INSULIN RESISTANCE IN CHRONIC KIDNEY DISEASE

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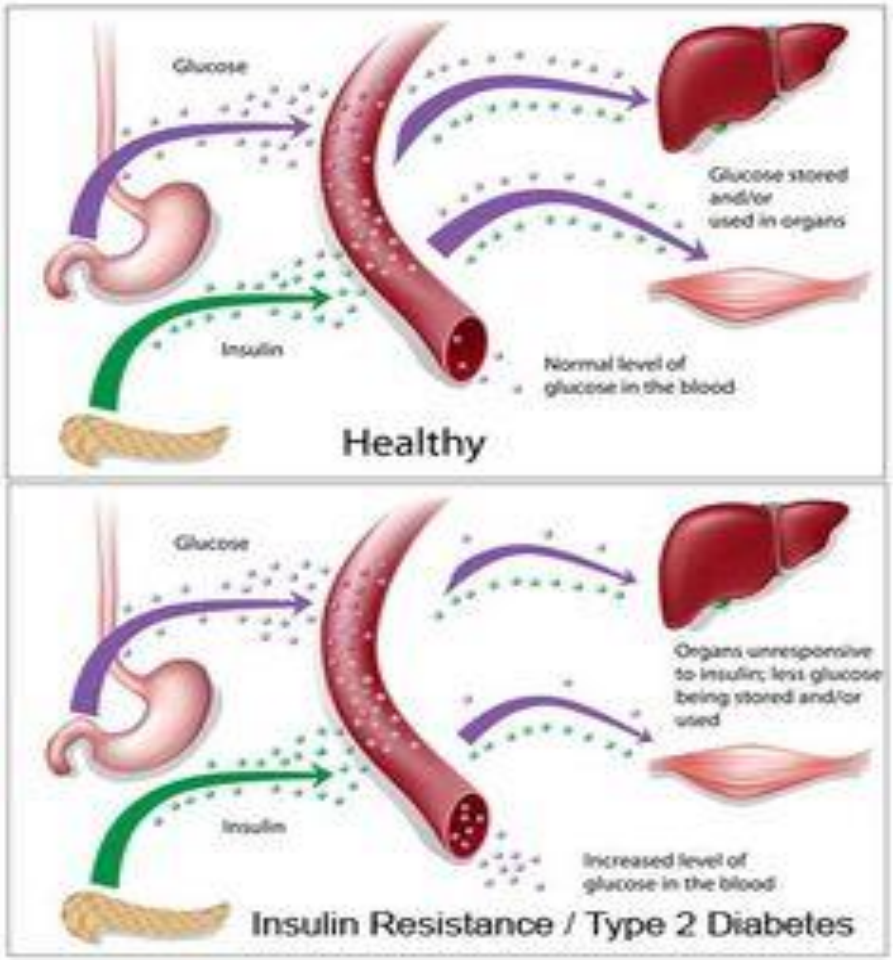
11 – 13 /12 / 2015

Dec 2007

What Is Insulin Resistance?



Reduced insulin sensitivity (IS) of target organ to the effect of insulin (hepatic glucose production**,** glucose uptake by skeletal muscle, lipolysis in adipose tissue and others)

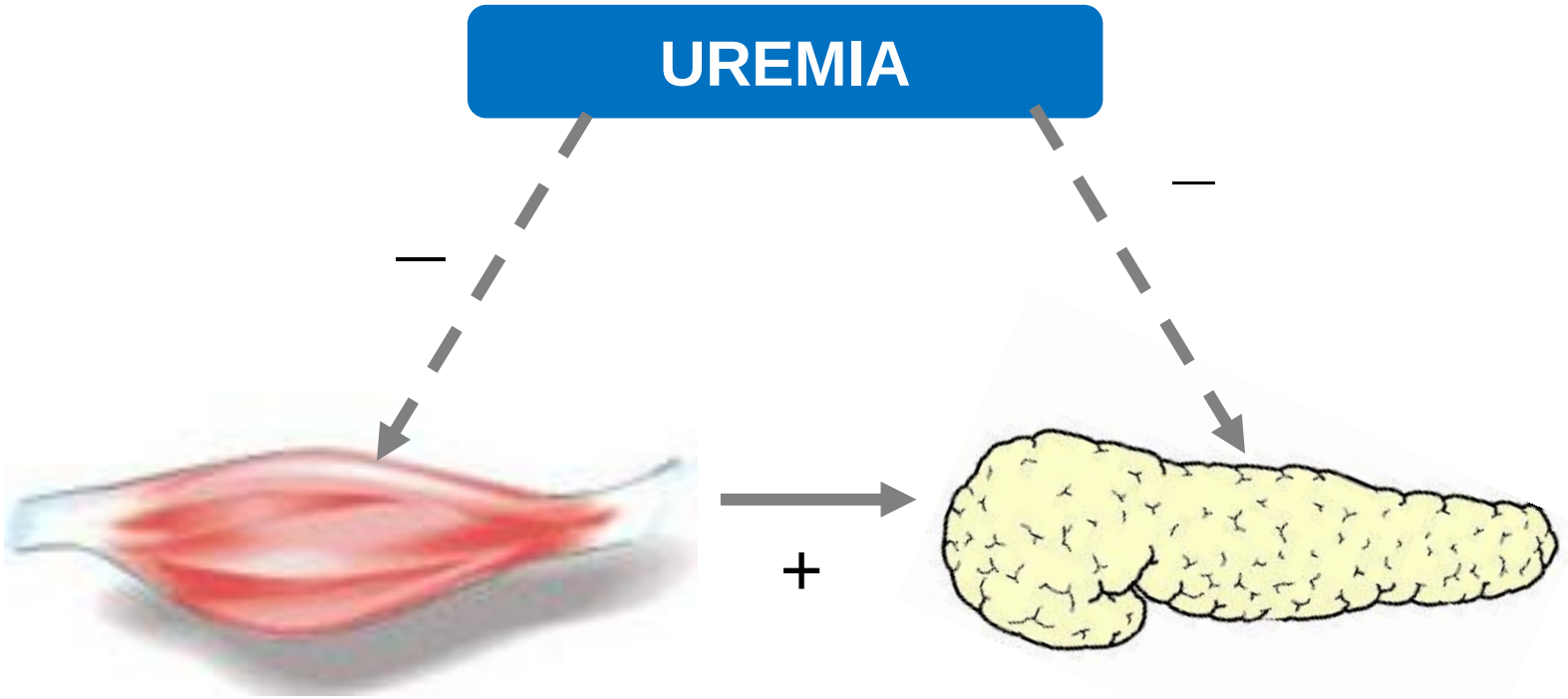
Can be physiologic (in pregnancy) or pathologic

Insulin resistance (IR) leads to: hyperinsulinemia, glucose intolerance, hyperglycemia, and dyslipidemia

Laetitia Koppe et al. Nephrol Dial Transplant (2014) 29: 1666–1674

IR in CKD and ESRD

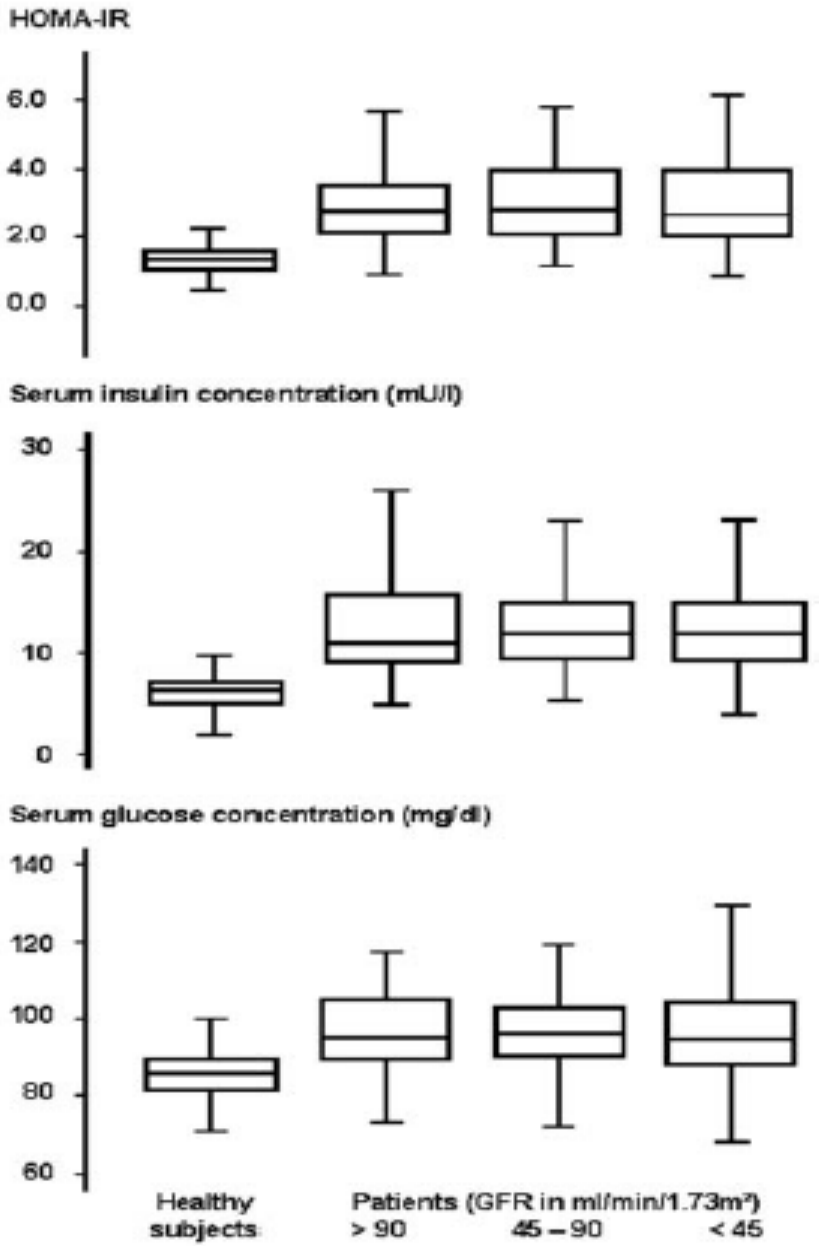
- Common in ESRD and CKD, but evidence on the latter is scarce.
- DeFronzo, using the 'gold standard' euglycemic hyperinsulinemic clamp, found evidence of IR in uremia in 1978



DeFronzo RA, Metabolism 27: 1866–1880, 1978 ; DeFronzo, et al, J Clin Invest 425-35,1978

Outline

- Mechanisms and Causes
- Assessment
- Consequences
- Interventions



Renal Insulin Resistance Syndrome, Adiponectin and Cardiovascular Events in Patients with Kidney Disease: The Mild and Moderate Kidney Disease Study

Bjoern Becker,* Florian Kronenberg,† Jan T. Kielstein,* Hermann Haller,* Christian Morath,‡ Eberhard Ritz,‡ and Danilo Fliser;* for the MMKD Study Group

