Prevalence and risk factor of chronic kidney disease in elderly diabetic patients in Korea

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Introduction

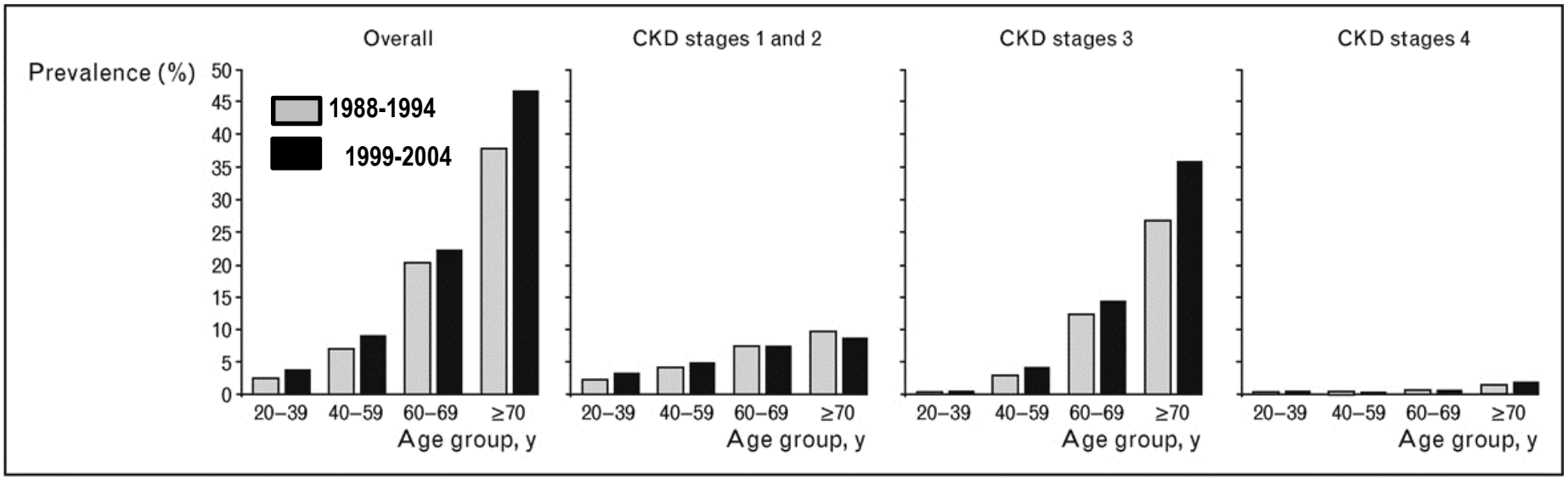
- CKD의 정의와 eGFR의 측정
- CKD의 risk factor와 mechanism
- 한국의 CKD prevalence 와 prognosis
- CKD의 치료와 노인당뇨병환자의 치료가이드라인-European Diabetes Working Party for Older People 2011 Clinical Guidelines for Type 2 Diabetes Mellitus

Definition of Chronic Kidney Disease

- Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR
  - Pathological abnormalities
  - Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
    - Albuminuria
    - Abnormal urinary sediment(casts, epithelial cells)
    - Abnormal imaging(polycystic kidneys, hydronephrosis)
    - Blood and urine markers of 'tubular syndromes'
    - Renal transplant recipients, Estimated GFR.

- GFR < 60ml/min/1.73m^2

Prevalence of CKD in NHANES data (1988~1994 & 1999~2004)



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Coresh J, et al. JAMA 2007;298:2038

Prevalence of CKD

Over age 30(World population) : 7.2%

Over age 65(World population) : 3.4~35.8%

Introduction

- Cause of CKD are various
  - Diabetes : most common cause
  - Hypertension
  - Glomerular kidney disease
  - Tubular and interstitial kidney disease
  - Obstructive uropathy
  - Pre-renal and vascular disorders

Classification of Stages of Chronic Kidney Disease

Stage	Designation	GFR (mL/min/1.73 m^2)	Action
0	Increased risk of CKD (diabetes, HiBP etc)	≥ 90	
1	Renal damage with normal or elevated GFR	≥ 90	Treatment of comorbid conditions, slowing progression, CVD risk reduction
2	Renal damage with mild reduction of GFR	60-89	Estimating progression
3	Moderate reduction of GFR	30-59	Evaluating & treating complications
4	Severe reduction of GFR	15-29	Preparation for kidney replacement Tx.
5	Renal failure	< 15 or dialysis	Replacement

Stage 3: screening for anemia, malnutrition, & metabolic bone disease

Stage 4: consultation with a nephrologist (preparation for kidney replacement therapy)

원인이 불명확한 경우(active urine sediment, absence of retinopathy, rapid decline in GFR),

치료가 어려운 경우, 진행된 경우 ⇒ Refer 고려

Herget-Rosenthal S, et al. Clin Biochem 2007;40:153

Measuring & classifying CKD

1. Measured GFR

- not practical

- annul rate of GFR decline; 0.8 to 1.4 mL/min/1.73 m^2 (DM 없는 65세 이상의 노인에서)

2. Estimated GFR

- from serum levels of endogenous filtration markers, creatinine & cystatin C

MDRD7	Estimated glomerular filtration rate (ml/min/1.73 m^2) = (170 × [serum creatinine (mg/dl)] − 0.999 × [age (years)] − 0.176 × [0.762 if woman] × [1.18 if African−American] × [blood urea nitrogen (mg/dl)] − 0.170 × [albumin (g/dl)] + 0.318) to give result in ml/min × body surface area/1.73
aMDRD	Estimated glomerular filtration rate (ml/min/1.73 m^2) = (186 × [serum creatinine (mg/dl)] − 1.154 × [age (years)] − 0.203 × [0.742 if woman] × [1.21 if African−American]) to give result in ml/min × body surface area/1.73
Cockcroft−Gault	Estimated creatinine clearance (ml/min) = [(140 − age) × weight]/[72 × serum creatinine (mg/dl)] (× 0.85 if woman)
Jelliffe	Estimated creatinine clearance (ml/min/1.73 m^2) = [98 − [0.8 × (age − 20)]] − [1 − (sex × 0.1)]/ serum creatinine (mg/dl); sex = 0 if man and 1 if woman to give result in ml/min × body surface area/1.73
Wright	Estimated creatinine clearance (ml/min) = [6550 − (38.8 × age)] × [1 − (0.168 × sex)] × body surface area (m^2)/serum creatinine (μmol/l); sex = 0 if man and 1 if woman
Martin	Estimated creatinine clearance (ml/min) = [163 × actual body weight (kg) × (1 − 0.00496 × age) × (1 − 0.252 × sex)]/serum creatinine (μmol/l); sex = 0 if man and 1 if woman

S-creatinine in μmol/l = S-creatinine in mg/dl × 88.4. Serum creatinine measured by Jaffé method. If more standardized serum creatinine measurements are used such as peroxidase antiperoxidase, then serum creatinine should be divided by a factor of 0.95. MDRD, modification of diet in renal disease; aMDRD, abbreviated modification of diet in renal disease.

