Association between Serum Trace Elements and Renal Toxicology in Elderly Diabetic Patients: A Cross-Sectional Study in Taiwan

血清中微量元素與腎毒理學之相關性研究 -以老年糖尿病病人爲例

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	All CKD	CKD stages				
		Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Prevalence (95% CI)						
National population*	11·93% (11·66–12·28)	1·02% (0·98–1·05)	3·79% (3·73–3·85)	6·81% (6·73–6·89)	0·22% (0·21–0·23)	0·10% (0·09–0·10)
High SES†	7·33% (7·31–7·35)	1·07% (1·06–10·7)	3·10% (30·9–3·11)	3·06% (3·05–3·07)	0·06% (0·06–0·06)	0·04% (0·04–0·04)
Low SES‡	19·87% (19·84–19·91)	0·84% (0·83–0·85)	4·75% (4·74–4·77)	13·59% (13·56–13·61)	0·50% (0·50–0·51)	0·19% (0·19–0·19)
Study cohort	10·10% (9·83–10·37)§	1·04% (0·71–1·29)	3·31% (3·03–3·59)	5·53% (5·26–5·82)	0·17% (0–0·46)	0·08% (0–0·36)
High SES†	6·38% (6·30–6·50)	1·01% (0·96–1·04)	3·02% (2·55–3·45)	2·38% (2·34–2·46)	0·05% (0·04–0·06)	0·03% (0·02–0·04)
Low SES‡	17·89% (17·66–18·14)	0·93% (0·84–0·96)	4·79% (3·78–5·82)	12·04% (11·80–12·20)	0·42% (0·37–0·45)	0·19% (0·16–0·22)
Awareness (95% CI)						
Study cohort	3·54% (3·37–3·68)	2·66% (2·29–3·03)	2·68% (2·44–2·92)	4·10% (3·90–4·30)	23·67% (20·17–27·23)	51·40% (45·52–57·28)
High SES†	3·94% (3·65–4·15)	2·76% (2·41–3·19)	2·66% (2·36–2·97)	4·70% (4·11–5·29)	34·59% (26·56–42·64)	58·89% (48·71–69·09)
Low SES‡	3·32% (3·06–3·54)	2·35% (1·52–3·08)	2·71% (2·31–3·09)	3·78% (3·41–4·19)	20·32% (16·58–24·02)	47·96% (40·94–55·06)