227 non-diabetic CKD patients

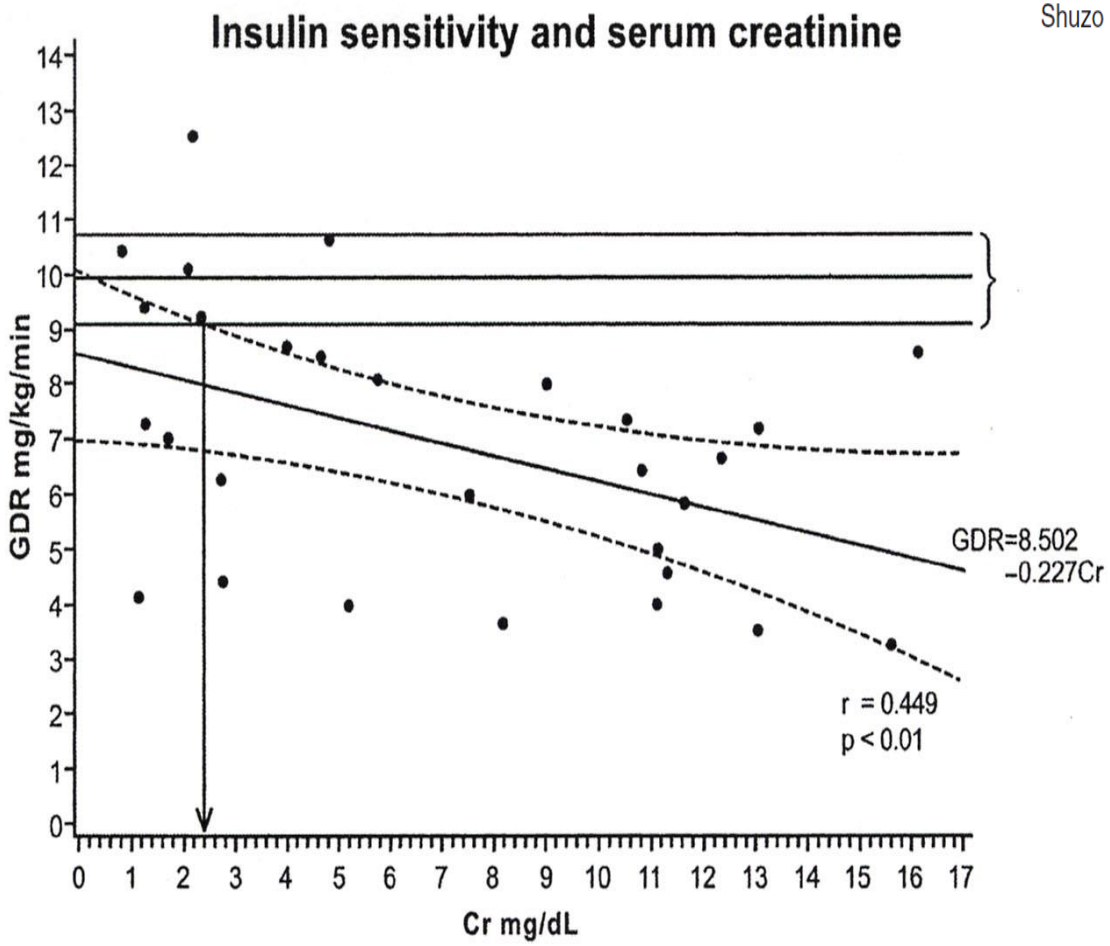
HOMA-IR, glucose and insulin were not different across 3 CKD groups, but higher as compared to healthy controls.

Becker B, JASN 16; 1091-1098, 2005

At what stage of CKD does IR appear ?

Insulin Resistance in Patients With Chronic Kidney Disease

Shuzo Kobayashi, MD, PhD, Kyoko Maesato, MD, Hidekazu Moriya, MD,
Takayasu Ohtake, MD, PhD, and Toshio Ikeda, MD, PhD

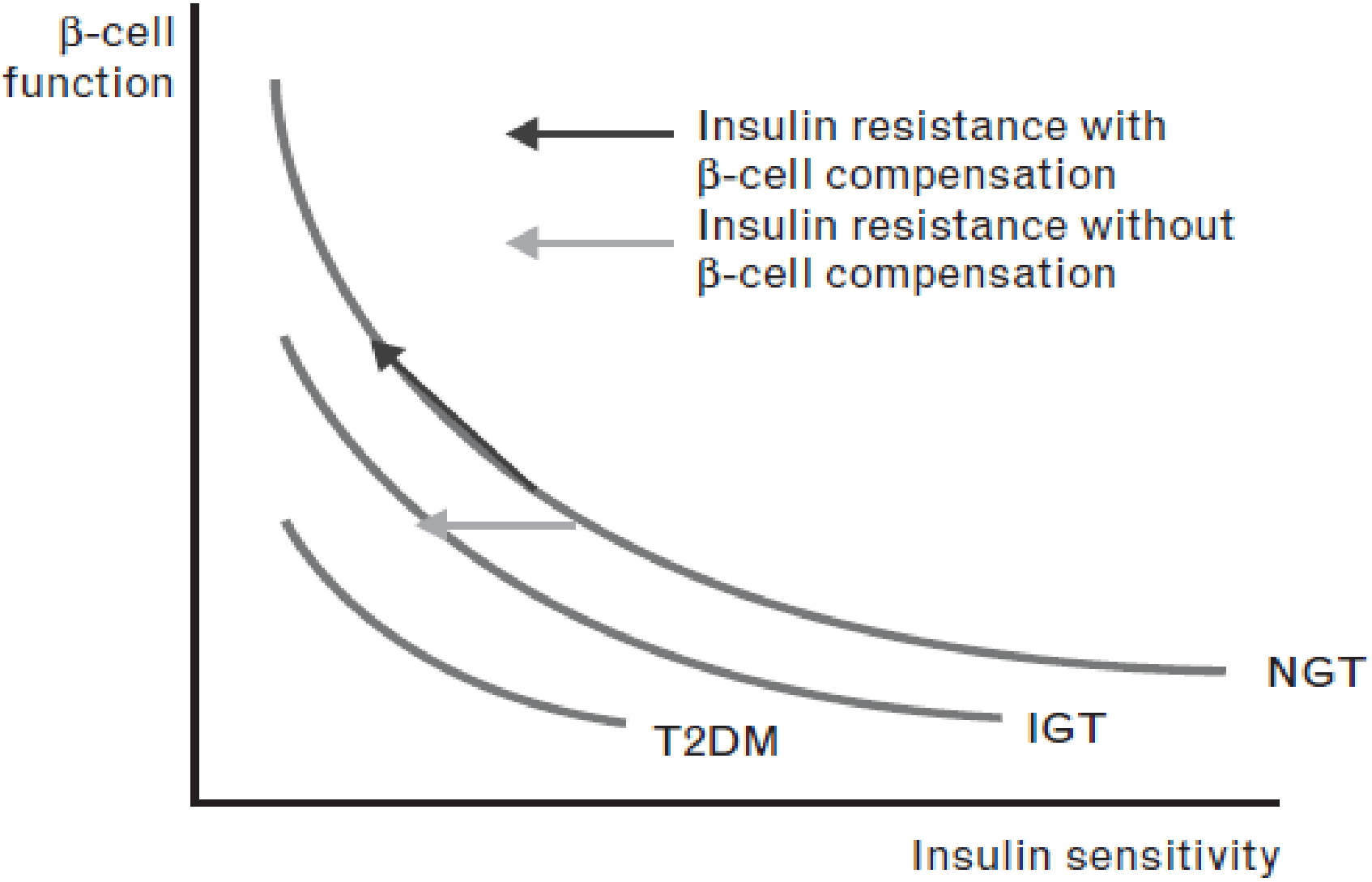


IS by Hyperinsulinemic euglycemic glucose clamp in 29 non-DM patients with different stages of CKD.

IS negativaly correlated with the decline in renal function.

Kobayashi et al.: AJKD 45: 275-280, 2005

Compensatory relationship between insulin sensitivity and β-cell function



Hien Phama et al, Current opinion in nephrology and hypertension, 20: 640-646, 2011.

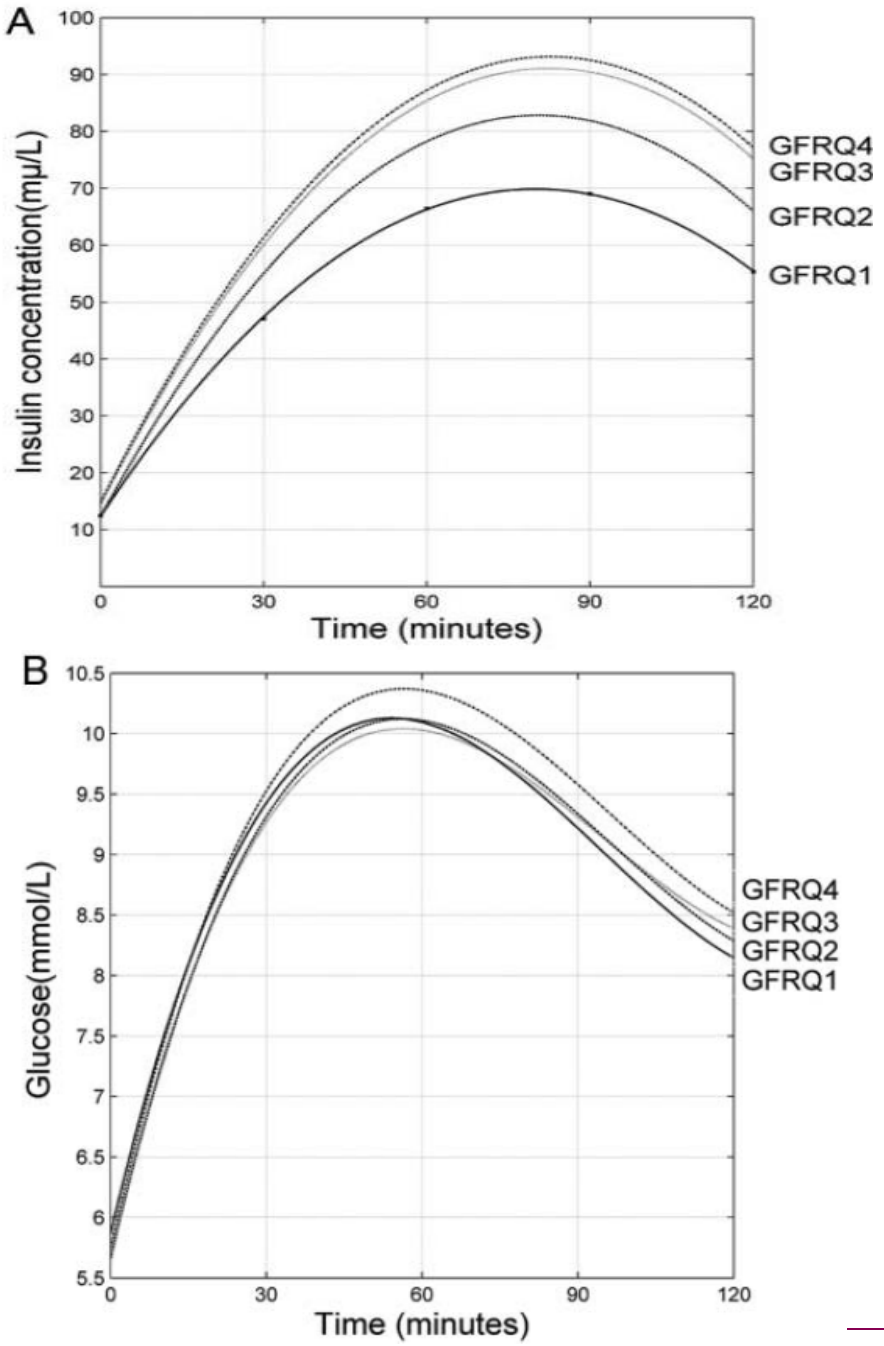
Karolinska Institutet

Kidney function, β-cell function and glucose tolerance in older men

Ting Jia,[1,2] Ulf Risérus,[3] Hong Xu,[1] Bengt Lindholm,[1] Johan Ärnlöv,[4,5] Per Sjögren,[3] Tommy Cederholm,[3] Tobias E. Larsson[1], T. Alp Ikizler[6], Juan J. Carrero[1,7]