Measuring & classifying CKD

2. Estimated GFR

C-G equation

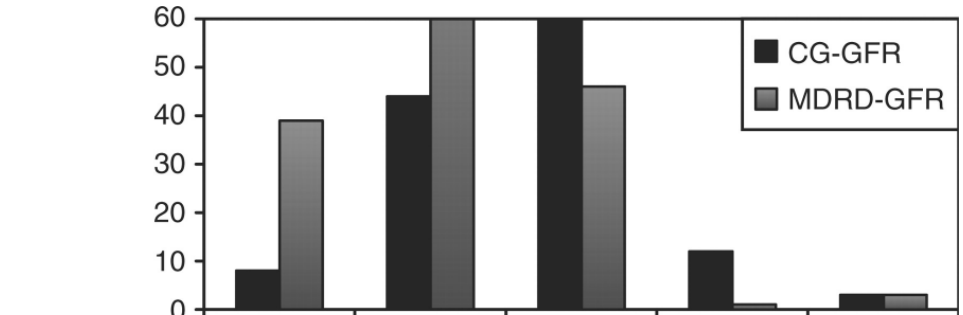
severely underestimate GFR in elderly people

not considered to be reliable for obese or edematous patients

MDRD equation

give a better prediction of true GFR than C-G equation

may be the estimation of choice in elderly patients



	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
CG-GFR	8	44	113	12	3
MDRD-GFR	39	91	46	1	3

al. Nephrol Dial Transplant 2007;22:2894

Serum markers of renal function

- **Creatinine**

  - most widely used surrogate marker of GFR

  - Results from the balance between muscle catabolism & renal excretion

  - However, inaccurate with increasing age

Table 2. Characteristics of Serum Creatinine as a Test for Renal Failure*

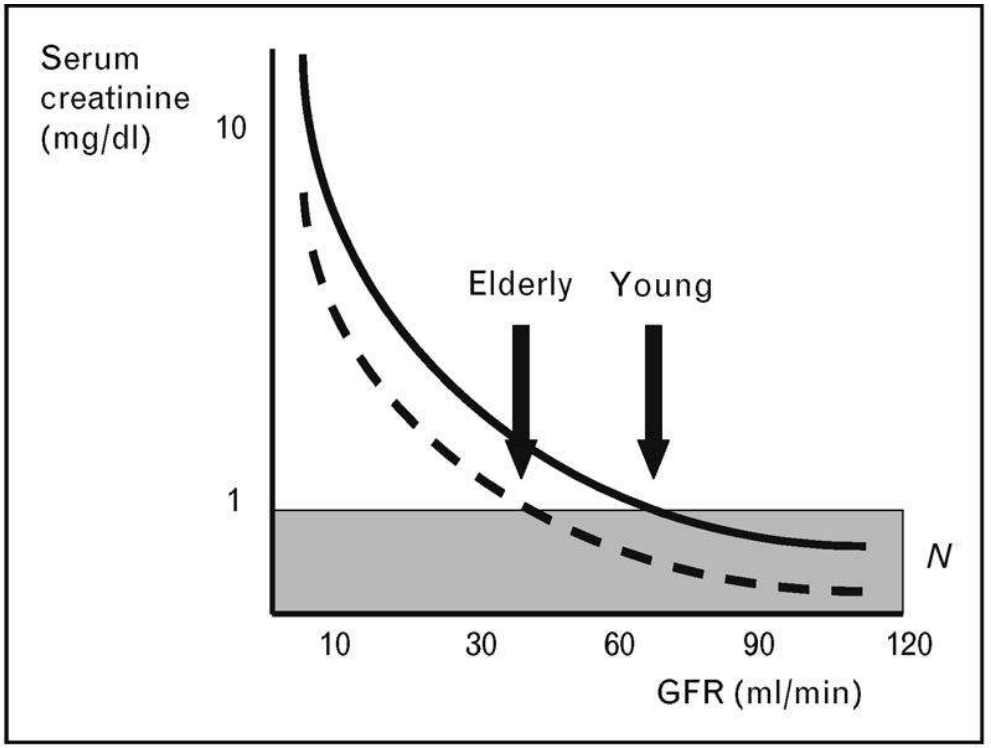
Characteristic	Overall	Women	Men
Renal Failure			
Sensitivity, %	12.6	7.3	22.9
Specificity, %	99.9	100.0	99.3
Negative likelihood ratio	0.87	0.92	0.77
Severe Renal Failure			
Sensitivity, %	45.5	29.7	77.8
Specificity, %	99.1	99.8	98.3
Negative likelihood ratio	0.55	0.70	0.23

*A serum creatinine level of 1.7 mg/dL (150 µmol/L) was used. Renal failure was defined as a Cockcroft and Gault formula glomerular filtration rate of 50 mL/min or less; severe renal failure, a Cockcroft and Gault formula glomerular filtration rate of 30 mL/min or less.

Swedko PJ, et al. Arch Intern Med 2003;163:356

Limitation of creatinine

- **Creatinine-blind area**
  - Even more so in the elderly person
  - Because the rate of creatinine production is less in elderly people due to age-related diminution of muscle mass, the normal range of serum creatinine for the general population may be inappropriately high for senescent people



The curve drifts to the left with increasing age. As a consequence, in elderly people, an increase in serum creatinine out of the normal range (*N*) happens later than in younger individuals, and thus signals a more pronounced reduction of glomerular filtration rate. GFR, glomerular filtration rate.