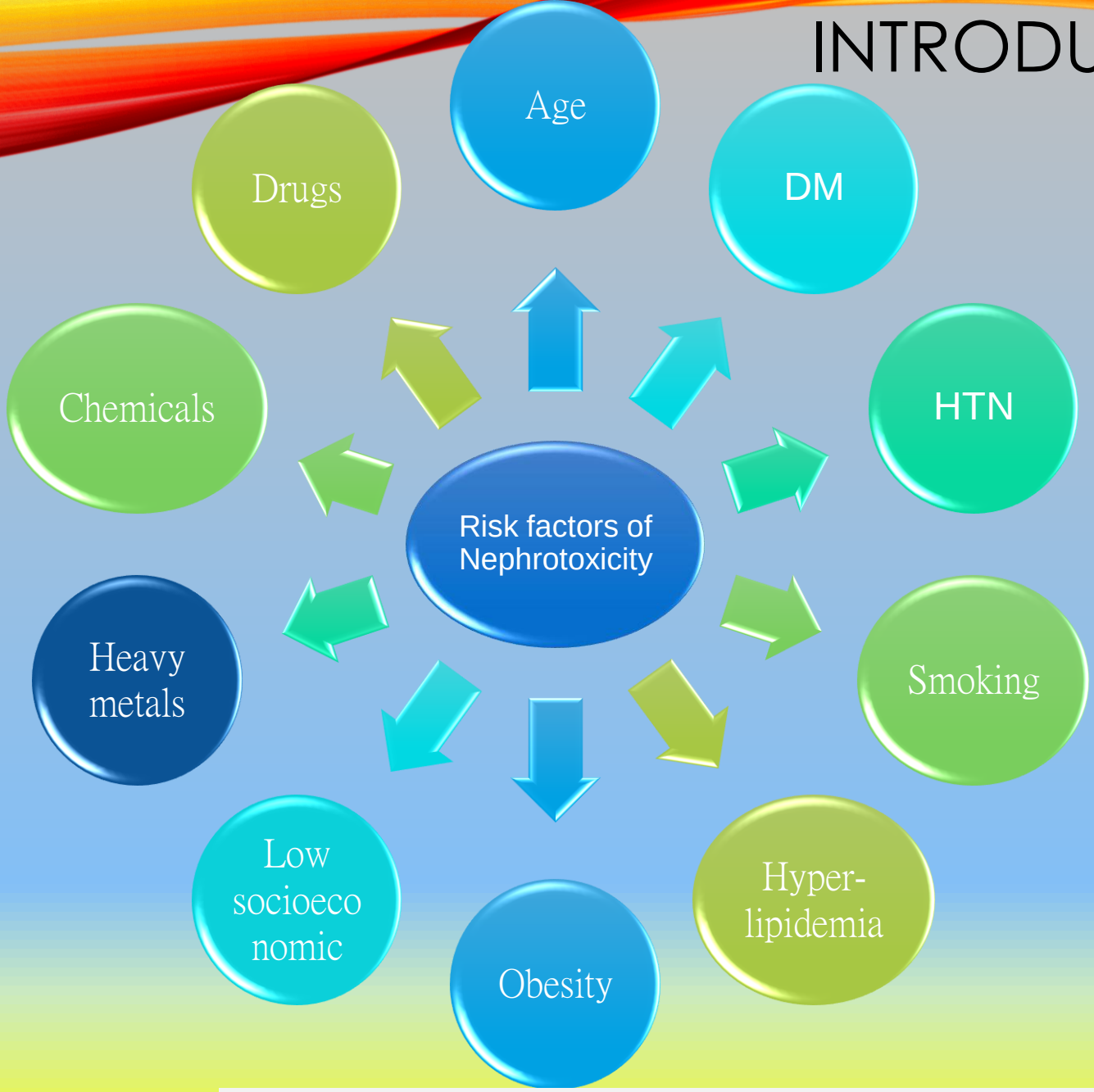
CKD=chronic kidney disease. SES=socioeconomic status. *Age and educational level had been standardised to Taiwan population at 2006. †Participants with high-school education or higher (N=275 655). ‡Participants with middle-school education or below (N=105 121). §The figure was adjusted downward from 12·3% of the study cohort as per panel definition to meet the persistent proteinuria requirement.

Table 2: **Prevalence and awareness of chronic kidney disease by socioeconomic status in cohort participants**

The national prevalence of CKD was 11.93% in Taiwan.

