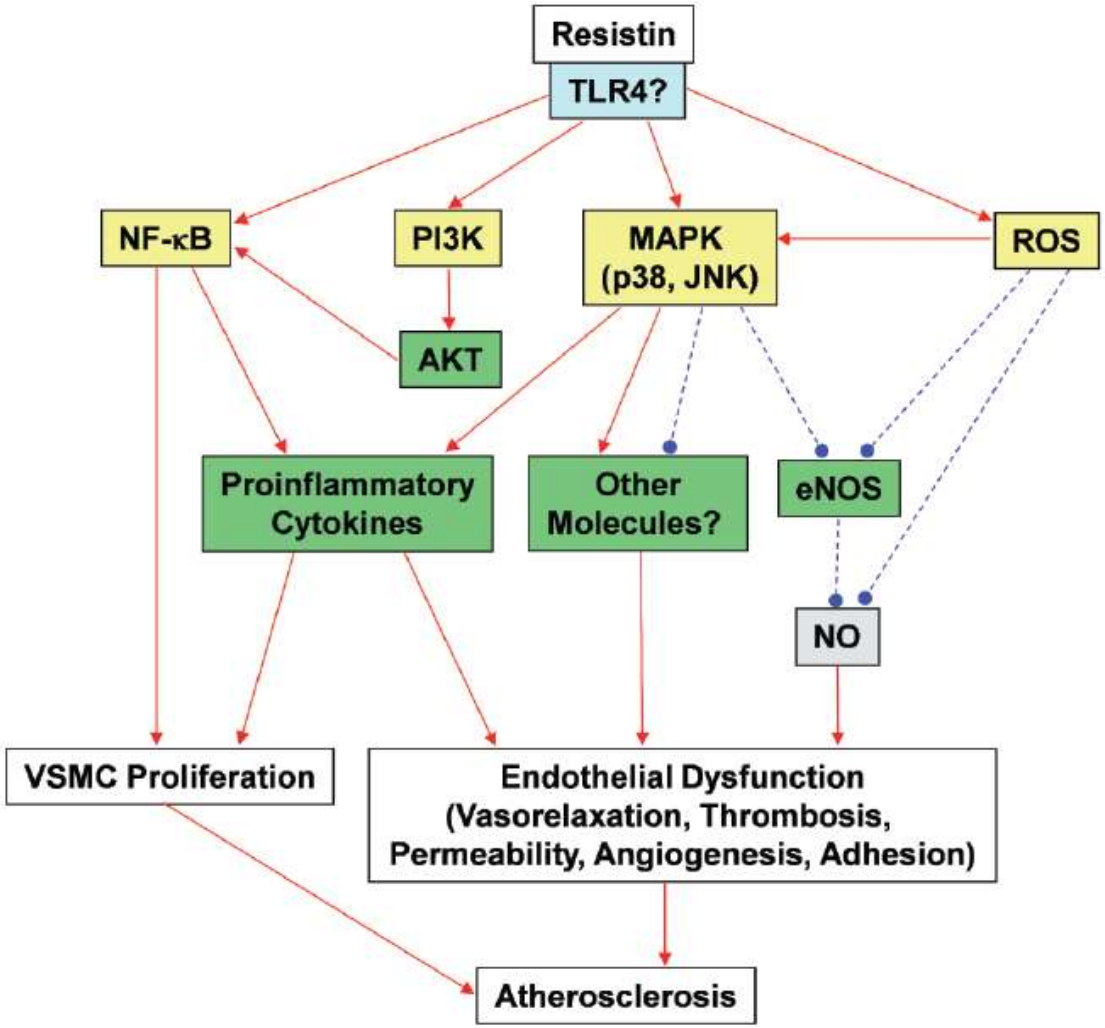


Fig. 2 - Correlation between plasma visfatin and flow-mediated dilatation (FMD) (A) and carotid intima-media thickness (CIMT) (B) in 117 patients with chronic kidney disease.