Fliser D. Curr Opin Nephrol Hypertens 2008;17:604

Serum markers of renal function

- **Cystatin C** or **Cystatin 3**

  - Produced in all cells with a nucleus

  - Found in virtually all tissues & bodily fluids

  - Potent inhibitor of lysosomal proteinases

  - Independent of age & sex (but not completely independent of body composition)

  - Predicting new-onset or deteriorating CVD & playing a role in brain disorders (Alzheimer)

Measuring & classifying CKD

New equation using

eGRF = 177.6 X $Scr^{-0.65}$ X $CysC^{-0.57}$ X $age^{-0.20}$ X (0.82 if female) X (1.11 if black)

- more accurate than creatinine or cystatin C alone (reduce bias by 50%)

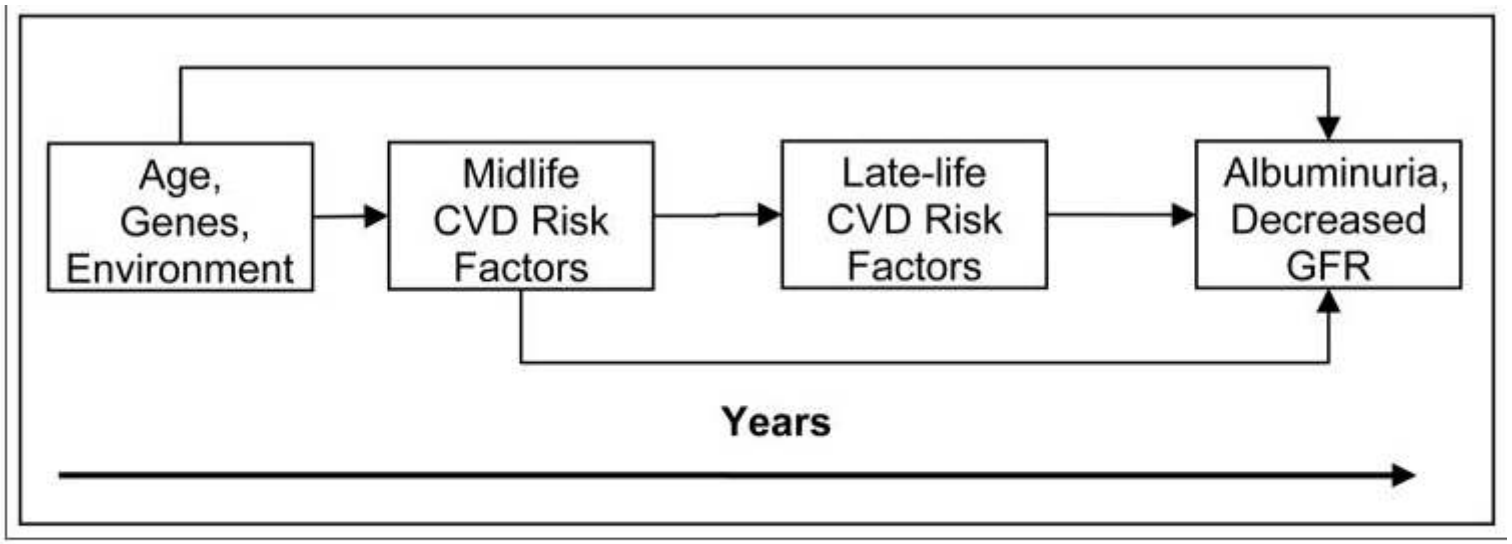
Stevens LA, et al. Am J Kidney Dis 2008;395

Mechanism underlying CKD in elderly

Cause of age-related increases in renal fibrosis (lead to glomerular sclerosis, tubular atrophy, vascular sclerosis, loss of renal function) ⇒ poorly understood

Collage accumulation in the glomerulus, peritubular capillary, & tubulointerstitium

← increased transcription of the gene encoding type III collage in animal model



CKD and ESRD in the Elderly: Current Prevalence, Future Projections, and Clinical Significance
Adv Chronic Kidney Dis. Adv Chronic Kidney Dis;17(4):293-301.

Figure 1

Concept model of factors modifying the prevalence of CKD in late life. GFR, glomerular filtration rate.

