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Renal artery calcified plaque associations with subclinical renal and cardiovascular disease

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Renal artery calcified plaque associations with subclinical renal and cardiovascular disease.

Background. The prognostic significance of renal artery calcified plaque (RAC) and its relationship with renal function, albuminuria, and systemic atherosclerosis are unknown.

Methods. Calcified atherosclerotic plaque was measured in the renal arteries of 96 unrelated Caucasian subjects with type 2 diabetes mellitus (DM) using four-channel multidetector–row computed tomography (MDCT4). Renal artery calcium was measured as the sum of ostial and main renal artery calcium scores. Participants also underwent MDCT scanning to measure coronary artery calcium (CAC), carotid artery calcium, common iliac artery calcium, infra-renal aorta calcium, and B-mode ultrasound to measure carotid artery intima-medial thickness (IMT). Spearman's rank correlation coefficients were used to assess associations between RAC and measures of subclinical renal and cardiovascular disease. Partial correlation coefficients were computed to adjust for the potential confounding effects of age, gender, body mass index (BMI), DM duration, smoking, and serum cholesterol and triglyceride levels.

Results. Characteristics of the study group were 54% (52/96) female with a mean ± SD (median) age 62.8 ± 8.4 (62.5) years, DM duration 10.6 ± 6.3 (8.0) years, hemoglobin A1C 7.5 ± 1.5 (7.2)%, BMI 32.1 ± 6.3 (31.1) kg/m^2, serum creatinine concentration 1.11 ± 0.18 (1.10) mg/dL, urine albumin:creatinine ratio (ACR) 105.3 ± 423.1 (17.6) mg/g, modified MDRD equation glomerular filtration rate (GFR) 64.3 ± 12.6 (63.6) mL/min, RAC 372 ± 799 (101), CAC 1819 ± 2594 (622), carotid artery calcium 264 ± 451 (72), and B-mode ultrasound carotid IMT 0.70 ± 0.12 (0.69) mm. Sixty-five percent of subjects (62/96) had detectable RAC. Renal artery calcium was significantly associated with CAC ($r = 0.50$, $P < 0.0001$), carotid artery calcium ($r = 0.58$, $P < 0.0001$), common iliac artery calcium ($r = 0.45$, $P < 0.0001$), infra-renal aorta calcium ($r = 0.70$, $P < 0.0001$), IMT ($r = 0.40$, $P = 0.0004$), diastolic blood pressure ($r = -0.33$, $P = 0.0009$), BMI ($r = -0.19$, $P = 0.0573$), and age ($r = 0.54$, $P < 0.0001$). There was no association between RAC and GFR ($r = -0.15$, $P = 0.1637$) or between RAC and urine ACR ($r = 0.07$, $P = 0.5083$).

Conclusion. Renal artery calcium is strongly associated with older age, diastolic blood pressure, BMI, carotid artery IMT, and coronary, carotid, common iliac artery, and infra-renal aorta calcium in Caucasians with type 2 diabetes mellitus. Renal artery calcium, similar to CAC and IMT, appears to be a useful noninvasive marker of subclinical atherosclerosis. However, RAC is not significantly associated with either GFR or albuminuria.

Key words: glomerular filtration rate, renal artery calcium, diabetes mellitus, albuminuria, coronary artery calcium, carotid artery intimal medial thickness, computed tomography..

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Coronary artery calcium (CAC) and carotid artery intimal medial thickness (IMT) are widely accepted measures of subclinical atherosclerosis. Carotid IMT predicts incident coronary heart disease [1, 2], and the prevalence and incidence rates of coronary heart disease increase with increasing CAC score [3, 4]. The prognostic value of renal artery calcified plaque (RAC) measurements using noninvasive computerized tomography (CT) has not been evaluated.

A high prevalence of renal artery atherosclerosis has been noted in those with coronary artery disease and generalized systemic atherosclerosis [5–9]. Arteriography cannot accurately quantitate the degree of arterial stenosis or detect the atherosclerotic burden eccentric to the vessel lumen. Additionally, the risks of renal failure caused by cholesterol emboli syndrome and contrast nephropathy limit its application in patients with chronic renal failure or diabetes [10].