Parameters	Decreasing quartiles of eGFR Q1(n = 254)	Q2(n = 254)	Q3(n = 254)	Q4(n = 253)	P for trend
β cell function assessment					
$AUC_{Ins0-30}$, μ*30 min/liter	855 (621–1172)	921 (657–1348)	923 (663–1333)	1002 (650–1464)	0.004
$AUC_{Ins90-120}$, μ*30 min/liter	3075 (2789–3450)	3155 (2877–3519)	3246 (2882–3667)	3325 (2926–3652)	<0.001
Estimated 1st phase insulin release, pM	976 (752–1214)	978 (772–1398)	1015 (781–1468)	1098 (751–1494)	<0.001
$Insulinogenic\ index_{30}$, μ/liter/min	3.8 (2.5–6.0)	4.2 (2.7–7.0)	4.5 (3.0–7.2)	4.7 (3.0–7.7)	0.008
Glucose tolerance					
$AUC_{Ins0-30}/AUC_{glu0-30}$	4.0 (3.0–5.4)	4.2 (3.2–6.3)	4.4 (3.2–6.4)	4.6 (3.2–6.8)	<0.001
$AUC_{Ins90-120}/AUC_{glu90-120}$	14.2 (11.7–17.1)	14.5 (12.1–17.7)	14.7 (12.4–18.0)	14.4 (12.2–17.6)	0.24
2-hour glucose concentration, mmol/liter	6.88 ± 1.91	6.85 ± 1.81	6.91 ± 1.78	7.10 ± 1.81	0.12
Impaired glucose tolerance,%	32	30	28	35	0.34
Composite β cell function					
Oral disposition index, DI_0	0.98 (0.60–1.62)	1.13 (0.64–1.76)	1.23 (0.78–1.90)	1.16 (0.69–1.82)	0.01
Insulin resistance assessment					
Clamp-derived MCR, mg min^{-1} kg^{-1}	6.25 ± 2.21	6.09 ± 2.22	6.07 ± 1.99	5.30 ± 2.00	0.006
Fasting glucose at OGTT, mmol/liter	5.29 (4.8–5.7)	5.39 (5–5.7)	5.3 (5–5.6)	5.3 (4.9–5.7)	0.90
Fasting insulin at OGTT, pmol/liter	10.9 (8.2–14.1)	10.9 (8.2–14.1)	10.9 (8.2–14.1)	10.9 (8.2–14.1)	0.37
OGTT-derived Matsuda Index	36.5 (23.3–56.4)	32.2 (22.2–50.5)	34.5 (24.6–48.3)	32.8 (21.7–45.8)	0.01

T Jia et al JCEM 2015;100(2):587-93 Allegra V et al KI 1990;38:1146-1150



- 466 non-diabetic CKD patients
- IR (clamp method) increased across decreasing eGFR, while β-cell function was higher.
- 2-hour post load glucose tolerance was not different.

- **Conclusion:** In CKD, increased β-cell function compensates for loss in IS that accompanies kidney dysfunction

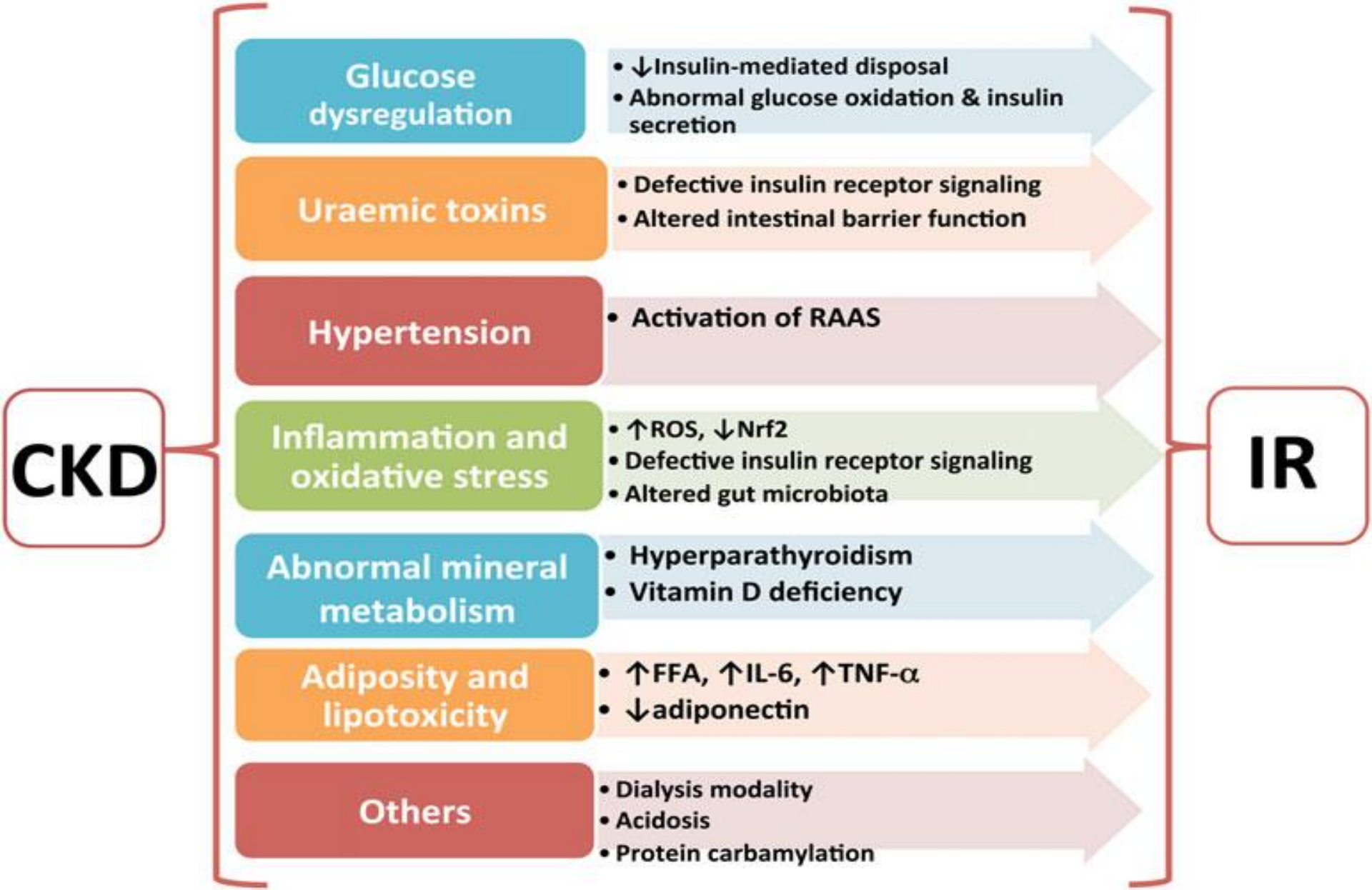
T Jia et al JCEM 2015;100(2):587-93

IR in CKD

- In normal conditions, 30–80% of circulating insulin is removed by kidney.
- The decline of renal function is associated with impaired insulin-induced glucose utilization of peripheral target tissues, and IR.
- The net balance between insulin resistance and β-cell function may be preserved in CKD.

Laetitia Koppe et al. Nephrol Dial Transplant (2014) 29: 1666–1674

Other Causes of IR in CKD



Clinical Correlates of Insulin Sensitivity and Its Association with Mortality among Men with CKD Stages 3 and 4

Hong Xu,[*†] *Xiaoyan Huang,*[*‡] *Johan Ärnlöv,*[§‖] *Tommy Cederholm,*[¶] *Peter Stenvinkel,*[*] *Bengt Lindholm,*[*] *Ulf Risérus,*[¶] *and Juan Jesús Carrero*[***]

Variables	eGFR Adjusted	
	Slope (95% CI)	*P* Value
Metabolic syndrome components		
Waist circumference, cm	−0.11 (−0.13 to −0.10)	<0.001
Triglycerides, mmol/L	−0.92 (−1.15 to −0.69)	<0.001
HDL, mmol/L	1.79 (1.33 to 2.27)	<0.001
Systolic BP, 10 mmHg	−0.11 (−0.20 to −0.02)	0.01
Diastolic BP, 10 mmHg	−0.28 (−0.46 to −0.10)	0.003
Fasting glucose, mmol/L	−0.98 (−1.26 to −0.69)	<0.001
Other biomarkers		
C-reactive protein, mg/L	−0.03 (−0.06 to 0.01)	0.15
IL-6, ng/L	−0.03 (−0.05 to −0.01)	0.006
UAER, 200 μg/min	0.08 (−0.24 to 0.40)	0.63

Metabolic syndrome components, and IL-6, were clinical correlates of insulin sensitivity (by clamp method) in 446 non-DM patients with CKD.

Xu H, et al CJASN 2014;9(12):2104-10

Inflammation, adipokines and insulin resistance

Table 4. Clinical determinants of insulin resistance measured by hyperinsulinemic euglycemic clamp

Variable	Adjusted Analysis[a]	
	Beta Coefficient (95% CI)	*P*
Adipose tissue		
total fat mass percent (DEXA) ($n = 12$)[a]	−0.31 (−0.427, −0.204)	<0.001
truncal fat percent (DEXA) ($n = 12$)[a]	−0.24 (−0.296, −0.189	0.01
Adipokines		
adiponectin (μg/ml)	0.15 (0.05, 0.25)	0.005
leptin (log; ng/ml)	−2.06 (−2.54, −1.58)	<0.001
resistin (log; ng/ml)	3.55 (1.33, 5.76)	0.002
Inflammatory markers		
IL-6 (log; pg/ml)	−1.43 (−2.47, −0.395)	0.007
CRP (log; mg/dl)	−1.08 (−1.88, −0.296)	0.007
Lipids		
triglycerides (mg/dl)	−0.14 (−0.037, 0.008)	0.21
LDL (mg/dl)	−0.02 (−0.07, 0.02)	0.32
HDL (mg/dl)	0.03 (−0.05, 0.12)	0.42

Adriana M Hung, et al CJASN 2011;6:767-774 Nephrol Dial Transplant (2011) 26: 2814–2819

Table 2. Results of Univariate Regression Analyses for GDR

Independent Variables	*P*	*r*
Age	NS	
Body mass index	0.038	−0.401
Blood pressure	NS	
Albumin	NS	
Blood urea nitrogen	0.014	−0.450
Creatinine	0.010	−0.457
Creatinine clearance	0.002	0.549
Insulin	0.029	−0.421
HOMA	0.0217	−0.425
iPTH	0.0207	−0.513
Lipoprotein(a)	NS	
Total cholesterol	NS	
TG	0.0237	−0.434
High-density lipoprotein cholesterol	NS	
Low-density lipoptrotein cholesterol	NS	
Apo A-1	NS	
Apo A-2	NS	
Apo B	NS	
Apo A-1/Apo B	0.047	0.396
Apo E	NS	
Hematocrit	NS	
Bicarbonate	0.0004	0.611
CRP	NS (0.076)	
Fibrinogen	0.0441	−0.390
LVMI	NS	

The independent clinical correlates of insulin sensitivity (clamp method) were bicarbonate levels and ApoA1/ApoB ratio

Table 3. Stepwise Multiple Regression Analysis of Factors Related to Insulin Sensitivity

Variables	Standard Coefficient	F	*P*
Bicarbonate	0.562	13.08	<0.001
Apo A-1/B	0.354	6.58	<0.05

Kobayashi et al.AJKD 45: 275-280, 2005

Which dietary modifications improves insulin sensitivity?