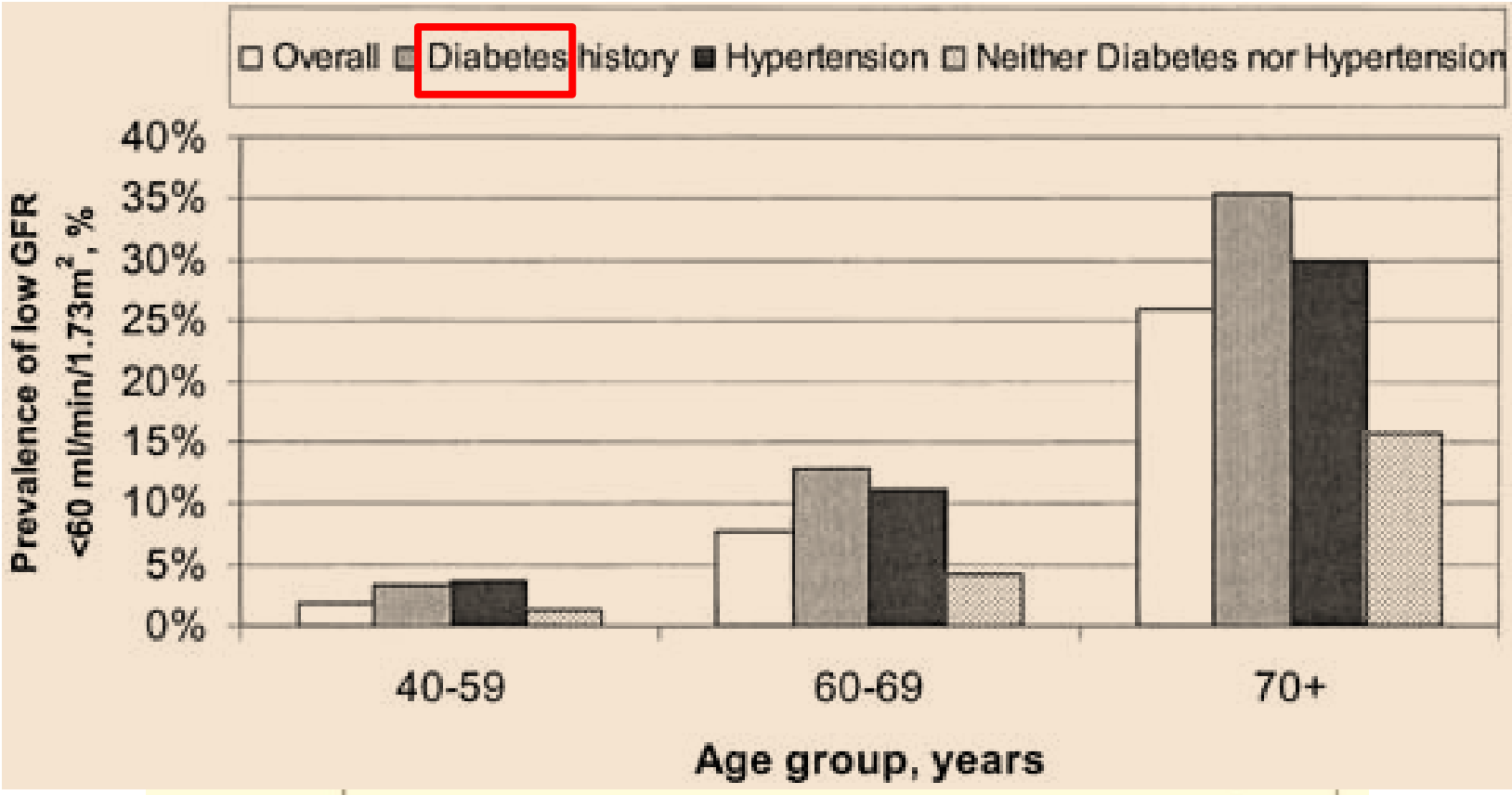
Chi Pang Wen et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462293 adults in Taiwan. ***Lancet.* 2008;371:2173-2182.**

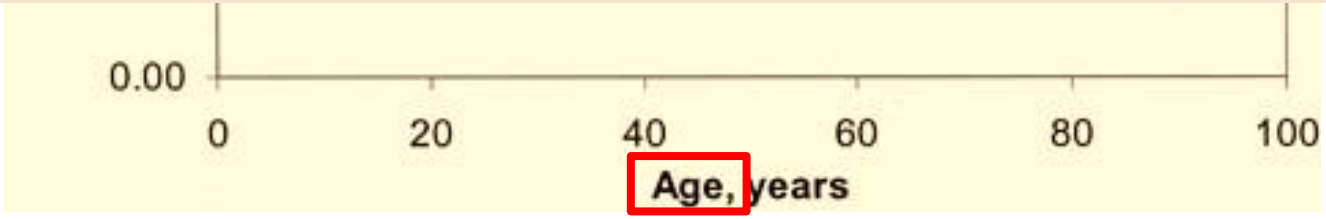
INTRODUCTION



The Prevalence and Risk Factors of Diabetic Nephropathy in Taiwanese Type 2 Diabetes-A Hospital-Based Study. *Acta Nephrologica Vol. 23, No. 2, 2009*

INTRODUCTION





THE GLOBAL BURDEN OF CHRONIC KIDNEY DISEASE AND THE WAY FORWARD.
Ethnicity & Disease, Volume 15, Summer 2005

Type 2 diabetes In Taiwan

- Prevalence of diabetic nephropathy
  - 40%

The Prevalence and Risk Factors of Diabetic Nephropathy in Taiwanese Type 2 Diabetes-A Hospital-Based Study. *Acta Nephrologica Vol. 23, No. 2, 2009*

INTRODUCTION

- The metabolism of several trace metals was altered in the patients of type 2 DM .