To determine the usefulness of measuring renal artery calcium with MDCT, we analyzed the relationships between renal artery calcified plaque and albuminuria, calculated glomerular filtration rate, and systemic atherosclerosis in an intensively studied population of Caucasian subjects with type 2 diabetes.

METHODS

Patient population

The Diabetes Heart Study (DHS) is a family-based study designed to identify genes producing susceptibility

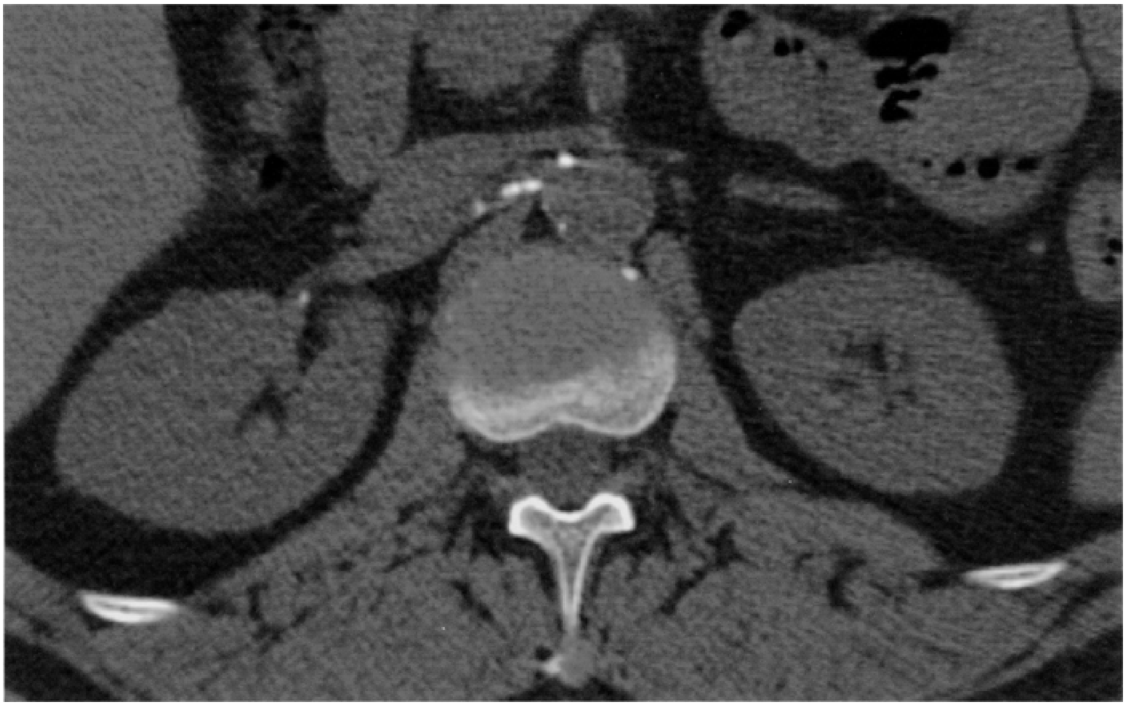

Fig. 1. Standard transverse CT image demonstrating calcified atherosclerotic plaque at the origin of the renal artery from the aorta and extending along the posterior wall of the proximal right renal artery.

to subclinical cardiovascular disease [11, 12]. Type 2 diabetic index cases (defined as diabetes onset at ≥35 years of age, in the absence of historic evidence of diabetic ketoacidosis) were recruited from hospital and community clinics. The initial 96 unrelated Caucasian type 2 diabetic subjects who enrolled in the DHS with serum creatinine concentrations ≤1.6 mg/dL were selected for measurement of RAC.

In the DHS, participants receive B-mode ultrasound for carotid artery IMT, computed tomography (CT) for coronary, aortic arch, carotid artery, abdominal aorta, and common iliac artery calcium, and bone densitometry. Participants also undergo electrocardiography, fasting serum and urine chemistries, and interviews for past medical history, medications, and lifestyle.

Imaging methods

Coronary artery calcium measurements were performed on a four-channel multidetector CT (MDCT4) with cardiac gating and capable of 500-millisecond temporal resolution using the segmented reconstruction algorithm (LightSpeed Qxi; General Electric Medical Systems, Waukesha, WI, USA). The techniques for the coronary and carotid scans have previously been described in detail [11, 13]. In brief, participants were placed in the supine position on the CT couch over a quality control calibration phantom (Image Analysis, Inc., Columbia, KY, USA) for scans of the heart and abdomen. Participants were repositioned for the carotid artery bifurcation scan of the neck and placed in a head holder to aid in positioning.