Mu J., Feng B. et al., J. Nephrol., 2011, 24, 177-184

Potential mechanisms by which resistin may mediate cardiovascular dysfunction



Jamaluddin M.S. et al.., Brit. J. Pharmacol., 2012, 165, 622–632

Resistin in patients with chronic kidney disease

PROGRESS IN UREMIC TOXIN RESEARCH

11

Resistin as a Cardiovascular and Atherosclerotic Risk Factor and Uremic Toxin

Gerald Cohen and Walter H. Hörl

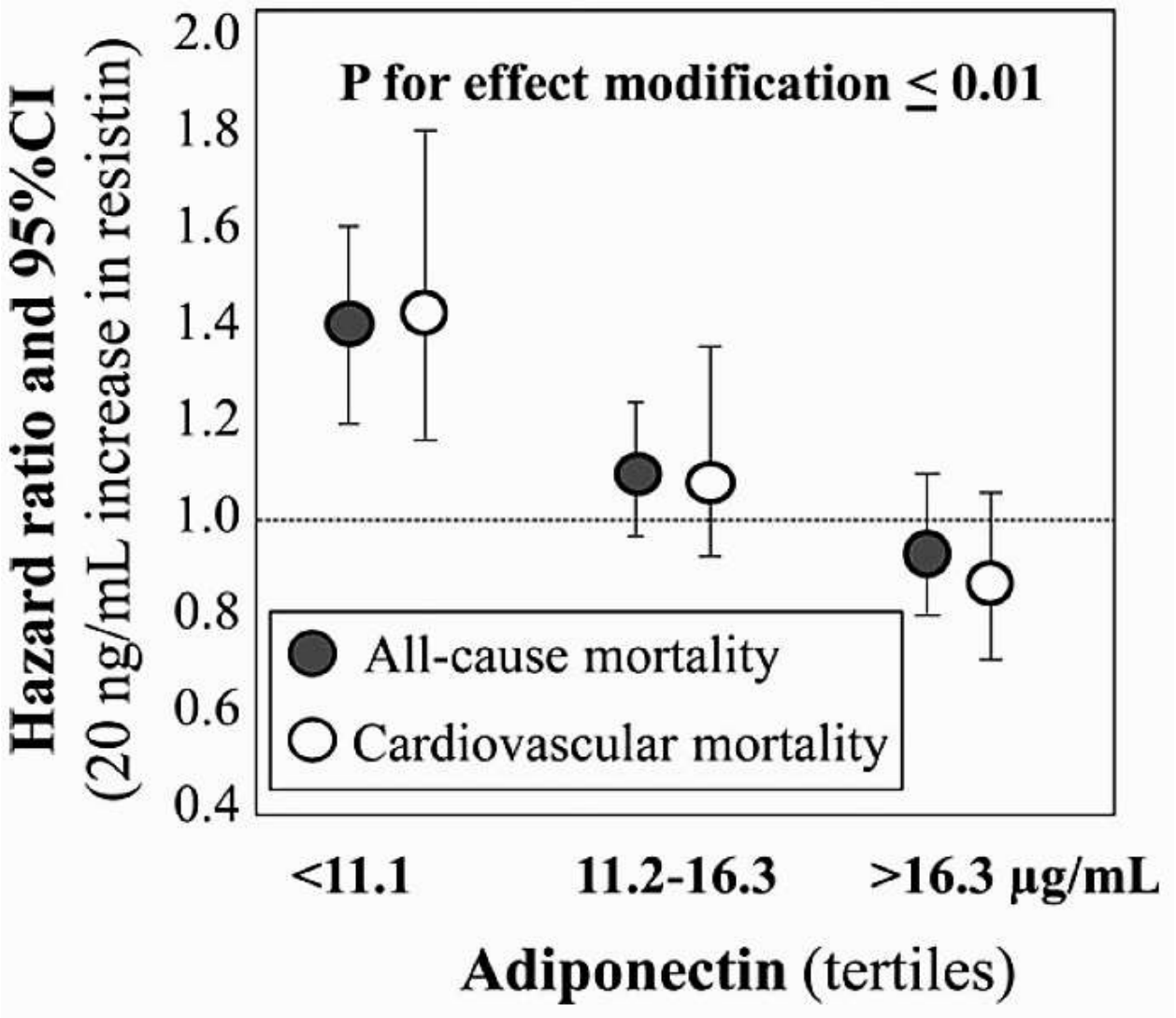
Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria

ABSTRACT

Resistin is a 12.5 kDa protein originally found to be secreted by mouse adipocytes. Whereas in rodents adipose tissue is the main source of resistin, in humans resistin is expressed primarily in macrophages. In a variety of pathophysiologic states, particularly in type 2 diabetes mellitus and in chronic kidney disease, the serum concentration of resistin is increased. Resistin reduces the glucose uptake in adipose tissue and skeletal muscle cells and may be involved in insulin resistance. A positive correlation between resistin levels and inflammatory markers has been described. Resistin has a potential role in cardiovascular disease and may contribute to an increased atherosclerotic risk by modulating the activity of endothelial cells. We recently found that resistin in concentrations measured in uremia is able to interfere with the chemotactic movement and the oxidative burst of neutrophils, cells of the first-line nonspecific immune defense. Therefore, resistin may also contribute to the disturbed immune response and as a consequence to the increased risk of infections in uremic and diabetic subjects.

Sem. Dial., 2009, 22, 373-377

Effect modification of plasma adiponectin (expressed in tertiles) on the link resistin-mortality



Spoto B. et al., Nephrol. Dial. Transplant., 2013, 28, Suppl. 4, iv181–iv187

Conclusions:

1. Fat tissue is a potent endocrine organ which secrets many hormones, cytokines and growth factors (adipokines)

2. Adipokines are involved in the pathogenesis of CV complications in CKD patients in different ways:

a. elevated leptin concentration may be involved in the pathogenesis of HT or anaemia in CKD patients but in anorexia

b. lower plasma leptin concentration - reflects wasting and inflammation and may lead to CV mortality and morbidity

c. inappropriate low adiponectin (omentin?) plasma concentration may cause endothelium dysfunction, insulin resistance and atherosclerosis

d. increased plasma resistin and visfatin levels are involved in pathogenesis lipid disorders, endothelial dysfunction and atherosclerosis

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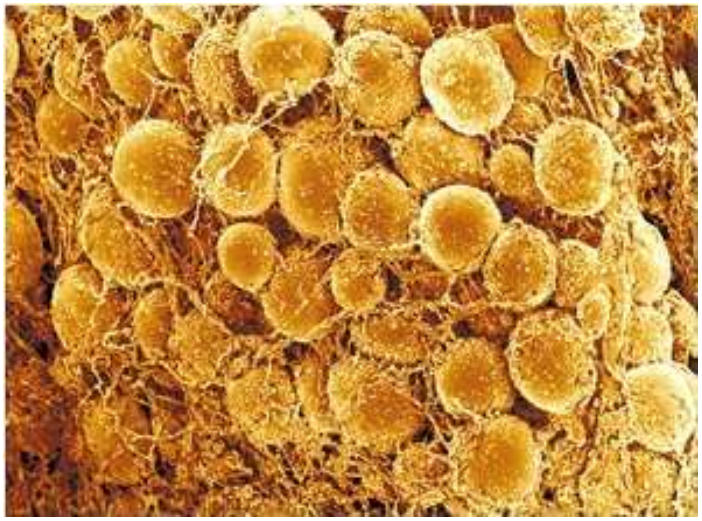
Role of Adipokines in CV complications in CKD patients

Therefore:



Adipokines

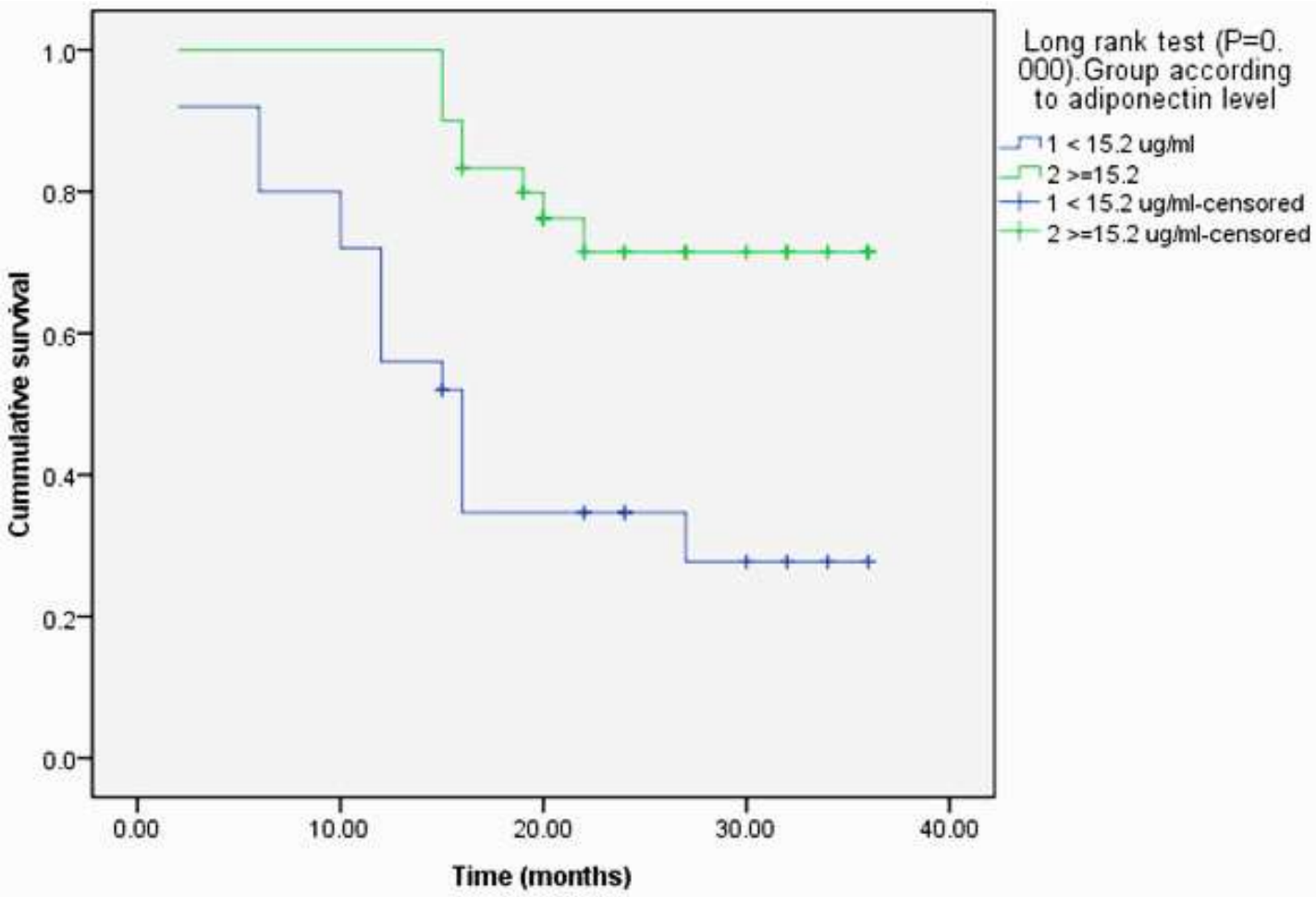
play an important role in CV complications in CKD patients !!!

Thank you very much for your attention!