Dietary intervention	Weight loss (short term, up to 2 years)	Insulin resistance
Energy-reduced diet (sustained)	Strong benefit	Strong benefit[1,2]
Reduction in total fat (<30%)	Modest benefit; less effective than low-carbohydrate, high-protein (HP) diets[5,24]	Modest benefit; but increased IR with excessive fat intake (>37%)[2,4,5,8]
Reduction of SFA (<7%)	Unknown if total energy intake is not reduced	Probably beneficial[2,4,5,8]
Reduction of TFA (as low as possible)	Unknown if total energy intake is not reduced	Inconsistent; probably modest benefit (animal studies)[2,4,5,8]
Increase in MUFA (>10%)	Unknown if total energy intake is not reduced	Modest benefit[5,8]
Increase in PUFA (>10%)	Unknown if total energy intake is not reduced	
n-3 PUFA		
n-6 PUFA		
Low-carbohydrate diets	Modest benefit, at least in the short term[24]	Unknown, perhaps adverse in HP setting[22,23,26,30]

Lower energy, diet SFA and carbohydrate intake and higer MUFA and PUFA associated with reduced insulin resistence

Martin O Weickert, Clinical Endocrinology, 2012,(77), 508-512

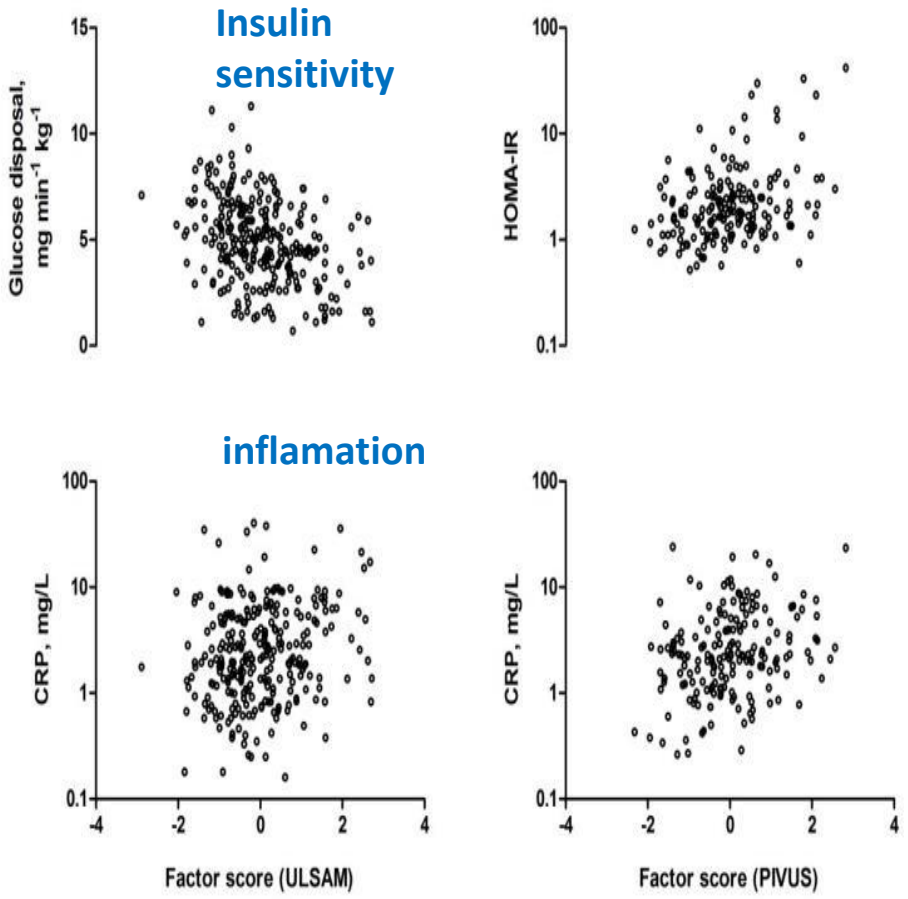
Original Article | Journal of INTERNAL MEDICINE

doi: 10.1111/joim.12130

Serum fatty acid patterns, insulin sensitivity and the metabolic syndrome in individuals with chronic kidney disease

X. Huang[1], P. Sjögren[2], J. Ärnlöv[3,4], T. Cederholm[2], L. Lind[5], P. Stenvinkel[1], B. Lindholm[1], U. Ris J. J. Carrero[1,6]

The worse the dietary fat quality (A diet rich in SFA and poor in LA, low PUFA/high SFA score), the higher the patient's systemic inflammation and the worse their insulin sensitivity.



X Huang et al , J Intern Med. 2014 Jan;275(1):71-83.

Assessment

Dynamic Assessment

- **Hyperinsulinemic euglycemic clamp-** insulin sensitivity (IS) gold standard

  Hyperinsulinemic hyperglycemic clamp-β cell function (BCF)
- **Frequently samples intravenous glucose tolerance test with minimal modelling (FSIGTT) -** IS and BCF
- **Oral glucose tolerance test (OGTT) -** IS and BCF

  ISI comp, MCR test, OGIS -IS

  empirical indices, model based indices-BCF

Fasting methods - IS and BCF

Homeostatic model assessment (HOMA-R)-IS

Quantitative insulin sensitivity check index (QUICKI)-IS

McCauley-IS

Homeostatic model assessment (HOMA-B)-BCF

Hien Phama et al, Current opinion in nephrology and hypertension, 20**:** 640-646,2011

A Comparison of Novel and Commonly-Used Indices of Insulin Sensitivity in African American Chronic Hemodialysis Patients

Adriana M. Hung,[*†] *Mary B. Sundell,*[†] *Phyllis Egbert,*[†] *Edward D. Siew,*[†] *Ayumi Shintani,*[†] *Charles D. Ellis,*[†] *Aihua Bian,*[†] *and T. Alp Ikizler*[*†]

Table 2. Correlation of the different IR indices with glucose-disposal rate by hyperinsulinemic euglycemic clamp in chronic hemodialysis patients

IR Index	All Patients	
	r_s	P
LAR	−0.72	<0.001
HOMA-AD	−0.67	<0.001
HOMA-IR	−0.58	<0.002
QUICKI	0.58	<0.004
McAuley's index	0.5	<0.03

The correlation coefficients are done by Spearman correlation (r_s). Statistical association was tested by GEE analysis in the 10 participants with all three visits included.

12 MHD patients

Adiponectin-based indices are best correlated with IR by HEGC.

HOMA-IR and QUICK are also valid alternatives

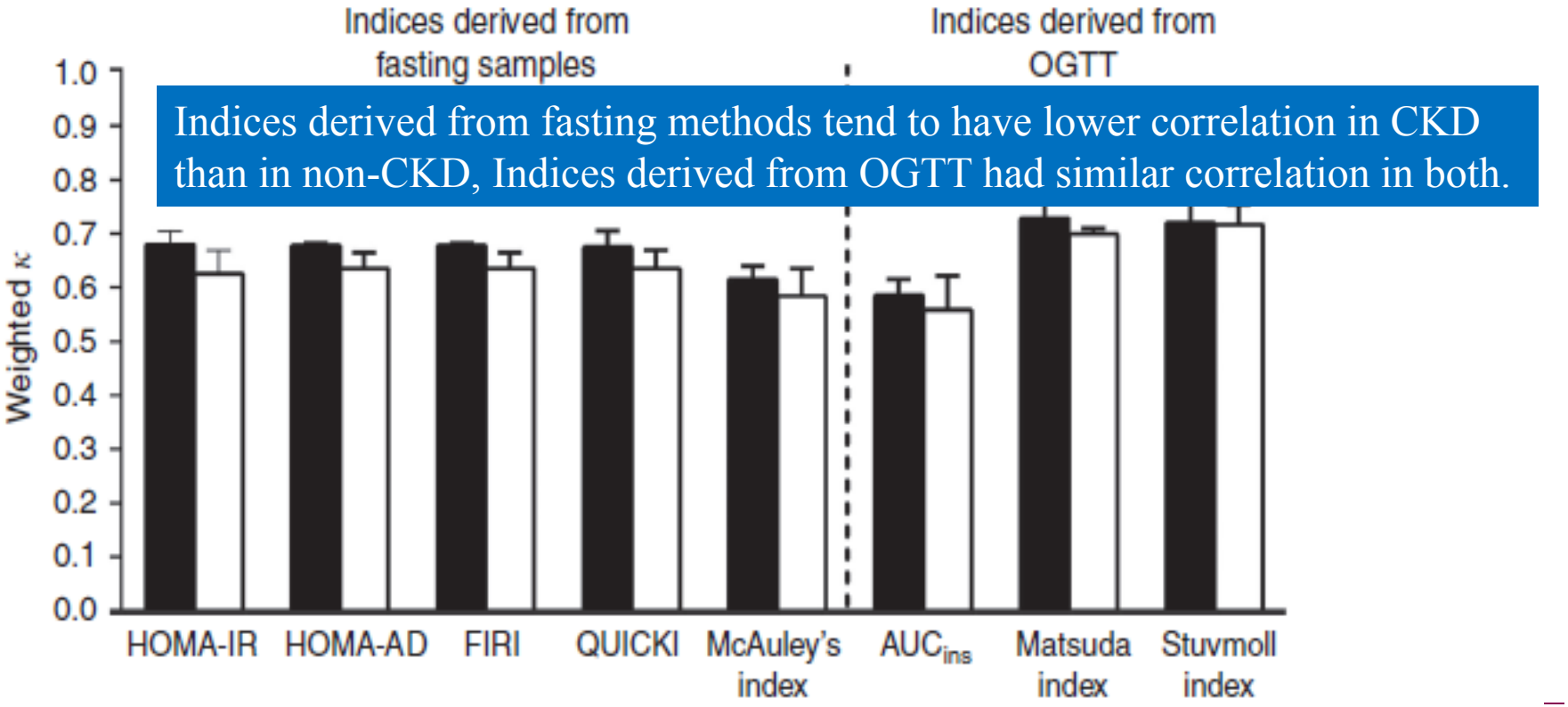
Adriana M Hung, et al CJASN 2011;6:767-774

http://www.kidney-international.org clinical investigation

Karolinska Institutet

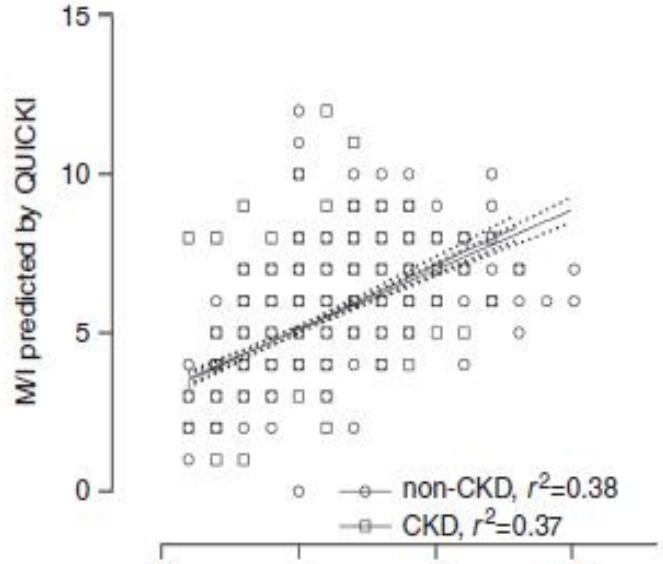
Validation of insulin sensitivity surrogate indices and prediction of clinical outcomes in individuals with and without impaired renal function