Biological trace element research 2008; 122(1): 1-18

- Several trace elements have been implicated in the decline of renal function
  - Arsenic
  - Cadmium
  - Copper
  - Lead
  - Mercury

Nephrol Dial Transplant (2002) 17:2-8

INTRODUCTION

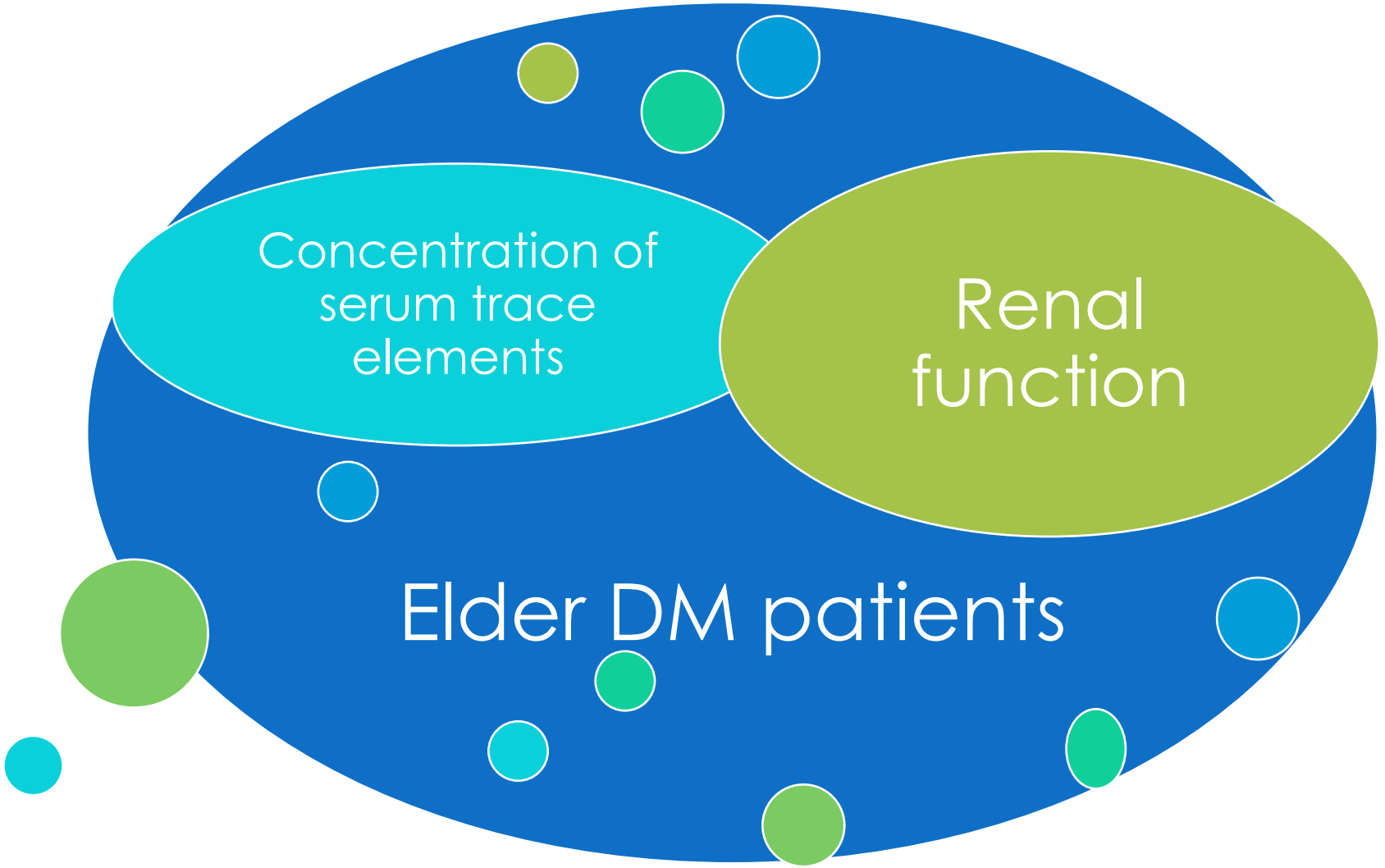
- The most important factor affect **trace element concentration** in patients is the **degree of renal failure.**

nutritional management of renal disease. 1996 p.396-414

- Excessive accumulation or depletion of trace elements may have significant clinical implications, include **risk for cancer, CVD, immune deficiency, anemia, renal function impairment…**