Melk A. Nephrol Dial Transplant 2003:18:2474

CKD Mechanisms

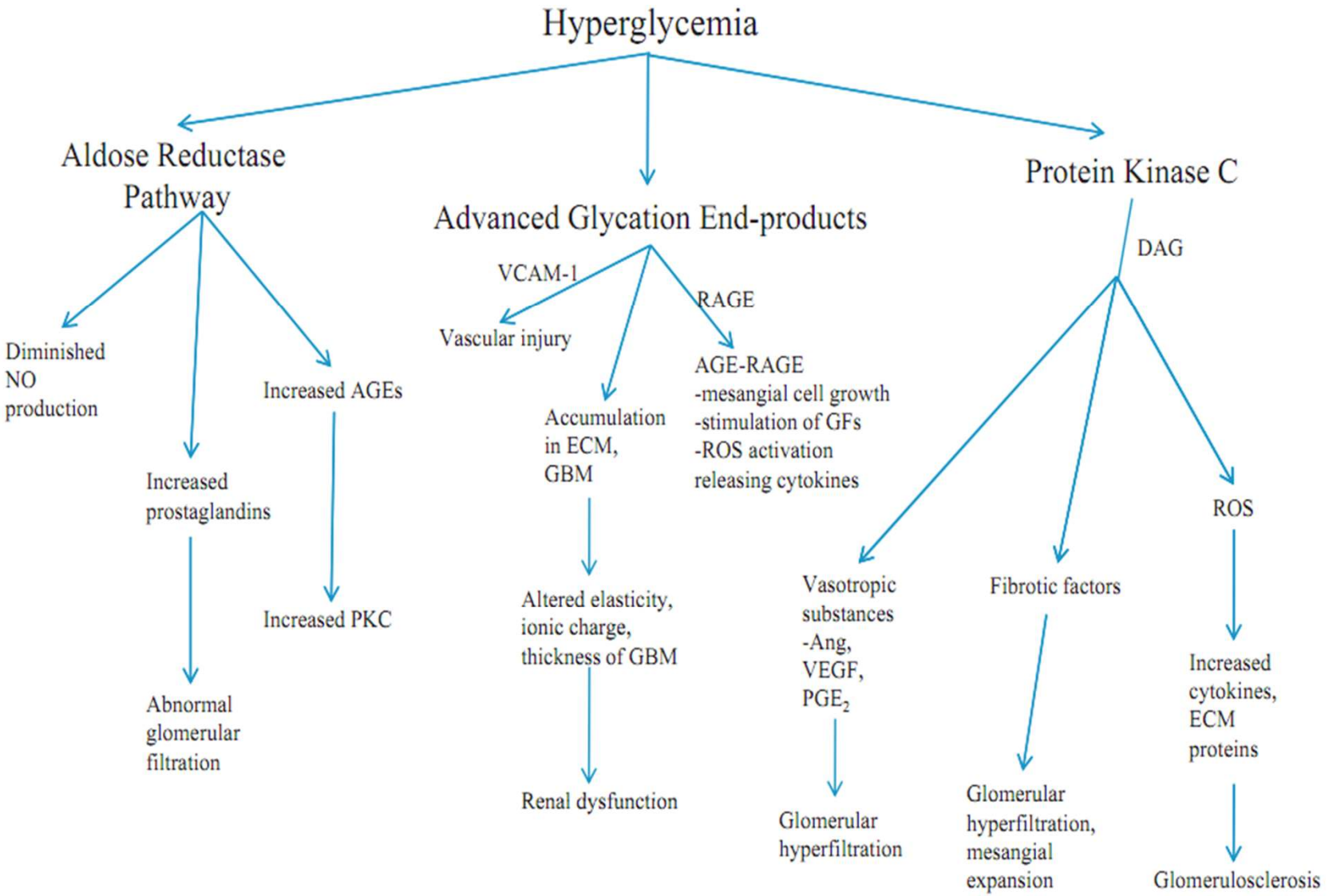


Fig. 1. Pathways of hyperglycemia causing renal damage. AR: aldose reductase; NO: nitric oxide; AGEs: advanced end-glycation products; PKC: protein kinase C; VCAM: 1-vascular cell adhesion molecule-1; RAGE: receptor for AGE; ECM: extracellular matrix; GBM: glomerular basement membrane; GFs: growth factors; ROS: reactive oxygen species; Ang: angiotensin; VEGF: vascular endothelial growth factor; PGE_2: prostaglandin E_2; DAG: diacylglycerol.

Risk factors(1)

- Elevated blood pressure
  - Well known to accelerate diabetic nephropathy
- Diabetes
  - 4.6 fold higher in urban African-Americans with duration of diabetes greater than 5 years as compared to < 1 years
- Cholesterol
  - Elevated levels are associated with increased risk of nephropathy
- Microalbuminuria
  - Without Microalbuminuria → Microalbuminuria : 2%/year
  - Microalbuminuria → Macroalbuminuria : 2.8%/year
  - Macroalbuminuria → elevated Creatinine or Renal replacement therapy : 2.3%/year

Risk factors(2)

- Smoking
  - In types 1 & 2 diabetes, albuminuria was greater in smokers
- Genetic factors
  - An insertion/deletion polymorphism of the ACE gene predicted severe structural kidney change in patients with microalbuminuria.
- AGE & BMI
  - Advancing age and obesity are also risk factors

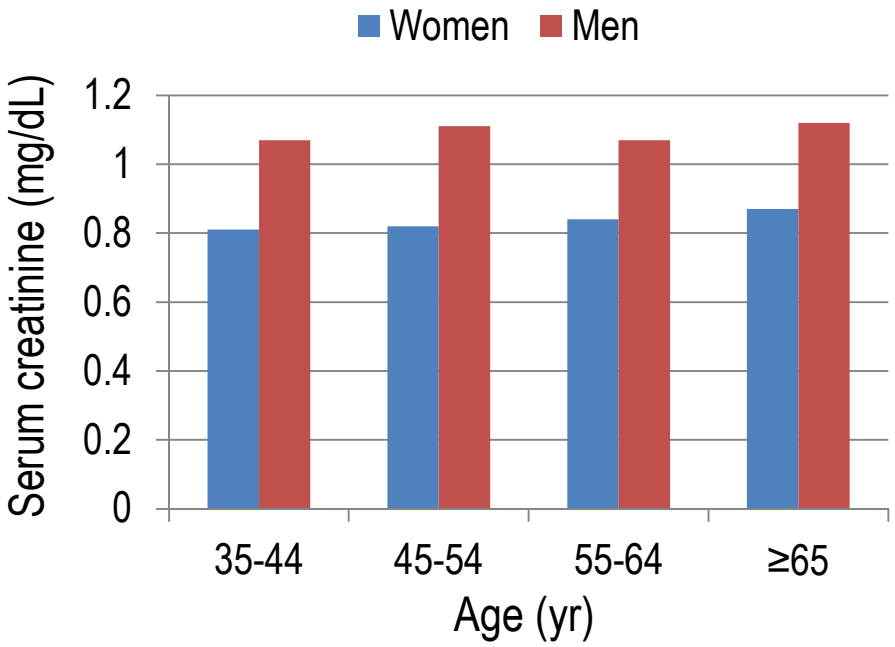
Prevalence of CKD in Urban Korea

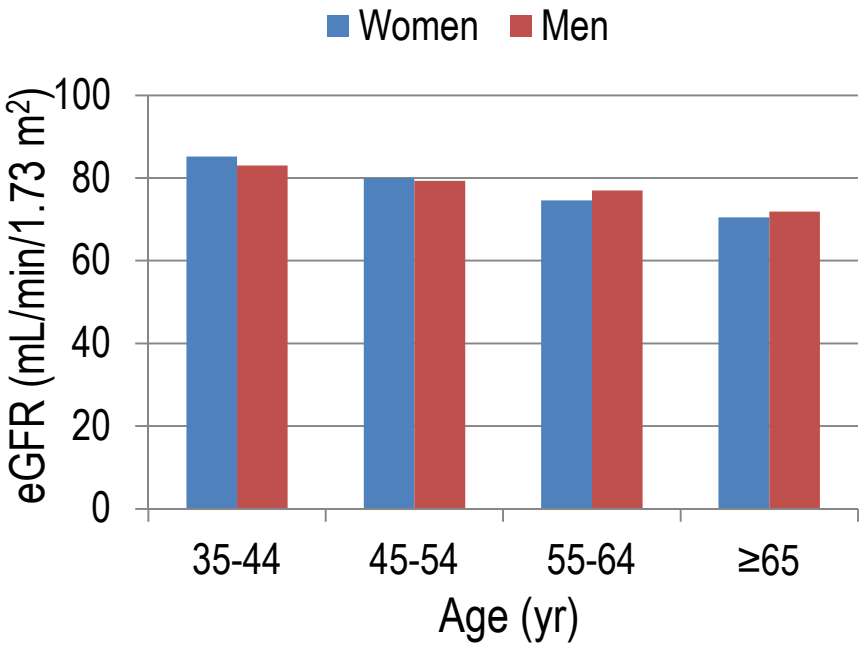
- 서울을 비롯한 7개 대도시에 35세 이상의 2356명 volunteer들을 모집(광고)
- eGFR using MDRD study equation
- Men; 48.8%; mean age 50.5±11.1 yr

Kidney function		Albuminuria			CKD	
eGFR	%	None	Micro	Macro	**Stage**	**No**
≥ 90	18.5	89.0	9.2	1.8	1	2.0
60-89	76.6	91.2	7.8	0.9	2	6.7
30-59	4.8	73.2	19.6	7.1	3	4.8
15-29	0.2	0.0	0.0	100.0	4	0.2
< 15	0.0	0.0	0.0	100.0	5	0.0
Total	100.0	89.8	8.6	1.6	**All**	**13.7**