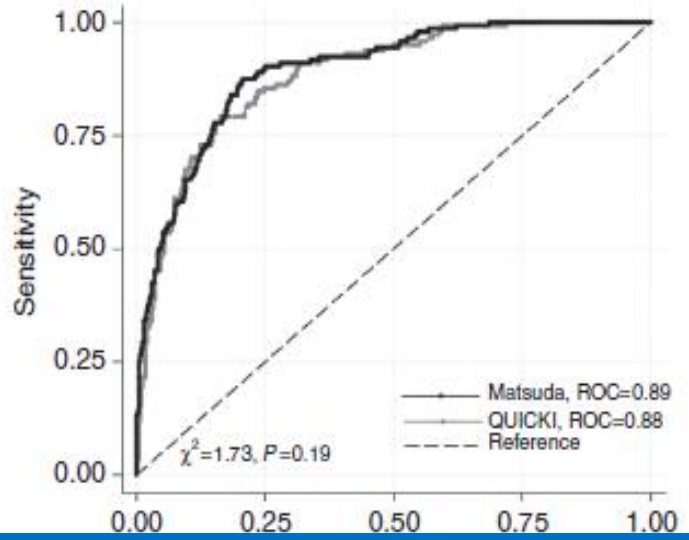
Ting Jia[1], Xiaoyan Huang[1,2], Abdul R. Qureshi[1], Hong Xu[1,3], Johan Ärnlöv[4,5], Bengt Lindholm[1], Tommy Cederholm[6], Peter Stenvinkel[1], Ulf Risérus[6] and Juan J. Carrero[1,7]



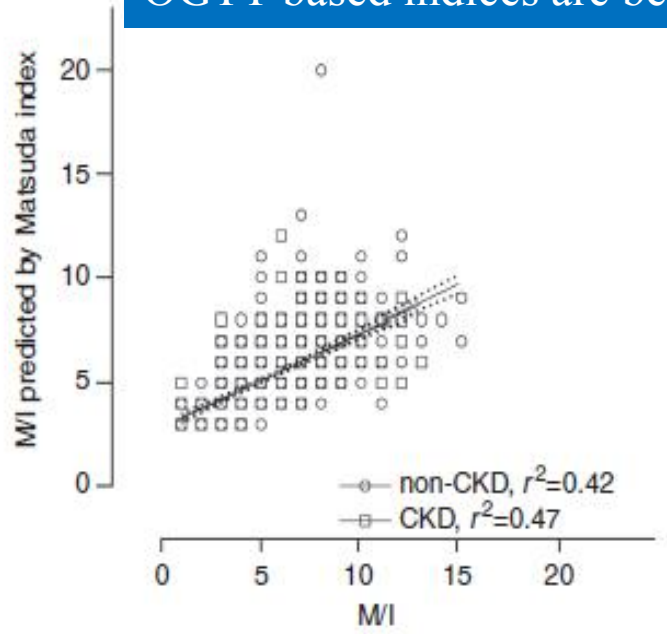
Indices derived from fasting methods tend to have lower correlation in CKD than in non-CKD, Indices derived from OGTT had similar correlation in both.

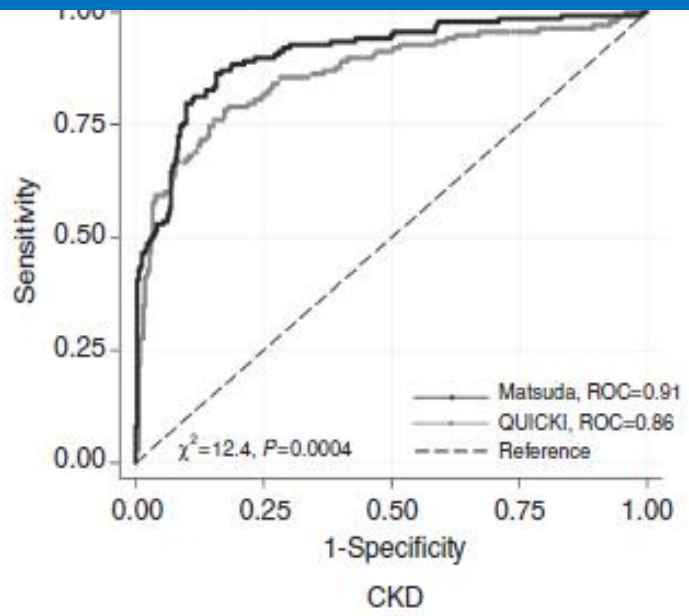
T Jia et al, Kidney Int. 2014 Aug;86(2):383-91.





ISIs provided satisfactory estimates IS in patients with CKD
OGTT based indices are better accuracy against HEGC than fasting sample





T Jia et al, Kidney Int. 2014 Aug;86(2):383-91.

Choosing the best assessment of Insulin sensitivity in CKD

- The gold-standard euglycemic–hyperinsulinemic clamps is the reference assessment of IS because it is not subjected to bias by GFR (retention of insulin and glucose)

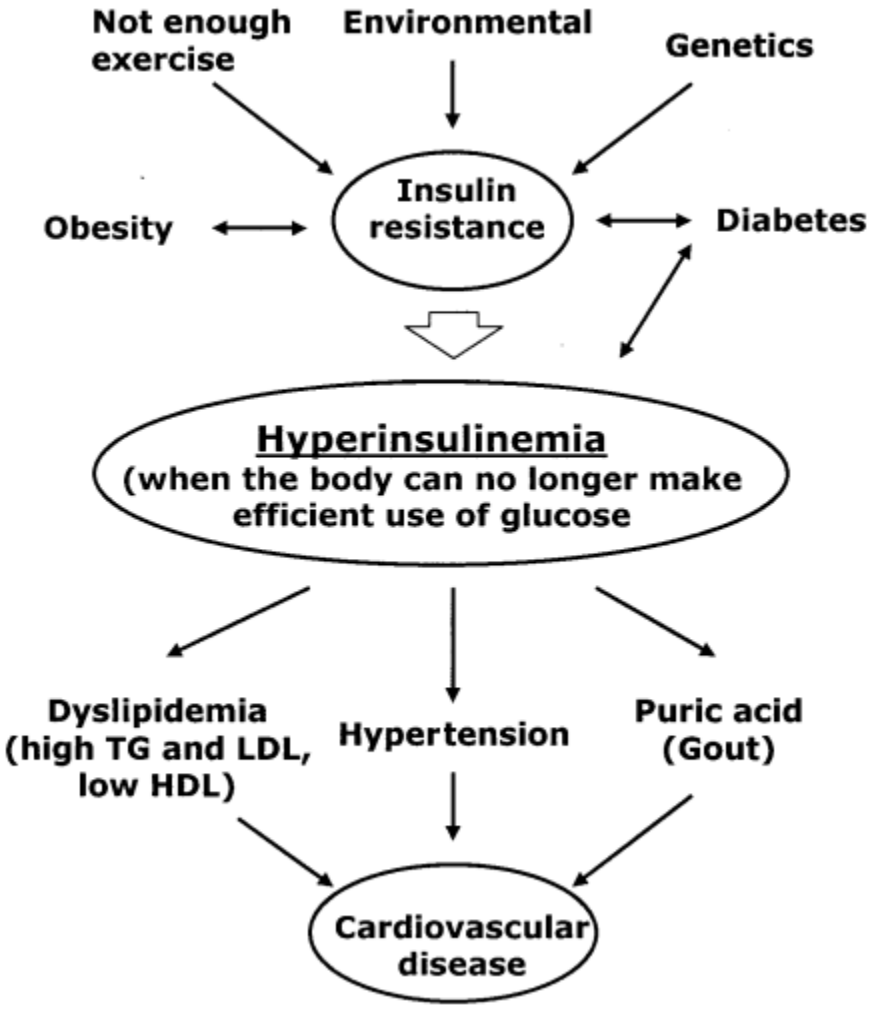
- All ISIs provided satisfactory estimates of the glucose disposal rate in patients with CKD.

- OGTT based indices are better correlate IR by HEGC than fasting samples.

T Jia et al, Kidney Int. 2014 Aug;86(2):383-91.

Consequences

- IR contributing to the pathophysiology of type 2 DM or other clinical disorders, accompanied by cardiovascular disease
- Results are scarce and conflicting in CKD
- Some – but not all - have showed that IR is an independent predictor of cardiovascular mortality in ESRD.