Andrzej Wiecek

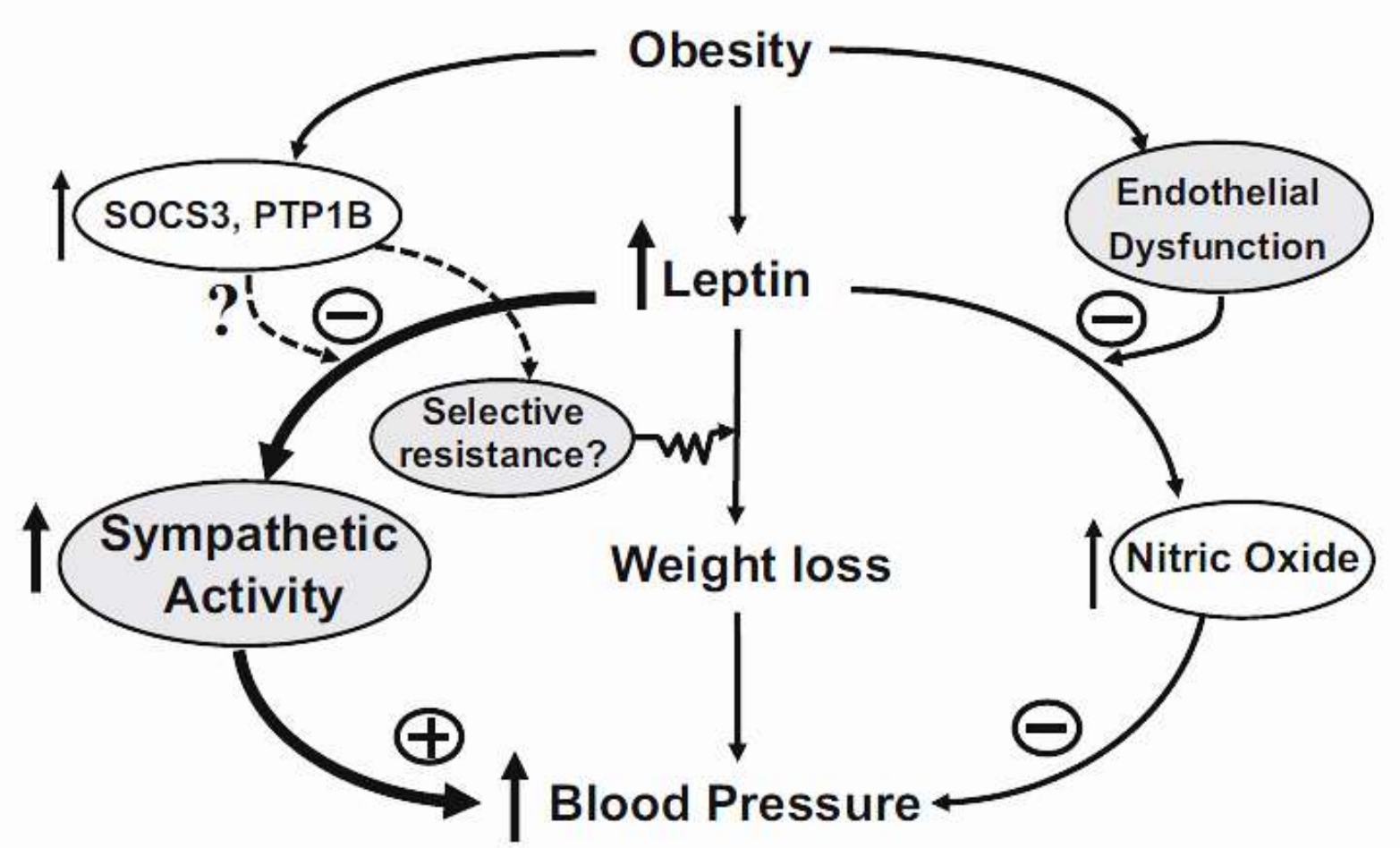
Katowice

Kaplan–Meier survival curves for analysis of time (months) to cardiovascular events. Patients were divided into two groups according to plasma adiponectin (ADPN) levels (group 1, ADPN < 15.2 mg/mL; group 2, ADPN >15.2 mg/mL)



El-Shafey E.D., Shalan M., Ther. Apheresis, Dial., 2014; 18(2):185–192

Possible interactions among leptin, sympathetic activity, endothelial dysfunction and nitric oxide synthesis, and negative regulators of leptin signaling in obesity hypertension



Hall J.E. et al., Circ Res., 2015; 116: 991-1006