M-L-18

Metabolic Syndrome and Chronic Kidney Disease

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History of Metabolic Syndrome

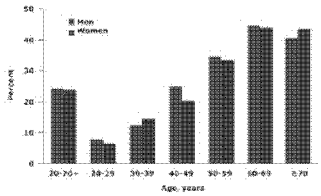
- Syndrome X ; Reaven GM, 1988
- Metabolic syndrome, Dysmetabolic syndrome, Cardiometabolic syndrome, Syndrome X, Insulin resistance syndrome, Deadly quartet, Obesity dyslipidemia syndrome
- WHO diabetes group : 1998
- NCEP-ATP III : 2001
- International Diabetes Federation :2004

Definitions Criteria for MS

Definition System	WHO (1998)	NCEP-ATP III (2001)	IDF (2004)
Criteria	Glucose abn'l + at least 2 other	Any 3 of 5 traits	Central obesity + at least 2 other
Glucose (mg/dL)	Fasting insulin ≥75% or FPG ≥ 110 or OGTT(2hr) ≥200	FPG≥110	FPG>100
TG (mg/dL)	≥150	≥150	≥150
HDL-C (mg/dL)	M <35 F <39	M <40 F <50	M <40 F <50
BP (mmHg)	≥ 140/90	≥ 130/85	> 130/85
Obesity	WHR > 0.9(M), 0.85(F) BMI ≥ 30 Waist girth≥94cm	Waist girth >102cm(M) > 88cm(F)	Waist girth >102cm(M) > 88cm(F) Asia : >90cm(M) >80cm(F)

Prevalence of NCEP ATP III Metabolic Syndrome

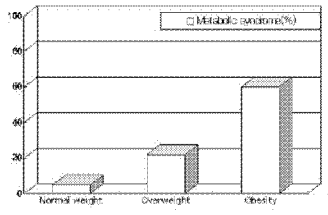
- NHANES III -



- 8,814 adults in the US, 1988-1994
- Overall prevalence of the MS : 22%
- Prevalence has continued to increase paticularly in women(NHANES 1999-2000)

Ford ES et al. NHANES III survey. JAMA 287:356,2002

Increased Body Weight is a Major Risk Factor for the MS



NHANES III survey, *Arch Intern Med* 163:427,2003

- BW increase ≥2.25Kg → 21~45% increase in the risk for MS
  Wilson PW et al. *Arch Intern Med* 1999
- Large waist circumference alone
  → 46% of individual develop the MS within 5 years
  Palaniapan L et al. Diabetes Care 2004

Metabolic Syndrome and Impaired Kidney Function

Authors	Design	Population	N	Predictor	Outcome	OR (95% CI)
Chen et al. [10]	Cross-sectional, nationally representative survey	NHANES III	6217	Metabolic syndrome	Prevalent GFR <60	2.50 (1.88–4.03)
				2 components		2.21 (1.15–4.24)
				3 components		3.35 (1.48–7.59)
				4 components		4.28 (2.05–8.93)
				5 components		6.85 (3.11–11.2)
				SBP ≥ 130/85 mmHg		2.35 (1.62–4.35)
				Plasma glucose ≥ 110 mg/dl		1.40 (0.95–2.06)
Kurella et al. [11**]	Prospective cohort	ARIC study	18095	Metabolic syndrome	Incident GFR <60	1.43 (1.19–1.73)
				2 components		1.33 (1.13–1.56)
				3 components		1.25 (1.02–1.53)
				4 components		1.64 (1.27–2.07)
				5 components		2.45 (1.32–4.54)
				SBP ≥ 130/85 mmHg		1.59 (1.39–2.35)
				Plasma glucose ≥ 110 mg/dl		1.11 (0.87–1.40)

ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; GFR, glomerular filtration rate; NHANES III, National Health and Nutrition Examination Survey III; OR, odds ratio.