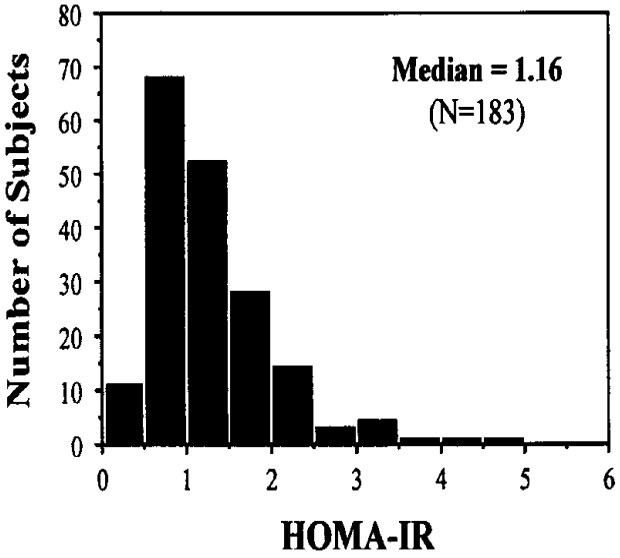


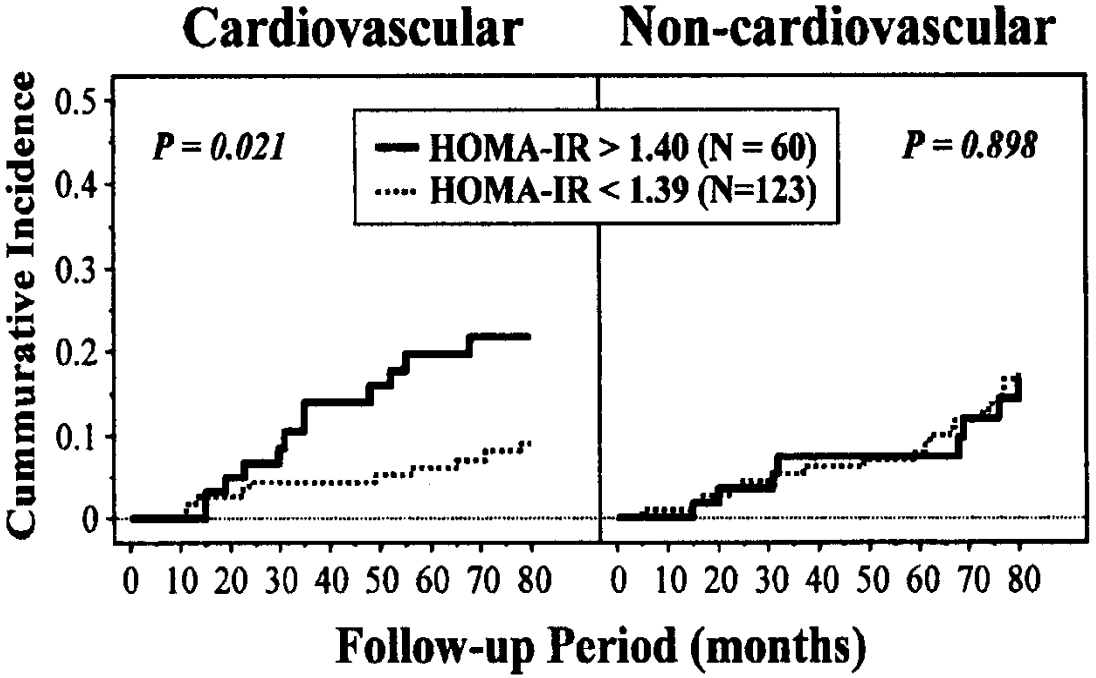
Sarah L et al CJASN 2014;9(12):638-40

J Am Soc Nephrol 13: 1894–1900, 2002

Insulin Resistance as an Independent Predictor of Cardiovascular Mortality in Patients with End-Stage Renal Disease

KAYO SHINOHARA,* TETSUO SHOJI,* MASANORI EMOTO,* HIDEKI TAHARA,* HIDENORI KOYAMA,* EIJI ISHIMURA,† TAKAMI MIKI,‡ TSUTOMU TABATA,§ and YOSHIKI NISHIZAWA*





183 HD patients, 22 events. Multivariate Cox model: HOMA-IR (top vs lower two tertiles) HR 4.5-4.8, The effect of HOMA-IR was independent of CRP.

Shinohara et al. JASN 13: 1894-1900, 2002;

Logistic regression showed that among 227 patients, those with CVD events had higher HOMA-IR at study inclusion

Becker B, JASN 16; 1091-1098, 2005

Clinical Correlates of Insulin Sensitivity and Its Association with Mortality among Men with CKD Stages 3 and 4

Hong Xu,†‡ *Xiaoyan Huang,*†‡ *Johan Ärnlöv,*§‖ *Tommy Cederholm,*¶ *Peter Stenvinkel,** *Bengt Lindholm,** *Ulf Risérus,*¶ *and Juan Jesús Carrero****

Table 4. Cox regression analysis between all-cause and cardiovascular mortality and glucose disposal rate in 446 nondiabetic men with CKD

Cox Regression Models	M (milligrams per kilogram per minute)	Hazard Ratio (95% CI)			
		Crude Model	Adjusted Model 1	Adjusted Model 2	Adjusted Model 3
All-cause mortality					
Continuous model	1-mg/kg per minute	0.96 (0.89 to 1.03)	0.94 (0.85 to 1.04)	0.95 (0.86 to 1.05)	0.96 (0.87 to 1.06)
Threshold model					
Quartile 1	≤4.1	Reference	Reference	Reference	Reference
Quartile 2–4	>4.1	0.76 (0.53 to 1.10)	0.73 (0.46 to 1.15)	0.77 (0.48 to 1.23)	0.80 (0.50 to 1.28)
Cardiovascular mortality					
Continuous model	1-mg/kg per minute	0.90 (0.81 to 1.01)	0.90 (0.78 to 1.04)	0.95 (0.83 to 1.09)	0.96 (0.83 to 1.10)
Quartile 1	≤4.1	Reference	Reference	Reference	Reference
Quartile 2–4	>4.1	0.55 (0.34 to 0.89)	0.56 (0.30 to 1.04)	0.67 (0.36 to 1.26)	0.68 (0.36 to 1.29)

In 446 CKD patients, IS as measured with euglycemic clamps was associated neither with all-cause, nor cardiovascular mortality

Xu H, et al CJASN 2014;9(12):2104-10

Effect modification IR and death: BMI, smoking, physical activity

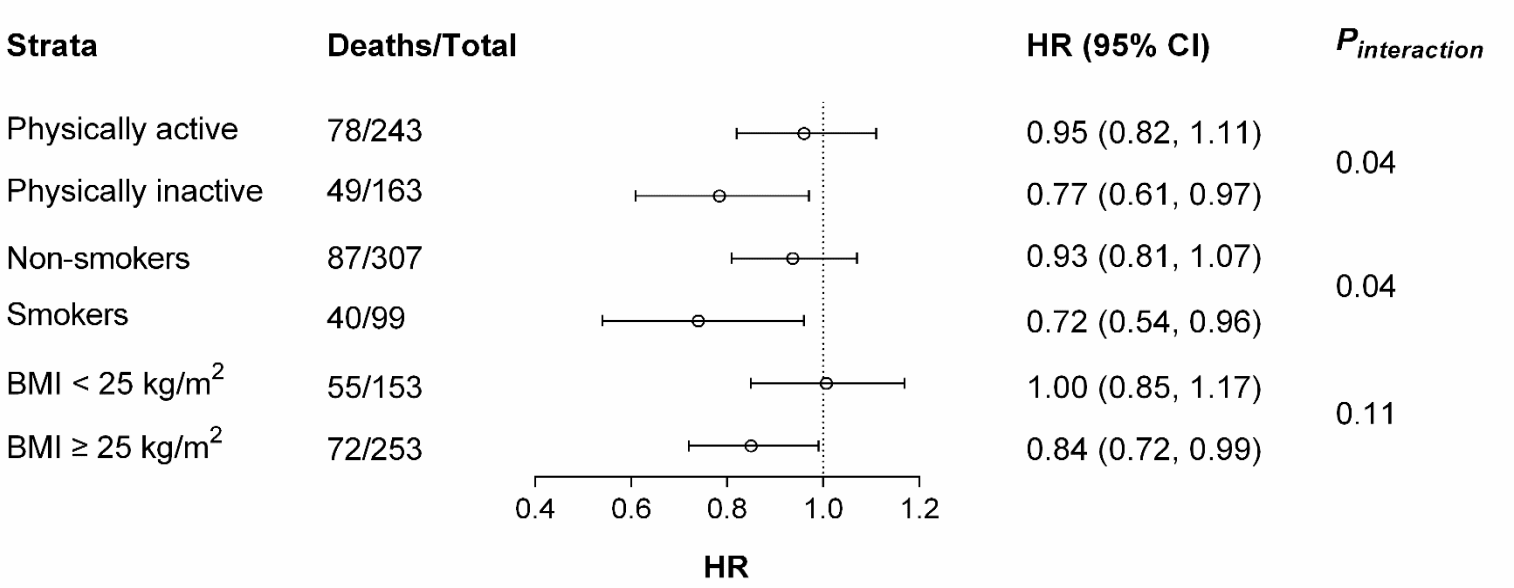


Figure 1

Subgroup analysis: IS appears as an independent correlate of mortality among individuals with unhealthy lifestyle: physically inactive, smokers, and BMI≥ 25 kg/m^2

Xu H, et al CJASN 2014;9(12):2104-10

Insulin Resistance, Cystatin C, and Mortality Among Older Adults

Ian H. de Boer, MD, MS[1]
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Bryan Kestenbaum, MD, MS[1]
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David S. Siscovick, MD, MPH[1]

well defined: impai
may promote insuli
retained uremic tox
tive vitamin D defi
tance may contribut

Table 2—*Associations of ISI, fasting insulin concentration, glucose concentration 2 h after glucose load, and fasting glucose concentration with all-cause mortality among 3,138 CHS participants*

	Deaths (*n*)	Incidence rate (percent/year)	Model 1	Model 2	Model 3	eGFR models: Model 4	eGFR models: Model 5
ISI							
≥4.91	428	4.2	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3.31–4.90	436	4.4	1.05 (0.92–1.21)	1.08 (0.94–1.24)	1.06 (0.92–1.21)	1.06 (0.93–1.22)	1.05 (0.92–1.21)
2.22–3.30	469	4.8	1.13 (0.99–1.30)	1.14 (0.99–1.31)	1.10 (0.96–1.26)	1.07 (0.93–1.22)	1.06 (0.92–1.21)
<2.22	477	4.9	1.26 (1.11–1.44)	1.21 (1.06–1.41)	1.17 (1.01–1.36)	1.11 (0.97–1.29)	1.12 (0.96–1.30)

Similar finding : 3138 elderly, 1810 death. IR as measured with OGTT was associated with all-cause mortality, but the significance was lost after further adjustment for eGFR

De Boer IH et al, Diabetes Care. 2012, 35:1355-1360.

Improving CKD outcomes by interventions of IR : Can We Do It?

1. Lifestyle modification
2. Dietary modification.
3. Physical activity.
4. Smoking cessation
5. Pharmacologic interventions that modulate IR:

- Metformin, Thiazolidinediones,RAAS blockers,
- Vitamin D therapy
- Antioxidants
- Dialysis modality
- Icodexin

VOLUME 344 MAY 3, 2001 NUMBER 18

IR was improved in Intervention group for healthy life style

PREVENTION OF TYPE 2 DIABETES MELLITUS BY CHANGES IN LIFESTYLE AMONG SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE

JAAKKO TUOMILEHTO, M.D., PH.D., JAANA LINDSTRÖM, M.S., JOHAN G. ERIKSSON, M.D., PH.D., TIMO T. VALLE, M.D., HELENA HÄMÄLÄINEN, M.D., PH.D., PIRJO ILANNE-PARIKKA, M.D., SIRKKA KEINÄNEN-KIUKAANNIEMI, M.D., PH.D., MAURI LAAKSO, M.D., ANNE LOUHERANTA, M.S., MERJA RASTAS, M.S., VIRPI SALMINEN, M.S., AND MATTI UUSITUPA, M.D., PH.D., FOR THE FINNISH DIABETES PREVENTION STUDY GROUP