Kim S, et al. J Korean Med Sci 2009;24(suppl 1):S11

Prevalence of CKD in Urban Korea





Age (yr)	All CKD	CKD stage 1	CKD stage 2	CKD stage ≥3
35-44	8.8	2.2	5.9	0.7
45-54	11.1	2.3	6.4	2.3
55-64	15.0	2.3	6.0	6.7
65 or more	31.0	0.6	10.5	19.8

Kim S, et al. J Korean Med Sci 2009;24(suppl 1):S11

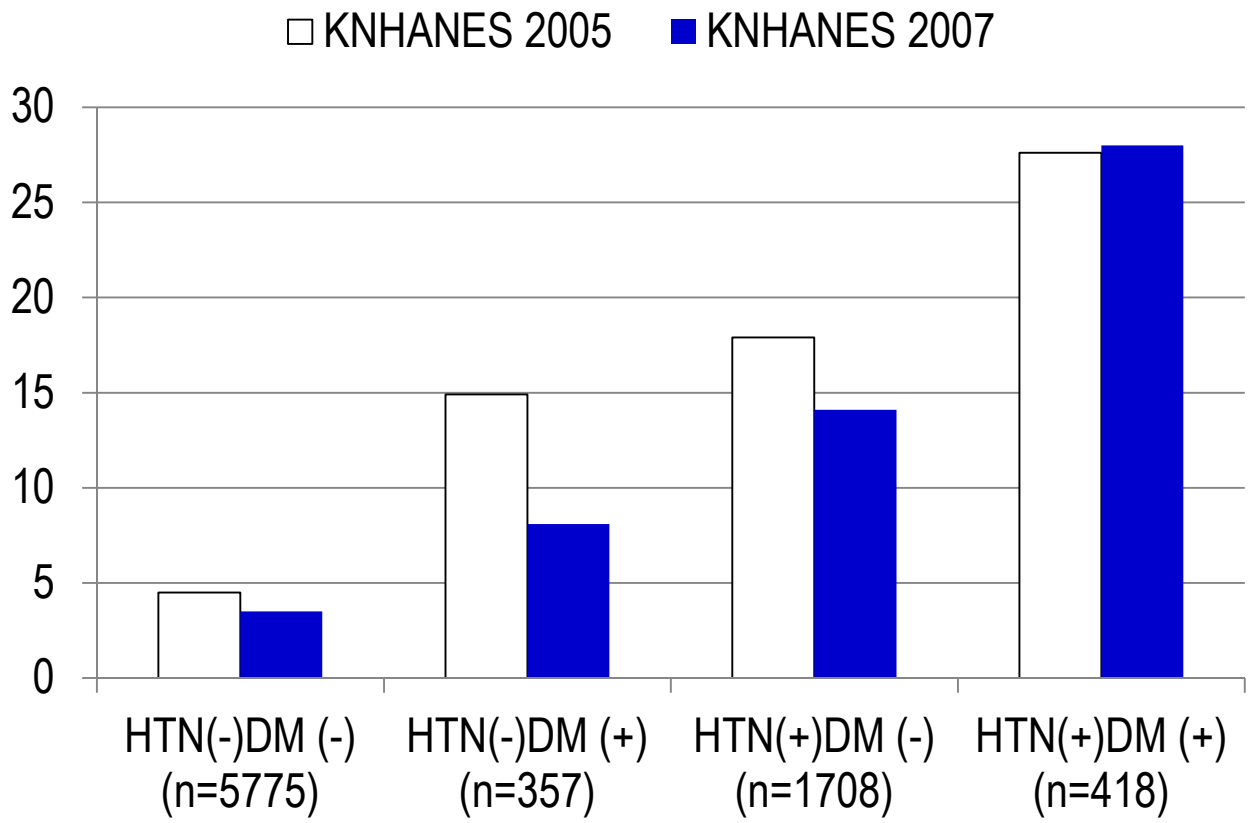
Trend in the prevalence of CKD in adult Korean population; data from KNHANES

	KNHANES 2005	KNHANES 2007	P value
N	5440	2960	
Age (years)	47.2±15.3	50.0±16.3	<0.001
Female (%)	57.4	58.0	0.598
Hypertension (%)	25.7	26.1	0.659
Antihypertensive drug (%)	13.4	15.8	0.002
Appropriate BP (%)	53.6	58.5	<0.001
Diabetes (%)	8.9	10.5	0.023
Controlled diabetes (%)	45.4	58.4	0.001
BMI (kg/m^2)	23.7±3.3	23.7±3.3	0.732
CKD (%)	**8.8**	**7.2**	**0.010**

eGFR using MDRD
CKD; eGFR < 60 mL/min/1.73 m^2
Appropriate BP; SBP < 130 mmHg & DBP < 80 mmHg
Controlled diabetes; HbA1c < 7.0%