Nephrol Dial Transplant (2002) 17:2-8

PURPOSE


Concentration of serum trace elements
Renal function
Elder DM patients

STUDY DESIGN

n=275

- Agree to participate this study

- Type 2 DM patients from OPD
- More than 65 y/o
- From March 2010 to September 2010

- Exclude ESRD with hemodialysis
- Exclude Taiwan aboriginal

n=244

- Questionnaire
- Blood samples
- Urine samples
- Medical records

CKD group
N= 132

- eGFR <60 or spot urine ACR > 30 mg/g

Non-CKD group
N= 112

- eGFR >60
- spot urine ACR < 30 mg/g

ESTIMATE RENAL FUNCTION

	新版台灣公式		目前國際公式
	Taiwanese MDRD	New Taiwanese equation	4-variable MDRD
計算公式	$175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ （if female） $\times 0.945$	$180.91 \times SCr^{-0.936} \times Age^{-0.227} \times 0.76$ （if female）	$186 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ （if female）
準確率（%）	☆94.8	☆92.4	84.3
誤差值（ml/min/1.73m^2）	☆-0.7	☆1.5	13.2

「建立國人腎絲球濾過率公式及慢性腎臟病的分期標準」
台大醫院吳寬墩醫師,高醫陳鴻鈞醫師.2011慢性腎臟病防治研究計畫

MATERIALS AND METHODS

- Collected the data
  - Age
  - Gender
  - Height
  - Weight
  - Level of education
  - Duration of type 2 DM
  - History of substance use
  - History of hypertension, Dyslipidemia
  - Standard questionnaires from cases or their family
- The biochemical laboratory blood tests were performed by certified laboratory.
- Checked the following data
  - BUN, Cr, HbA1c, lipid profile and urine albumin with urine Cr.

MATERIALS AND METHODS

- The tests of blood levels of trace elements
  ➔ Se, Cr, Al, As, Pb, Cd, Zn, Cu
- Inductively Couple Plasma Mass Spectrometry (*ICPMS*) of Thermo Scientific XSERIES 2

MATERIALS AND METHODS

- Compare groups
  - male vs female
  - CKD group vs Non-CKD group
- Database processing and statistical analyses
  - SPSS v.19 statistical package.
  - P value < 0.05: statistically significant.

RESULT

Table 1. Difference characteristic between genders

		Male n=131	Female n=111	P value
Age (years), mean±SD		72.77±5.44	71.83±5.35	0.177
Education level				<0.001*
No education		9	49	
No education, but recognized words		16	6	
Primary school to High school		81	49	
College		25	7	
Hypertension				0.409
	Yes	103	93	
	No	27	18	
Dyslipidemia				0.498
	Yes	106	94	
	No	25	17	
Smoking				<0.001*
	Yes	62	4	
	No	69	107	
Alcohol				<0.001*
	Yes	41	3	
	No	90	108	
CKD				0.438
	Yes	67	63	
	No	64	48	
eGFR, mean±SD		63.47±19.23	64.40±24.74	0.748
HbA1c (%), mean±SD		7365±1.25	7.84±1.39	0.276
DM duration (years), mean±SD		9.66±7.31	12.13±7.74	0.011*
Serum Creatinine (mg/dL) , mean±SD		1.20±0.48	0.95±0.40	<0.001*
BMI (kg/m^2), mean±SD		25.58±3.43	24.86±3.43	0.109