Peralta CA et al. *Curr opin in nephrol hyperten* 15:361-365, 2006

MS and the Risk of CKD among Nondiabetic Adults

- 10,096 nondiabetics
- CKD : eGFR < 60 ml/min/1.73m^2
- 9 years follow up, NCEP-ATP III

- Results
  1. 691 persons(7%) : CKD onset
  2. Odd ratio : 1.43 (95%CI, 1.18–1.73)
  3. Compared with participants with no trait of the MS
     : one (1.13), two (1.53), three (1.75), four (1.84), Five (2.45)

- **Conclusion : MS is independently associated with an increased risk of incident CKD in nondiabetic adults**

Kurella M et al. *JASN* 16:2134-2140, 2005

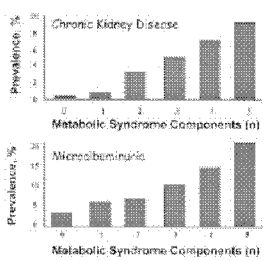
Microalbuminuria by Metabolic Syndrome

Study	Design	Population	N	Outcome	Measure of association
Palaniappan et al. 2003 [14]	Cross-sectional	NHANES III	5656	Albumin : creatinine ratio 30–300 mg/g	OR 2.2 (1.4–3.3) for women OR 4.1 (2.5–6.9) for men
Chen et al. 2004 [10]	Cross-sectional	NHANES III	6217	Albumin : creatinine ratio 30–300 mg/g	OR 1.89 (1.34–2.67)
Ostchega et al. 2004 [15]	Cross-sectional	Ambulatory untreated hypertensives	447	24h albumin excretion	17.7 mg versus 11.5 mg per 24h; $P < 0.05$
Wule et al. 2005 [16]	Cross-sectional	Ambulatory hypertensives with no CKD	959	24h albumin excretion rate in eighths	OR 2.43 (1.44–4.18)

CKD, Chronic kidney disease; NHANES III, National Health and Nutrition Evaluation Survey III; OR, odds ratio.

Peralta CA et al. *Curr opin in nephrol hyperten* 15:361-365, 2006

Risk for CKD and Microalbuminuria according to Number of MS Elements



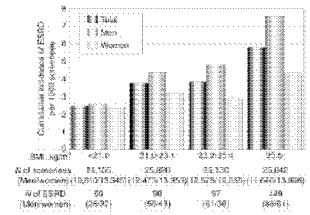
Chen J et al. *JASN* 14:469-477, 2003

Independent risk factors of CKD

- **DM or abnormality of glucose metabolism**
- **HT**

- ***Abdominal obesity ?***
- ***Dyslipidemia ?***

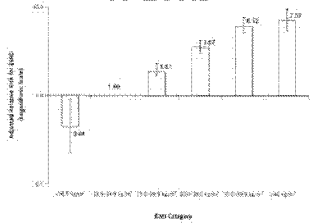
BMI and the Risk of ESRD



- 100,753 Japanese adults, 17yrs F/U(1983-2000)
- OR of BMI for development of ESRD
  : 1.273 in men (95% CI 1.121-1.446, p=.0002)
  0.950 in women(95% CI 0.825-1.094. ns)

Iseki K et al. *Kl* 65:1870-1876, 2004

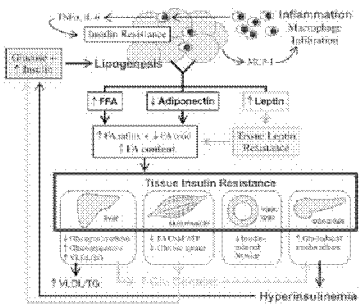
BMI , an Independent Predictor of ESRD



- 320,252 American adults, 15-35 yrs F/U, Retrospective
- Higher baseline BMI remained an independent predictor for ESRD after additional adjustments for baseline blood pressure level and presence or absence of diabetes mellitus.

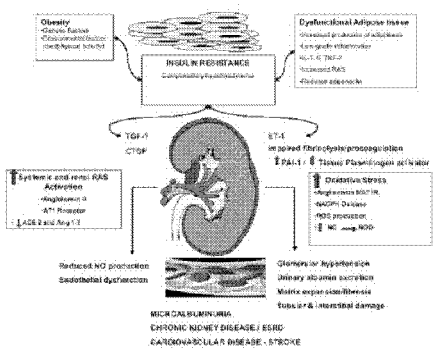
Hsu C et al. *Ann Intern Med* 144:21-28, 2006

Pathogenesis of Obesity-Initiated Metabolic Syndrome



Bagby SP. *JASN* 15:2775, 2004

Relationship between Obesity and Insulin Resistance with the development of CKD/CVD