Lee SW, et al. Nephrol Dial Transplant 2011;26:3975

Trend in the prevalence of CKD in adult Korean population; data from KNHANES



Lee SW, et al. Nephrol Dial Transplant 2011;26:3975

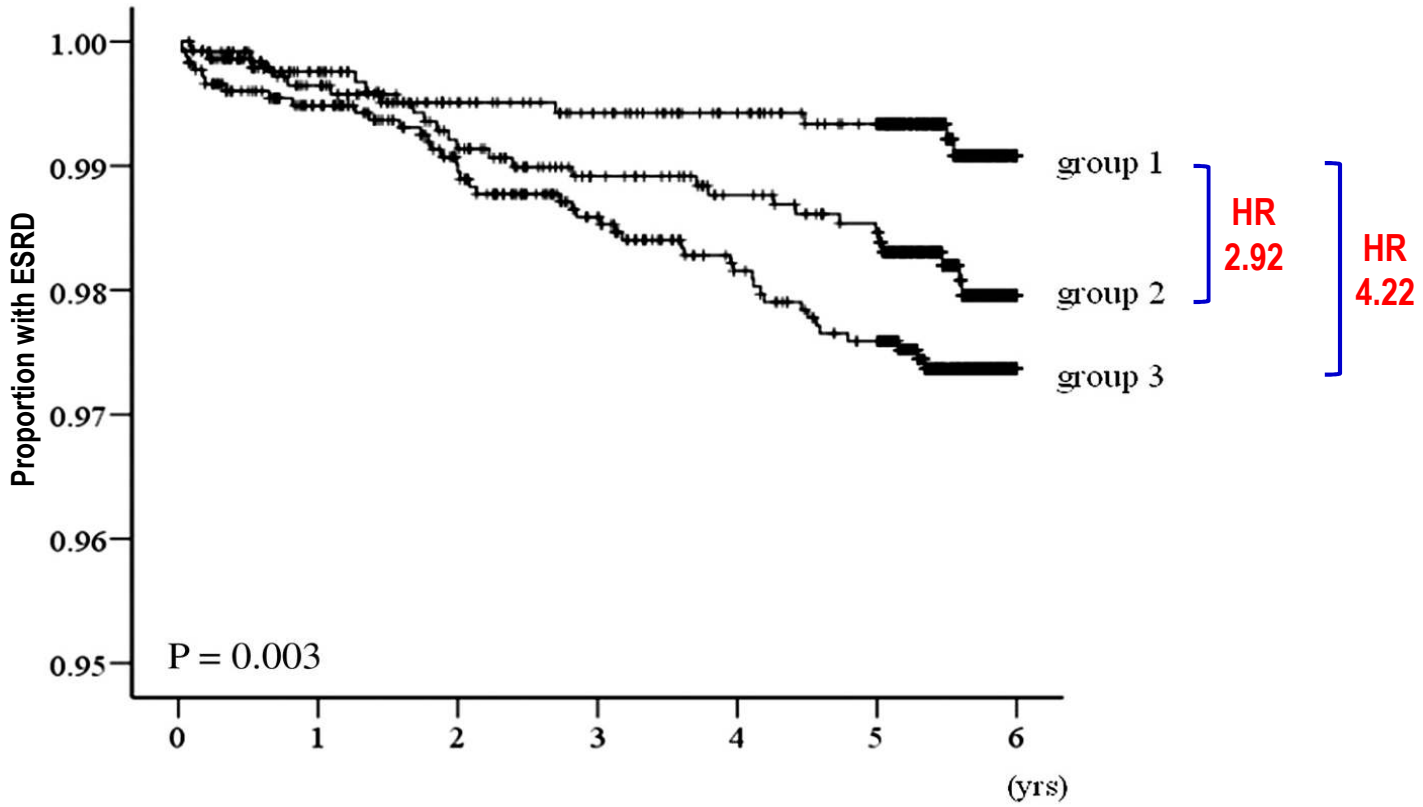
HbA1c & the incidence of ESRD in diabetes

- 25 years or older diabetic patients (E10-E14) visited at BSNUH during 2004
- 4474 patients: mean age 66.2±11.6 years, mean diabetes duration 8.56 years
- F/U period; 5.29 ±1.22 years

	All	Baseline HbA1c			P value
		< 6.50 (Group 1)	6.50-7.49 (Group 2)	≥ 7.50 (Group 3)	
N	4474	1255	1438	1781	
ESRD (%)	2.0	1.3	1.8	2.7	0.017
Mortality (%)	9.8	9.4	9.0	10.8	0.199
489 patients older than 80 years					
ESRD (%)		3.8	0.7	0.6	0.034
1346 patients with diabetes duration more than 10 years					
ESRD (%)		1.2	0.7	2.6	0.047