RESULT

Table 2. Serum trace elements level Comparison between genders

	Male(n=132)	Female (n=112)	P-value
	mean±SD	mean±SD	
Al, *u*g/L (ppb)	56.39 ± 54.84	45.62 ± 48.57	0.109
As, *u*g/L (ppb)	7.35 ± 5.54	6.64 ± 4.66	0.282
Cd, *u*g/L (ppb)	0.32 ± 0.48	0.27 ± 0.13	0.256
Pb, *u*g/dL	1.94 ± 1.74	1.73 ± 3.28	0.522
Cr, *u*g/L (ppb)	6.46 ± 9.17	4.80 ± 7.49	0.123
Cu, mg/L (ppm)	0.94 ± 0.35	1.05 ± 0.43	0.032*
Se, *u*g/L (ppb)	347.98 ± 99.96	326.71 ± 99.02	0.098
Zn, mg/L (ppm)	7.11 ± 3.62	6.85 ± 6.90	0.596

RESULT

Table3. Difference characteristic between CKD and non-CKD groups

	CKD	Non-CKD	P value
	n=132(54%)	n=112(46%)	
Age (years), mean±SD	73.07±5.59	71.56±5.07	0.028*
Education level			0.047*
No education	40(66.7%)	20(33.3%)	
No education, but recognized words	13(59.1%)	9(40.9%)	
Primary school to High school	67(51.5%)	63(48.5%)	
College	12(37.5%)	20(62.5%)	
Hypertension (Yes)	121(91.7%)	77(69.4%)	<0.001**
Dyslipidemia (Yes)	109(82.6%)	93(83.0%)	0.924
Smoking (Yes)	36(27.3%)	31(27.7%)	0.944
Alcohol (Yes)	25(18.9%)	20(17.97%)	0.828
Gender			0.534
male	68(51.5%)	64(57.1%)	
HbA1c (%), mean±SD	7.88±1.33	7.53±1.28	0.037*
DM duration (years), mean±SD	12.36±7.93	8.87±6.70	<0.001**
BMI (kg/m^2), mean±SD	25.78±3.77	24.58±2.87	0.005*
eGFR	51.24±21.77	77.92±11.71	<0.001**

RESULT

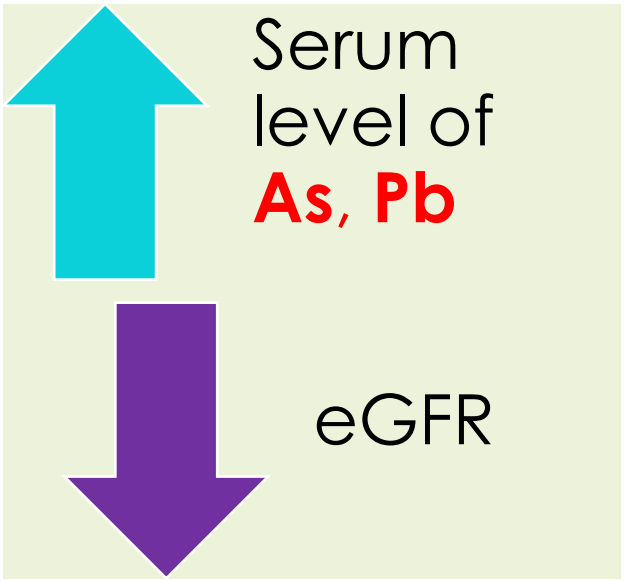
Table 4. trace elements level Comparison between CKD and non-CKD groups