The abdomen scan series was used to measure renal artery, infra-renal aorta, and common iliac artery calcium. The technical factors for this series were: 120 kV, 250 mA, 0.8-second gantry rotation helical mode (7.5 mm/s), 2.5-mm slice thickness, and standard reconstruction kernel. The display field of view was 35 cm, resulting in a pixel dimension of 0.68 by 0.68 mm. The calcified renal artery plaque were identified and measured by a single radiologist (J.J.C). The right and left renal arteries were evaluated in two segments: ostial and main renal artery proper (Figs. 1 and 2). Ostial plaques were defined as calcified plaque at the origin of the renal artery but contiguous with the adjacent abdominal aorta. Accessory renal arteries, when identified, were evaluated with the same criteria. One participant was excluded secondary to having a horseshoe kidney, previous urologic surgery, and multiple accessory renal arteries. CT scans of all three vascular territories (coronary, carotid, and renal) were analyzed on a G.E. Advantage Windows Workstation with the SmartScores software package (General Electric Medical Systems) using a modified Agatston scoring method, which adjusts for slice thickness and uses the conventional threshold of 130 Hounsfield units.

Carotid artery IMT measurements were performed with participants in the supine position using high resolution B-mode carotid ultrasonography with a 7.5-mHz transducer and a Biosound Esaote (AU5) ultrasound machine, as has previously been described [12].

Fig. 2. Coronal-oblique reformat of the CT images, demonstrating the abdominal aorta with extensive calcified atherosclerotic plaque. The plane of the image was selected to demonstrate the right kidney, renal artery, and aorta in a single image. Calcified plaque is present in the proximal right renal artery and at the ostia.

Statistical methods

Renal artery calcium was measured as the sum of ostial and main renal artery calcium scores. Common iliac artery calcium was measured as the sum of both common iliac artery calcium scores. Coronary and carotid artery calcium and carotid IMT were measured as previously reported [11–13]. The sample means, standard deviations, medians, minima, and maxima were computed for the continuous characteristics (e.g., age, diabetes duration, BMI, blood pressure, serum cholesterol and triglyceride levels) and the measures of subclinical renal and cardiovascular disease (RAC, CAC, IMT, and GFR). For the discrete demographic characteristics, such as gender and smoking, the proportions were calculated.

The associations between RAC and measures of subclinical renal and cardiovascular disease were presented by the Spearman's rank correlation coefficients. Partial correlation coefficients were computed to adjust for the potential confounding effects of age, gender, BMI, diabetes duration, smoking, and serum cholesterol and triglyceride levels. The partial correlation coefficients were obtained by computing the Spearman's

Table 1. Demographic characteristics of study population[a]

Variable	Mean	Std dev	Median	Minimum	Maximum
Age *years*	62.77	8.37	62.45	44.58	79.53
Diabetes duration *years*	10.57	6.28	8	2	30
BMI *kg/m²*	32.13	6.32	31.13	20.53	50.03
Systolic BP *mm Hg*	141.67	18.37	142.0	103.5	199.0
Diastolic BP *mm Hg*	71.24	10.17	70.50	46.5	101.5
Hemoglobin A1C %	7.47	1.46	7.2	5.2	12.7
Urine ACR *mg/g*	105.32	423.12	17.57	0.95	3505.88
GFR *mL/min*	64.27	12.63	63.62	40.53	98.07
BUN *mg/dL*	18.01	5.39	17.0	8	43
Serum creatinine *mg/dL*	1.11	0.18	1.1	0.7	1.6
HDL cholesterol *mg/dL*	43.30	11.64	41.0	18	81
LDL cholesterol *mg/dL*	105.26	37.29	100.0	38	236
Triglycerides *mg/dL*	204.46	108.92	188.0	38	660
Total renal artery Ca	372.48	799.19	101.0	0	4558
Ostial renal artery Ca	201.71	406.90	18.50	0	2780
Main renal artery Ca	170.77	500.52	1.00	0	3782
Coronary artery Ca	1818.84	2594.12	622	0	12124
Carotid artery Ca	264.04	451.49	61	0	3044
Carotid artery IMT *mm*	0.70	0.12	0.69	0.47	1.21
Common iliac artery Ca	2843.60	4563.09	875.00	0	25651
Infra-renal aorta Ca	10343.83	12794.21	5583.00	0	64118