TABLE 2. CHANGES IN SELECTED CLINICAL AND METABOI TO THE END OF YEAR 1 IN THE SUBJECTS IN THE INTERVE

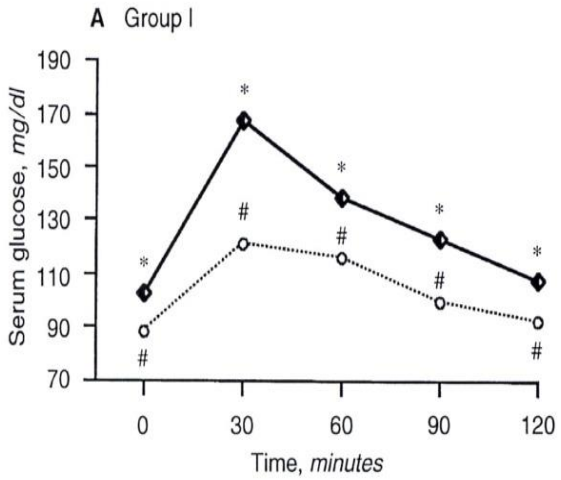
VARIABLE	INTERVENTION GROUP (N=256) mean ±SD	95% CI
Change in weight		
In kilograms	−4.2±5.1	−4.8 to −3.6
Percent change	−4.7±5.4	−5.0 to −4.4
Change in waist circumference (cm)	−4.4±5.2	−5.1 to −3.9
Change in plasma glucose (mg/dl)		
Fasting	−4±12	−6 to −2
2 Hr after oral glucose challenge	−15±34	−19 to −11
Change in serum insulin (μg/ml)		
Fasting	−2±9	−3 to −1
2 Hr after oral glucose challenge	−29±64	−37 to −21

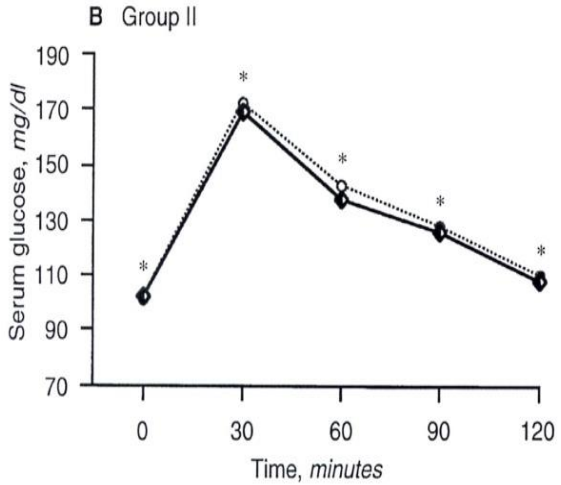
TABLE 4. SUCCESS IN ACHIEVING THE GOALS OF THE INTERVENTION BY ONE YEAR, ACCORDING TO TREATMENT GROUP.*

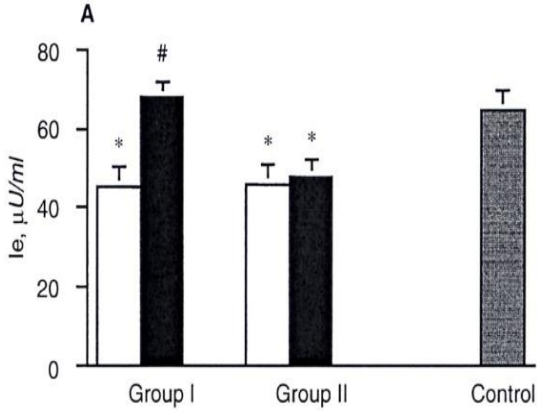
GOAL	INTERVENTION GROUP	CONTROL GROUP	P VALUE†
	% of subjects		
Weight reduction >5%	43	13	0.001
Fat intake <30% of energy intake	47	26	0.001
Saturated-fat intake <10% of energy intake	26	11	0.001
Fiber intake ≥15 g/1000 kcal	25	12	0.001
Exercise >4 hr/wk‡	86	71	0.001

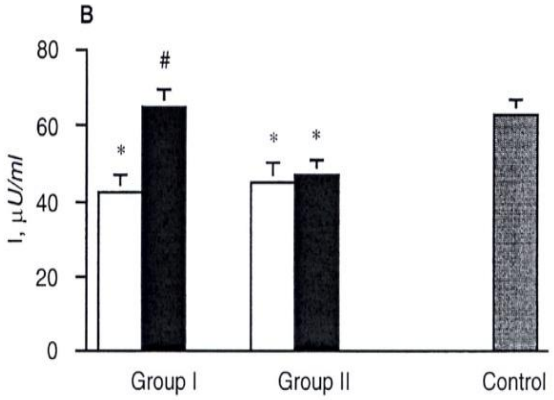
Jaaakko Tuomilihital et al, N Engl J Med 344:1343–1350

1,25-Dihydroxyvitamin D3 corrects insulin sensitivity in uremia





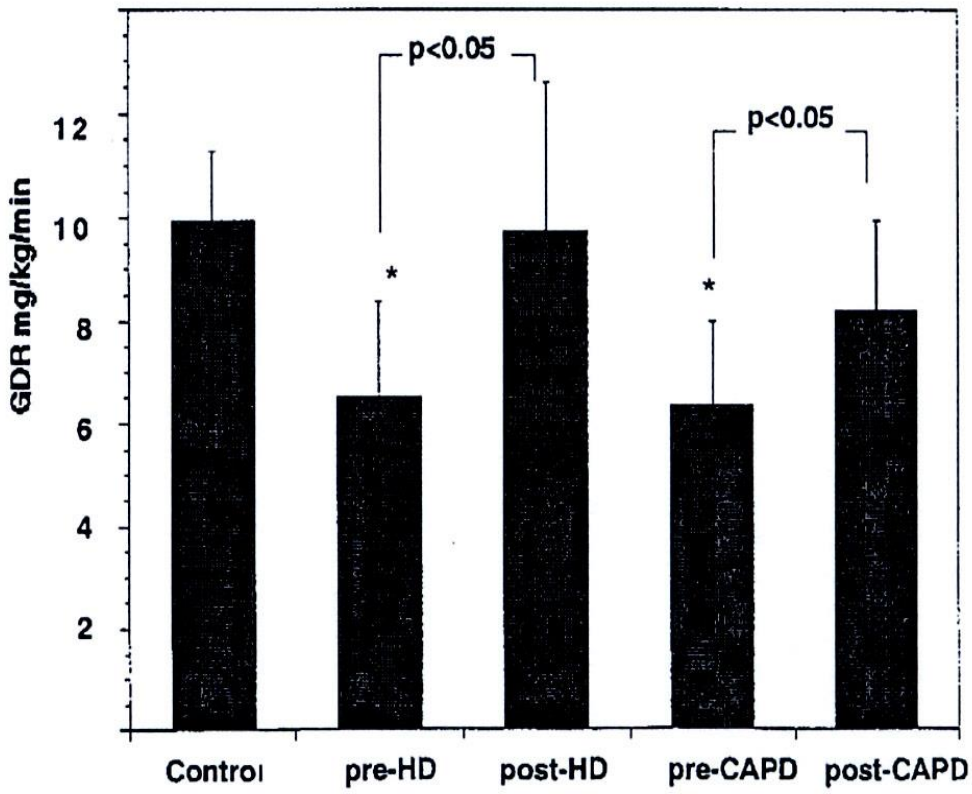




A series of the intervention studies showed that calcitriol administration improved IR in ESRD with HD

Mak et al. Kidney Int 53, 1353-1357, 1998; Kaukzky W et al, KI 1995;47:200-206; Quesadai etal NDT 1990:5; 1013-1017

Impact of dialysis therapy on insulin sensitivity



HD: n = 10; CAPD: n = 9
IS by hyperinsulinemic euglycemic clamp

Markedly improved insulin sensitivity in both HD and CAPD patients after 4-5 weeks of dialysis

Kobayashi et al.: NDT 15: 65-70, 2000

Nephrol Dial Transplant (2015) 0: 1–3
doi: 10.1093/ndt/gfv280

In Focus

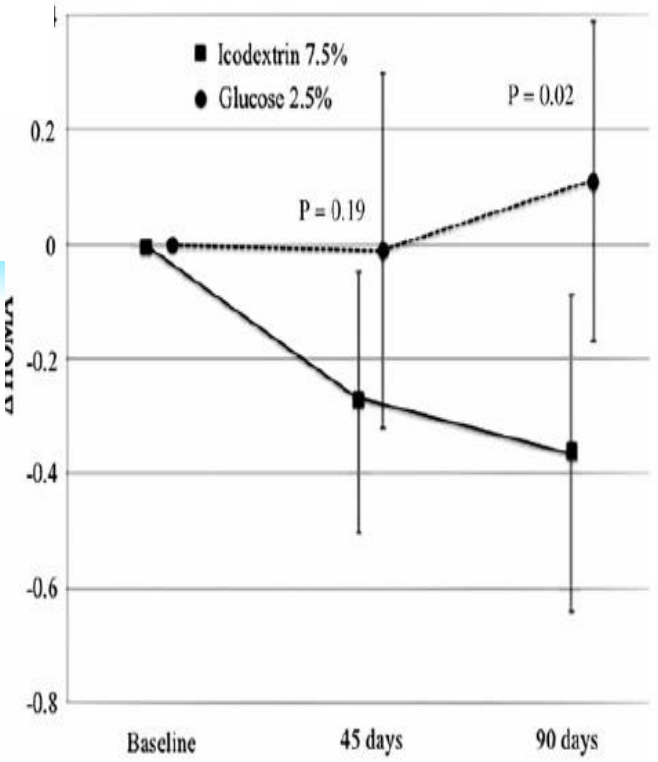
Reducing insulin resistance in patients undergoing peritoneal dialysis through the use of icodextrin-based solutions

Hong Xu[1], Juan Jesús Carrero[1,2] and Bengt Lindholm[1]

Icodextrin reduces insulin resistance in non-diabetic patients undergoing automated peritoneal dialysis: results of a randomized controlled trial (STARCH)

Table 2. Adjusted post-intervention levels of the primary and secondary outcomes[a]

Variables	Control group (glucose only) Value (95% CI)	Intervention group (icodextrin) Value (95% CI)
Fasting glucose (mg/dL)	94.5 (88.7–100.2)	92.8 (87.5–98.2)
HbA1c (%)	4.83% (4.67–4.99%)	4.71% (4.53–4.88%)
HOMA index*	1.89 (1.62–2.17)	1.49 (1.23–1.74)
Insulin (mmol/L)*	7.89 (6.84–8.93)	6.32 (5.34–7.29)



Markedly decreased HOMA-IR in intervension group with icodextrin after 90 days.

de Moraes TP et al .NDT 2015 (30): 1905-1911; H Xu et al .NDT 2015 (30): 1783-1785

What did I say?