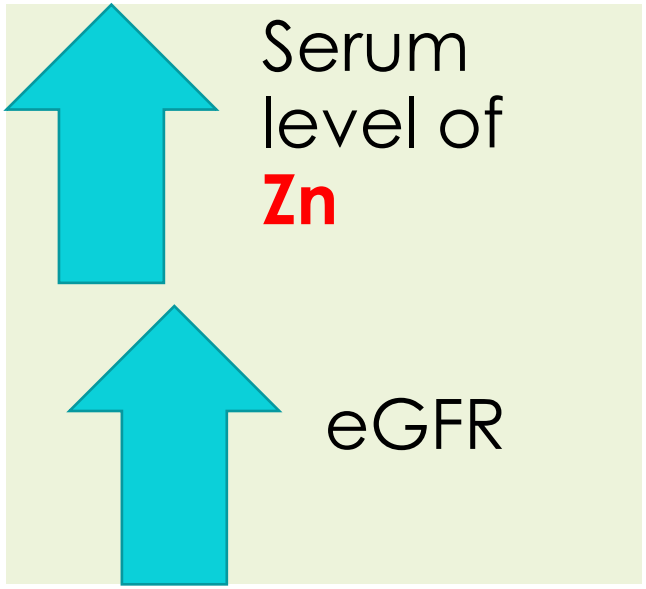
	CKD group (n=132)	Non-CKD group (n=112)	P-value
	mean ± SD	mean ± SD	
Al, *u*g/L (ppb)	52.495 ± 56.049	50.211 ± 47.560	0.734
As, *u*g/L (ppb)	7.623 ± 5.302	6.320 ± 4.915	0.049*
Cd, *u*g/L (ppb)	0.300 ± 0.328	0.291 ± 0.411	0.855
Pb, ug/dL	2.001 ± 3.173	1.655 ± 1.540	0.293
Cr, *u*g/L (ppb)	5.562 ± 8.716	5.857 ± 8.188	0.786
Cu, mg/L (ppm)	1.007 ± 0.401	0.976 ± 0.377	0.543
Se, *u*g/L (ppb)	332.376 ± 103.441	345.105 ± 95.542	0.322
Zn, mg/L (ppm)	7.109 ± 3.749	6.846 ± 3.748	0.586

RESULT

Table 5. Multiple Linear regression analysis

eGFR =165.046 **-0.482(Duration of DM)** - 0.138(HbA1c)+ 0.947(Gender) - 4.597(E1)+ 0.749(E2)+ 9.030(E3) **-1.015(Age)** -0.079(Al) +0.440(Cr) **-0.974(As)** +0.031(Se) -4.638(Cd) **-1.339(Pb)** -5.912(Cu) **+0.860(Zn)** -0.384(SMOKING) **-9.470(HTN)** -0.727(DYSLIPIDEMIA) +0.703(ALCOHOL) -0.534(BMI)





RESULT

Table 6. Logistic regression model of effects of trace elements (CKD vs non-CKD group)

Trace elements	Adjusted OR (95% CI)	P value
As	OR: 1.083	
Se	OR: 0.978	
Pb	1.084(0.935-1.258)	0.283
Cu	1.085(0.524-2.247)	0.825
Zn	1.022(0.949-1.101)	0.560

Adjusted variables: Sex, age, smoking, BMI, hypertension, dyslipidemia, HbA1c, duration of type 2 DM

Discussion

RENAL FAILURE

- Arsenic and chromium tend to increase.
- selenium and zinc tend to decrease.
- Elements levels Increased
  - industrial or environmental exposure
  - Intake
  - Smoke
  - dialysate
- Elements levels Decreased
  - Protein-bound elements may be loss in proteinuria

Nephrol Dial Transplant (2002) 17:2-8

Discussion

Cu

- Serum copper level showed increase in women
  - absorbing a greater percentage than male
  - hormonal status
    - estrogens increase serum copper concentrations

Farzin et al Biol Trace Elem Res (2009) 129:3

Discussion

Pb

- Elevated blood Pb levels was associated with lower eGFR
  - *even blood Pb levels below 10ug/dL*

Ekong EB, Jaar BG, Weaver VM. 2006. Lead-related nephrotoxicity: a review of the epidemiologic evidence. Kidney Int 70(12):2074–2084.

- Lower levels of lead exposure continue to contribute to nephrotoxicity.

Associations of blood lead, cadmium, and mercury with estimated glomerular filtration rate in the Korean general population: analysis of 2008-2010 Korean National health and Nutrition Examination survey data. Environ Res. 2012 Oct;118:124-9

Discussion

Zn

Table 2 Oxidation-related metals at different stages of chronic kidney disease (CKD).