Lastra G. *Adv Chronic Kidney Dis* 13:365, 2006

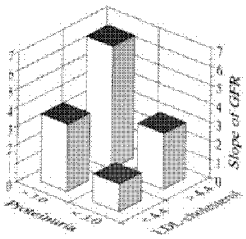
Lipid Abnormalities in CKD

- **LDL↑, TG↑, VLDL↑, LP(a)↑, HDL↓**
- **More severe in patients with proteinuria, particularly those with nephrotic syndrome**
- **Mechanisms through which lipids accelerate the progression of renal disease ; complex**
  - LDL cholesterol can bind to specific receptors in mesangial cells and stimulate cell hypertrophy
  - LDL mediate oxidative tissue injury in mesangial cells
  - Oxidized LDL may attract monocytes directly or indirectly, via activation of MCP-1
  - LDL can stimulate fibronection and collagen formation
  - LDL may acitvate the formation of vasoactive substances, such as endothelin, thromboxane, and angiotensin II

Lipid Reduction on Renal Disease

- For almost 100 years, it has been suggested that hyperlipidemia could cause renal injury
- Studies in experimental animals have suggested that treatment with statins may retard the progression of kidney disease
- No large investigations examining the effects of cholesterol reduction on nephropathy.

Rate of Progression of Renal Insufficiency

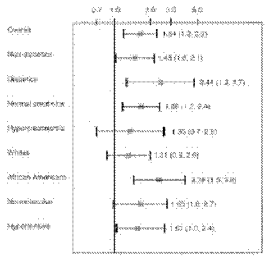


- 73 Swedish adults Non-DM (43 CGN)
- 3.2±0.7 yrs F/U
- GFR at entry 41.3±15.3ml/min x 1.73 m^2 BSA

- Conclusion ; LDL cholesterol and apoB, but not TG, HDL, and apoA, abnormalities of renal insufficiency contribute to the progression of renal failure in human chronic renal disease.

NDT 12:1908-1915, 1997

RR of a Rise in sCr for a 3 Fold Higher Baseline TG Level

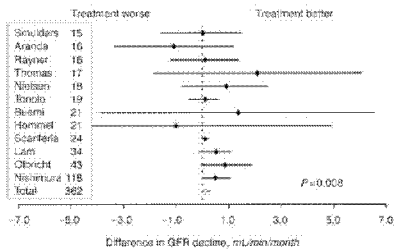


- 12,728 ARIC participants
- Baseline sCr < 2.0mg/dL(male) < 1.8mg/dl(female)
- Mean F/U 2.9 yrs
- Relationship of plasma lipids to a rise in sCr ≥ 0.4mg/dl

- Conclusion ; High TG and low HDL, but not LDL cholesterol, predict an increased risk of renal dysfunction

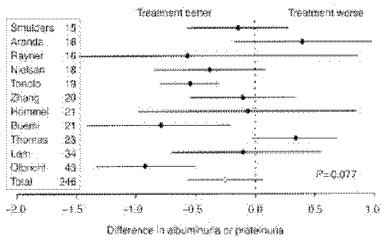
Muntner P et al. *KI* 58:293-301, 2000

Effect of Lipid Reduction on the Progression of Renal Disease - A Meta-analysis -



Fried LE et al. *KI* 59:260-269, 2001

Effect of Lipid Reduction on Albuminuria or Proteinuria - A Meta-analysis -



Fried LE et al. *KI* 59:260-269, 2001

Treatment of Metabolic Syndrome

◆ **Nonpharmacological strategies ; cornerstone**
- **Weight reduction via healthy dieting and regular physical activity**

◆ **Drug therapy**
1. **metformin, thiazolidinediones** : insulin resistance
2. **statin, fibrate** : dyslipidemia
3. **ACEi / ARB** : angiotensinogen role in obesity

◆ **Therapy of obesity**
- **Drugs : orlistat, sibutramine**
- **Bariatric surgery**

A Critical Look at the Metabolic Syndrome

◆ **Criteria** are ambiguous or incomplete, and differing

◆ Insulin resistance as **the unifying etiology** is uncertain

◆ The **CVD risk** associated with the syndrome appears to be no greater than the sum of its parts

◆ **Treatment** of the syndrome is not different than treatment for each of its components

◆ **The medical value** of diagnosing the syndrome is unclear

Kahn RB et al. *Diabetes Care* 28:2289-2304, 2005