1. IR is common in CKD and a consequence of kidney dysfunction.
2. Mechanisms leading to IR are largely unclear in CKD, but uremic toxins, acidosis, vitamin D deficiency, and others show associations with IR in human and experimental studies.
3. Clinically, IR can be estimated by a variety of methods. Although HEGC is the gold standard, estimated IS indices (HOMA, QUICKI; OGTT-derived) provide satisfactory estimates of IR in CKD to be use at bedside.
4. IR is in general linked to worse outcomes (CVD- and all-cause mortality).
5. Some prevalent but modifiable risk factors in CKD further contribute to worsen insulin resistance: obesity, sedentary lifestyle, or unhealthy diet.
6. Various interventions targeting IR may be beneficial in CKD patients: Vitamin D therapy, dialysis modality, icodextrin based solution

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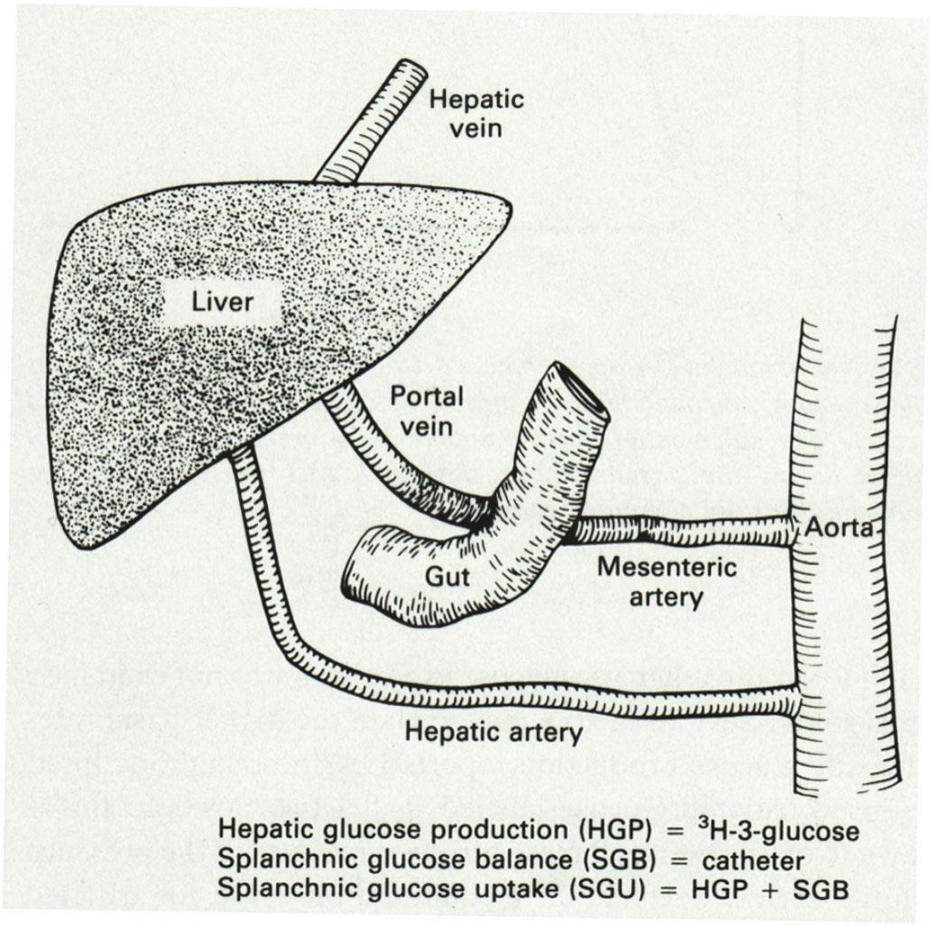
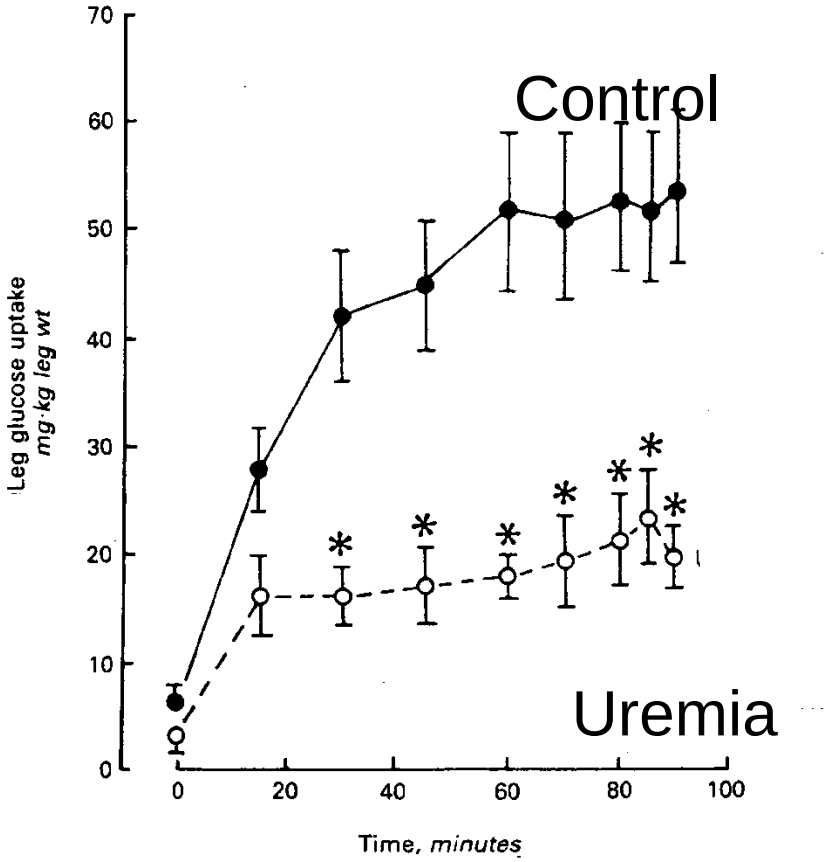
Net splanchnic glucose balance and splancnic glucose uptake in uremic and control subjects during the postabsorptive state and after euclycemic hyperinsulinemia





DeFronzo, et al: J Clin Invest 425-35,1978

DeFronzo, et al .J Clin Invest 67:563-68,1981

Body mass index and fat mass are the primary correlates of insulin resistance in nondiabetic stage 3–4 chronic kidney disease patients[1–3]

M Luisa Trirogoff, Ayumi Shintani, Jonathan Himmelfarb, and T Alp Ikizler

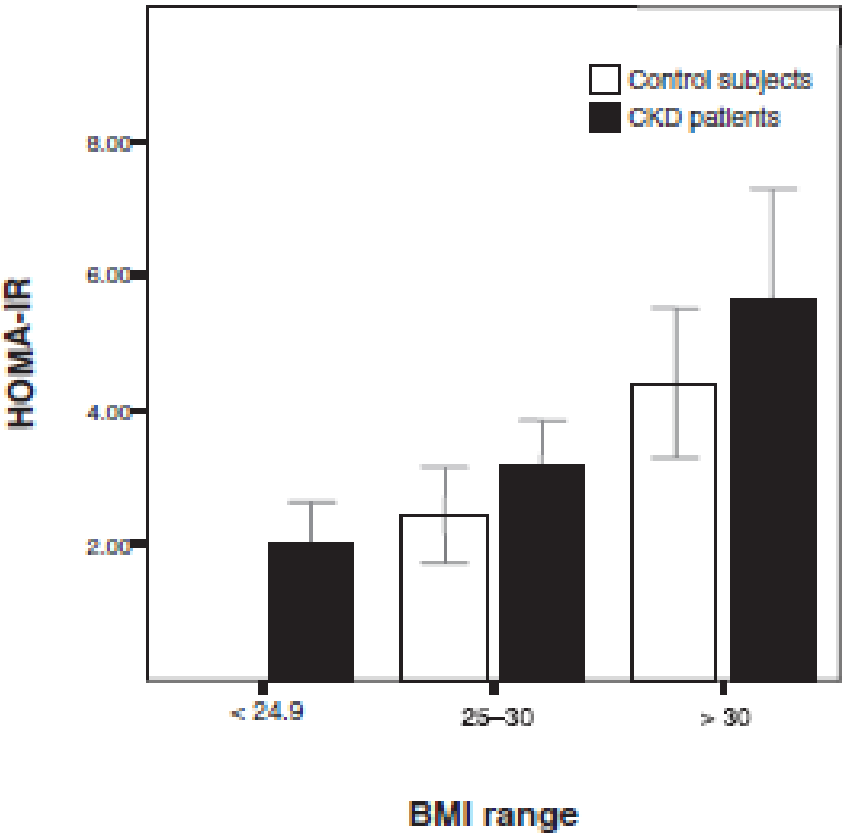
Association between homeostasis model assessment of insulin resistance and inflammatory cytokines and adipokines, body mass index, body fat percentage, and estimated glomerular filtration rate (eGFR) in study participants with and without chronic kidney disease[1]

	Value	r_s	P	P_{adj}[2]
IL-1β (pg/mL)	16.9 ± 91.6[3]	−0.241	0.012	0.214
IL-6 (pg/mL)	3.9 ± 3.3	−0.057	0.561	0.195
IL-10 (pg/mL)	2.4 ± 7	−0.113	0.247	<0.001
IL-12 (pg/mL)	4.25 ± 16.4	−0.133	0.172	0.074
IL-8 (pg/mL)	9.2 ± 10.9	−0.221	0.022	0.058
Adiponectin (μg/mL)	23.9 ± 17.8	−0.240	0.007	0.095
Resistin (ng/mL)	16.6 ± 8.5	0.035	0.701	0.492
TNF-α (mg/L)	1.4 ± 5.0	−0.213	0.028	0.465
CRP (mg/L)	4.22 ± 6.4	0.147	0.096	0.639
BMI (kg/m^2)	29.1 ± 6.2	0.496	<0.001	<0.001
Body fat (%)	31.6 ± 13.0	0.286	0.001	<0.001
eGFR	45.9 ± 24	−0.01	0.910	0.647

[1] n = 107. IL, interleukin; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein. Associations were calculated by using Spearman's correlations. eGFR was calculated by modified MDRD equation: $186 \times sCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) × 1.212 (if African American).

[2] Adjusted for age and sex.

[3] $\bar{x}$ ± SD (all such values).



M Larisa Trirogoff et al, AJCN 86: 1642-1648, 2007

Inflammation and insulin resistance

Karolinska Institutet

Among individuals with CKD, IL-6 is a strong predictor of IR

Table 3. Significant associations with IR, stratified by CKD among Health ABC participants

Participant characteristics	Overall (with eGFR), odds ratio (95% CI)[a]	Overall (with CKD), odds ratio (95% CI)	Without CKD, odds ratio (95% CI)[a]	With CKD, odds ratio (95% CI)[a]
Age (per 1 year)	1.00 (0.96–1.04)	1.00 (0.96–1.04)	1.00 (0.96–1.05)	1.02 (0.93–1.13)
Race (black)	1.90 (1.41–2.56)	2.05 (1.54–2.74)	1.99 (1.44–2.74)	2.63 (1.32–5.24)
Sex (women)	1.10 (0.80–1.52)	1.00 (0.73–1.36)	1.16 (0.81–1.66)	0.70 (0.34–1.43)
CKD	NA	1.57 (1.15–2.74)	NA	NA
eGFR (per 10 mL/min/1.73m^2	0.92 (0.87–0.98)	NA	NA	NA
Current smoker	0.62 (0.39–0.98)	0.62 (0.39–0.99)	0.51 (0.29–0.88)	NS
Log triglycerides per SD	1.59 (1.39–1.82)	1.60 (1.40–1.83)	1.49 (1.27–1.75)	1.94 (1.41–2.69)
HDL per SD	NS	NS	0.82 (0.68–0.99)	NS
Log adiponectin per SD	0.58 (0.51–0.67)	0.59 (0.52–0.68)	0.57 (0.49–0.67)	
Log IL6 per SD	NS	NS	NS	1.47 (1.07–1.97)
Log visceral fat per SD	2.05 (1.71–2.46)	2.15 (1.81–2.56)	2.06 (1.69–2.50)	2.47 (1.64–3.72)
Log subcutaneous fat per SD	1.62 (1.30–2.00)	1.80 (1.49–2.17)	1.82 (1.46–2.25)	2.01 (1.31–3.08)
Log muscle fat per SD	1.19 (1.00–1.42)	NS	NS	NS

Nephrol Dial Transplant (2011) 26: 2814–2819