Oh SW, et al. Nephrol Dial Transplant 2011;26:2238

HbA1c & the incidence of ESRD in diabetes



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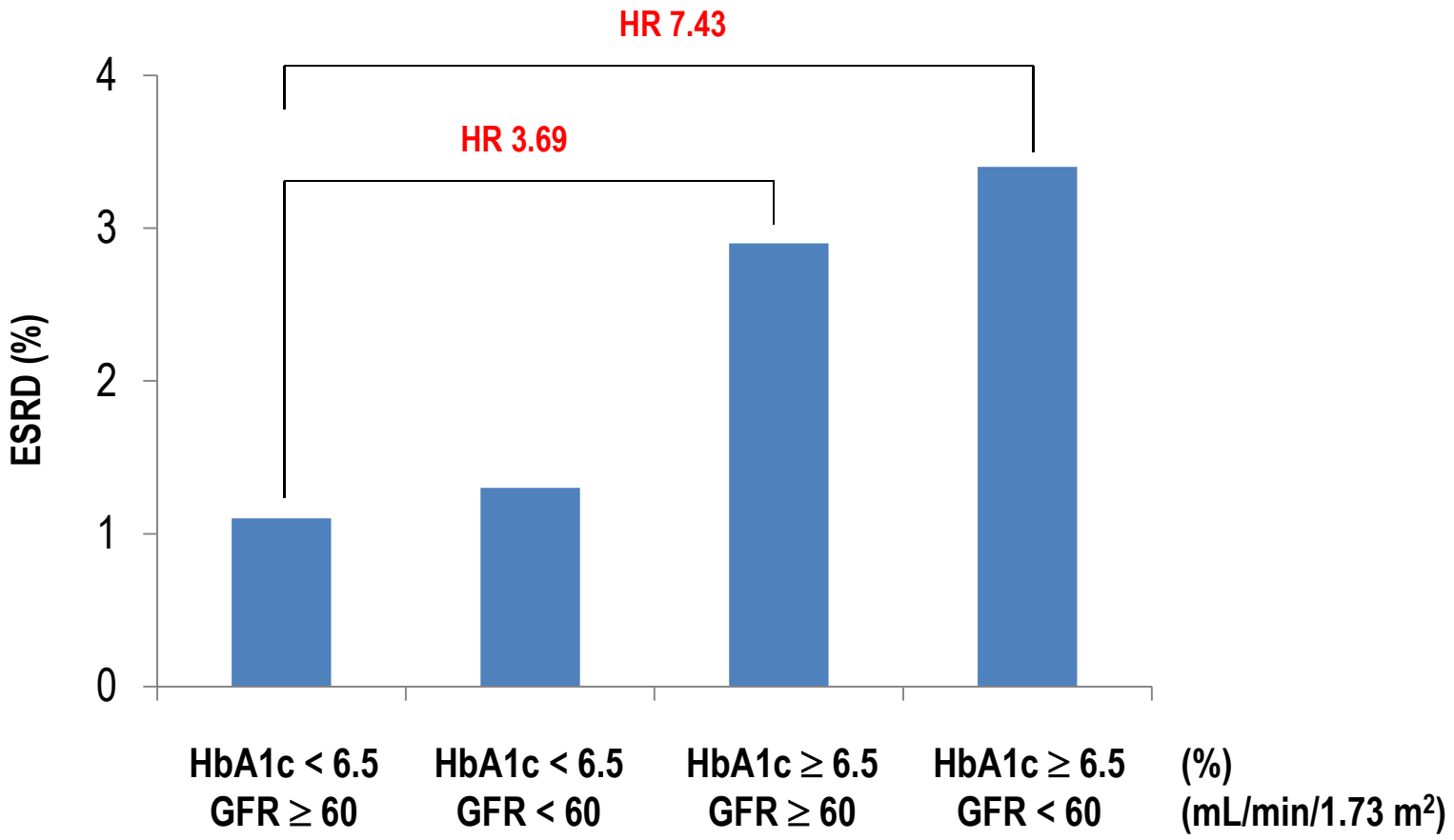
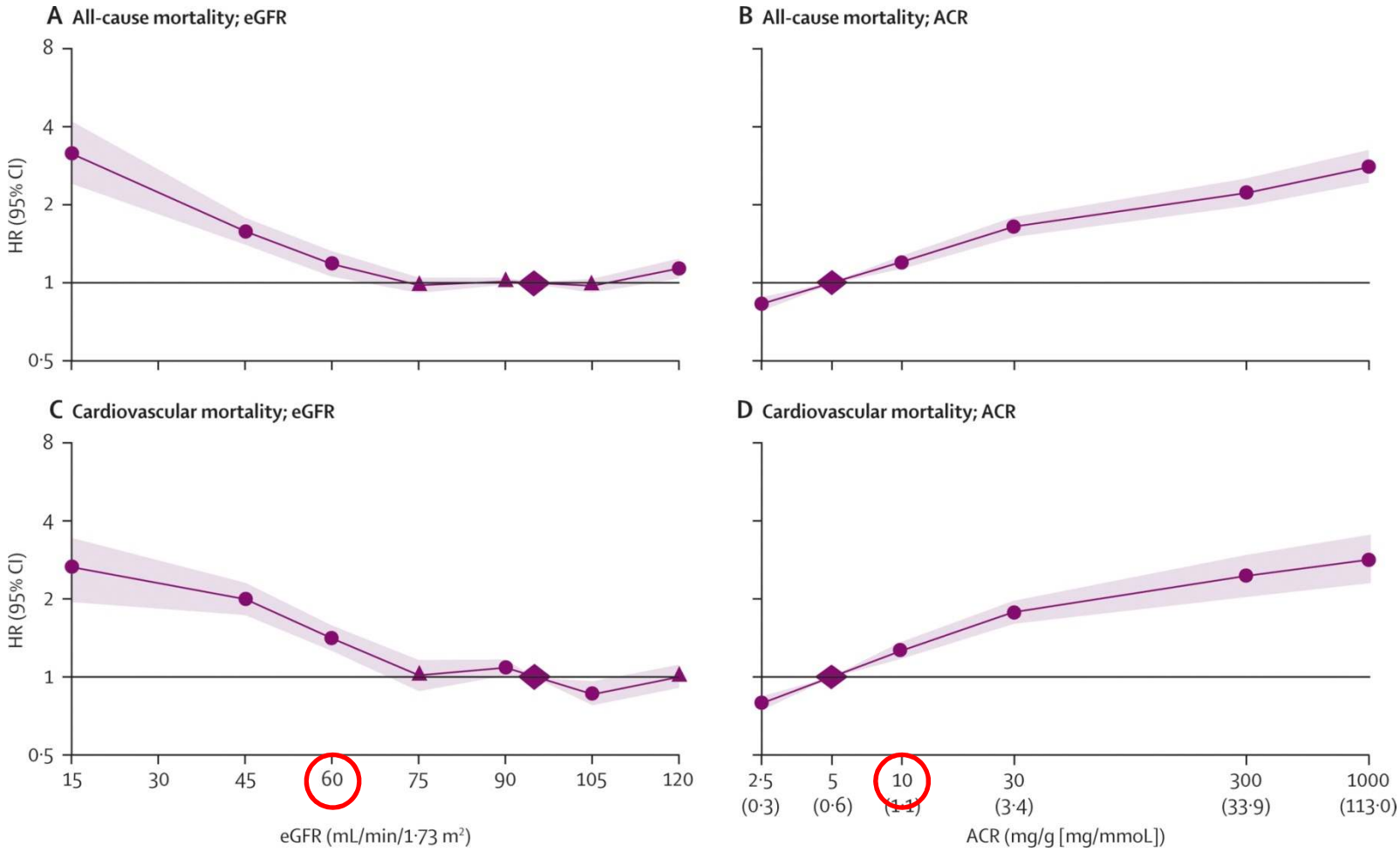
HbA1c & the incidence of ESRD in diabetes

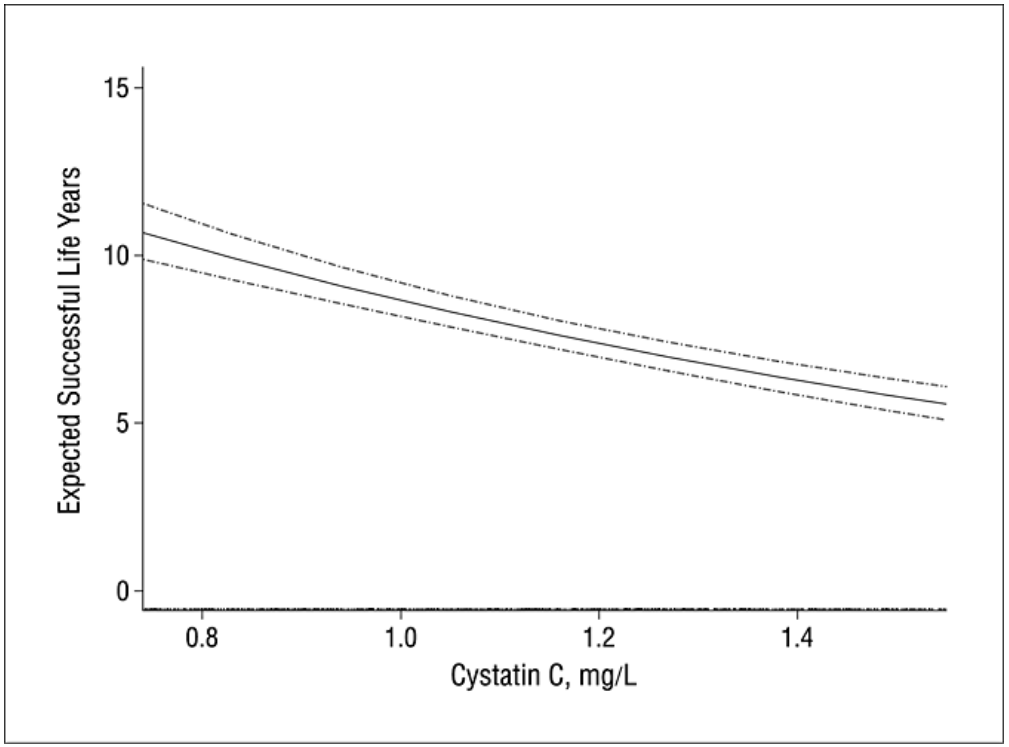


Oh SW, et al. Nephrol Dial Transplant 2011;26:2238

Association of eGFR & albuminuria with mortality
(a collaborative meta-analysis)