Parameter	Stage 1 (n = 16)	Stage 2 (n = 51)	Stage 3 (n = 70)	Stage 4 (n = 8)	Average	p
Copper (ppm)	1.04 ± 0.18	1.07 ± 0.21	1.09 ± 0.20	1.24 ± 0.17	1.09 ± 0.2	0.133
Iron (ppm)	1.26 ± 0.45	1.27 ± 0.38	1.16 ± 0.44	1.36 ± 0.59	1.22 ± 0.43	0.347
Zinc (ppm)	0.88 ± 0.13	0.83 ± 0.17	0.76 ± 0.16	0.69 ± 0.13	0.80 ± 0.17	0.005*
Selenium (ppb)	146.3 ± 20.0	144.1 ± 23.2	141.2 ± 23.2	145.4 ± 17.8	143.0 ± 22.5	0.799

Data are presented as mean ± standard deviation (SD).
*$p < 0.01$.
ppb = parts per billion; ppm = parts per million.

- A decrease in zinc concentration in CKD patients from Stages 1 to 4.
- Zinc concentrations in patients with CKD vary depending on individual diets and medications.
- Serum zinc level was lower in patients on chronic hemodialysis than the control group.
- Zinc deficiency will increase oxidative stress.

Changes in levels of copper, iron, zinc, and selenium in patients at different stages of chronic kidney disease. C.-T. Shih et al. **Genomic Medicine, Biomarkers, and Health Sciences** Volume 4, Issue 4 , Pages 128-130, December 2012

Discussion

As

- Increase oxidative stress
- Carcinogen
  - skin, lung, bladder
- Non-cancer health effect:
  - reproductive, cardiovascular, pulmonary, neurologic, skin
- Seafood, groundwater, air contamination

Internal exposure to trace elements in Non-smoking residents Living in Northern Taiwan Industrial City. Tser-Sheng Lin. Biol Elem Res (2011) 144:36-48

Discussion

Se

- **Low** serum **Se** levels
  - a frequent finding in patients with acute kidney injury or chronic kidney disease.

- **Se** status and immune function improve after oral and intravenous Se supplementation in renal patients
  - reducing the products of oxidative stress.

J Nephrol. 2012 Sep 18:0. doi: 10.5301/jn.5000213

LIMITATION

- Cross-sectional study
  - it is difficult to know the relationship of cause and effect.

- Blood trace elements level represent the recent exposure.

LIMITATION

- Other factors influence renal function
  - Chinese herb intake, NSAIDs, Antibiotics
  - Hg, Be, Si, CS2
  - Dioxane, Toluene, Phenol….
  - Food or supplements intake

THANK YOU!

THANK YOU!

THANK YOU!

THANK YOU!

THANK YOU!

THANK YOU!

THANK YOU!

THANK YOU!

THANK YOU!

THANK YOU!

Table 4. Classification of chronic kidney disease (CKD)

		Classification by severity	
Stage	Description	GFR mL/min/1.73 m^2	Related terms
1	Kidney damage with normal or ↑ GFR	≥90	Albuminuria, proteinuria, hematuria
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria, proteinuria, hematuria
3	Moderate ↓ GFR	30–59	Chronic renal insufficiency, early renal insufficiency
4	Severe ↓ GFR	15–29	Chronic renal insufficiency, late renal insufficiency, pre-ESRD
5	Kidney failure	<15 (or dialysis)	Renal failure, uremia, end-stage renal disease

Abbreviations are: GFR, glomerular filtration rate; ESRD, end-stage renal disease.
Related terms for CKD stages 3 to 5 do not have specific definitions, except ESRD.

Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO)
Kidney International, Vol. 67 (2005), pp. 2089–2100

ESTIMATE RENAL FUNCTION

Simplified Modification of Diet in Renal Disease (MDRD) formula

4-variable or abbreviated MDRD 公式

$$186 \times Cr^{-1.154} \times age^{-0.203} \times (0.742, \text{ if female}) \times (1.212, \text{ if African American})$$

Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO)
Kidney International, Vol. 67 (2005), pp. 2089–2100

Discussion

Cd

- **Elevated blood cadmium levels were associated with lower eGFR in women**
- **a risk factor for chronic kidney disease**

Blood Cadmium and Estimated Glomerular Filtration Rate in Korean Adults. Environmental Health Perspectives • volume 119 | number 12 | December 2011