CKD Prognosis Consortium. Lancet 2010;375:2073



- **Successful aging**

  remaining free of 3 major classes of disease (cancer, CVD, COPD)

  and without a persistent physical disability or cognitive impairment

Sarnak MJ, et al. Arch Intern Med 2008;168:147

TABLE 1. Management of diabetic nephropathy by stage of renal function

Stage	Description	GFR (ml/min per 1.73 m^2 body surface area)	Management recommendations	Drug regimens
1	Kidney damage with normal or mildly increased GFR	≥90	A1c goal ~ 7.0% BP goal <130/85 LDL goal <100 mg/dl	Add ACE/ARB if urine microalbumin ≥30 mg/g creatinine
2	Kidney damage with mildly decreased GFR	60–89	A1c goal ~ 7.0% BP goal <130/85 LDL goal <100 mg/dl	ACE/ARB recommended for all patients
3	Moderately decreased GFR	30–59	A1c goal ~ 7.0% BP goal <130/85 LDL goal <100 mg/dl Refer patients not meeting treatment goals to nephrology for preparation of impending renal failure Monitor for anemia Monitor for secondary hyperparathyroidism	ACE/ARB recommended for all patients Discontinue metformin, all sulfonylureas except glipizide, nateglinide, α-glucosidase inhibitors, GLP-1 analogs Reduce doses of dipeptidyl peptidase-4 inhibitors Add erythropoietin if Hgb <9 mg/dl Add calcitriol when 1,25-dihydroxyvitamin D is low or when PTH >2 × upper limits of normal
4	Severely decreased GFR	15–29	A1c goal ~ 7.0% BP goal <130/85 LDL goal <100 mg/dl Refer to nephrology for preparation of impending renal failure and consideration of shunt placement Monitor for anemia Monitor for secondary hyperparathyroidism	ACE/ARB recommended for all patients with careful monitoring of serum K Insulin therapy recommended for most patients with diabetes Add erythropoietin if Hgb <9 mg/dl Add calcitriol when 1,25-dihydroxyvitamin D is low or when PTH >2 × upper limits of normal
5	End-stage renal failure	<15 or dialysis	Dialysis or kidney transplantation	

BP, Blood pressure; ACE, angiotension-converting enzyme inhibitors; Hgb, hemoglobin.

Approach to the patient with type 2 diabetes and progressive kidney disease.
J Clin Endocrinol Metab. 2010 Jul;95(7):3103-10.

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Diabetes & Metabolism

Diabetes & Metabolism 37 (2011) S27-S38

European Diabetes Working Party for Older People 2011 Clinical Guidelines for Type 2 Diabetes Mellitus. Executive Summary

A Report of the European Diabetes Working Party for Older People (EDWPOP) Revision Group on Clinical Practice Guidelines for Type 2 Diabetes Mellitus

Expert Revision Group

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Renal disease

1. At the time of diagnosis and annually thereafter, all older people with type 2 diabetes have a measured serum creatinine, an estimated glomerular filtration rate, and an albumin-creatinine ratio undertaken. *Evidence level 1+, Grade of recommendation B.*
2. In older people with type 2 diabetes who have a raised albumin/creatinine ratio (>2.5 mg/mmol, women; > 3.5 mg/mmol, men), treatment with an ACE inhibitor is recommended – extrapolated data. *Evidence level 1+, Grade of recommendation B.*
3. In older patients with diabetes and microalbuminuria, maintaining a blood pressure target of 140/80 or less, and a HbA1c range of 6.5-7.5%, may help to reduce the development of chronic kidney disease (CKD). *Evidence level 2++, Grade of recommendation B.*
4. Specialist review by a nephrologist at an earlier stage of CKD may prevent late referrals of older patients with diabetes for renal replacement therapy and improve outcomes. *Evidence level 2++, Grade of recommendation B.*

Glucose regulation

1. For older patients with type 2 diabetes, with single system involvement (free of other major co-morbidities), a target HbA1c range of 7-7.5% should be aimed for (DCCT aligned). *Evidence level 1+, Grade of recommendation A. The* precise target agreed will depend on existing cardiovascular risk, presence of microvascular complications, and ability of individual to self-manage.
2. For frail (dependent; multisystem disease; care home residency including those with dementia) patients where the hypoglycaemia risk is high and symptom control and avoidance of metabolic decompensation is paramount, the target HbA1c range should be 7.6-8.5%. *Evidence level 1+, Grade of recommendation A.*
3. For older patients with type 2 diabetes, with single system involvement (free of other major co-morbidities), a fasting glucose range of 6.5-7.5 mmol/l can be regarded as indicating good control. *Evidence level 2++, Grade of recommendation B.*
4. For frail patients including those residing in care homes, a fasting glucose range 7.6-9.0 mmol/l should minimise the risk of hypoglycaemia and metabolic decompensation. *Evidence level 2+, Grade of recommendation C.*

Blood pressure regulation

1. The threshold for treatment of high blood pressure in older subjects with type 2 diabetes should be 140/80 mmHg or higher present for more than 3 months and measured on at least three separate occasions during a period of lifestyle management advice (behavioural: exercise, weight reduction, smoking advice, nutrition/dietary advice). *Evidence level 2++, Grade of recommendation B.*
2. In non-frail subjects with diabetes older than 80 years, an acceptable blood pressure on treatment is a systolic of 140-145 mmHg, and a diastolic less than 90 mmHg. *Evidence level 1+, Grade of recommendation B.*
3. For frail (dependent; multisystem disease; care home residency including those with dementia) patients, where avoidance of heart failure and stroke may be of greater relative importance than microvascular disease, an acceptable blood pressure is <150/90 mmHg. *Evidence level 2+, Grade of recommendation C (extrapolated data).*
4. In older patients with a sustained blood pressure (≥140/80 mmHg) and in whom diabetic renal disease is absent, first-line therapies can include: use of ACE inhibitors, angiotensin II receptor antagonists, long-acting calcium channel blockers, beta blockers or thiazide diuretics. *Evidence level 1+, Grade of recommendation A.*
5. In older patients with a sustained blood pressure (≥140/80 mmHg) with microalbuminuria or proteinuria, treatment with an ACE inhibitor or angiotensin II receptor antagonist is recommended. *Evidence level 1+, Grade of recommendation B.*
6. Use of a perindopril-based regimen in older patients with type 2 diabetes (with or without hypertension) improves both microvascular and macrovascular outcomes. *Evidence level 1+, Grade of recommendation A.*

경청해 주셔서 감사합니다