Abbreviations are: Std dev, standard deviation; BMI, body mass index; ACR, albumin:creatinine ratio; GFR, glomerular filtration rate; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Ca, calcium.
[a]Sample size: 96 and varied by no more than one except for GFR ($N = 91$), BUN ($N = 91$), LDL ($N = 90$), and carotid artery IMT ($N = 76$).

rank correlation coefficient between the residuals from models regressing RAC and one of the measures of subclinical renal and cardiovascular disease, respectively, onto age, gender, BMI, diabetes duration, smoking, and serum cholesterol and triglyceride levels. SAS software was used for all statistical analyses (Cary, NC, USA).

RESULTS

Characteristics of the Caucasian diabetic study group included 54.2% (52/96) female, 63.5% (61/96) current or former cigarette smokers, 68.4% (65/95) hypertensive (blood pressure >140/90 mm Hg or prescribed antihypertensive medications), and 50% (48/96) were prescribed cholesterol-lowering medications (45.8% statins, 4.1% fibric acid derivatives). Subjects had a mean ± SD (median) age 62.8 ± 8.4 years (62.5), DM duration 10.6 ± 6.3 (8.0) years, hemoglobin A1C 7.5 ± 1.5% (7.2), BMI 32.1 ± 6.3 kg/m^2 (31.1), serum creatinine concentration 1.11 ± 0.18 mg/dL (1.10), urine albumin:creatinine ratio (ACR) 105.3 ± 423.1 mg/g (17.6), and modified MDRD equation glomerular filtration rate (GFR) 64.3 ± 12.6 mL/min (63.6) (Table 1).

Sixty-five percent of subjects (62/96) had detectable RAC [ostial RAC was observed in 55.2% (53/96) and main renal artery calcium in 50% (48/96)]. Radiographic characteristics included: mean ± SD (median) total RAC 372 ± 799 (101), CAC 1819 ± 2594 (622), carotid artery calcium 264 ± 451 (72), and carotid IMT 0.70 ± 0.12 mm (0.69) (Table 1).

Renal artery calcium associations are listed in Tables 2 and 3. Renal artery calcium was positively associated with CAC ($r = 0.50$, $P < 0.0001$), carotid artery calcium ($r = 0.58$, $P < 0.0001$), infra-renal aorta calcium ($r = 0.70$, $P < 0.0001$), common iliac artery calcium ($r = 0.45$, $P < 0.0001$), carotid IMT ($r = 0.40$, $P < 0.0004$), and age ($r = 0.54$, $P < 0.0001$), and was negatively associated with diastolic blood pressure ($r = -0.33$, $P = 0.0009$) and BMI ($r = -0.19$, $P = 0.057$). There was no significant association between RAC and GFR ($r = -0.15$, $P = 0.1637$) or between RAC and ACR ($r = 0.07$, $P = 0.5083$). A trend toward a significant association was observed between ostial RAC and GFR ($r = -0.18$, $P = 0.0821$), while no association was observed between either ostial RAC or main renal artery calcium and ACR (both $P > 0.5$).

Table 2. Correlation between renal artery calcium and covariates

Covariate	N[a]	r^b	*P* value
Age *years*	96	0.54	<0.0001
Diabetes duration *years*	96	0.19	0.0606
BMI *kg/m²*	96	−0.19	0.0573
HDL cholesterol *mg/dL*	96	0.03	0.7972
LDL cholesterol *mg/dL*	90	−0.07	0.5098
Triglycerides *mg/dL*	96	−0.13	0.1962

[a]N, sample size.
[b]*r*, Spearman's rank correlation coefficient.

The significant RAC correlations with CAC, carotid artery, infra-renal aorta, and common iliac artery calcium were not markedly altered when smoking status, age, gender, DM duration, BMI, HDL cholesterol, and triglycerides were included in the partial correlation coefficient analyses (all remained $P < 0.001$, Table 3). Because of collinearity between carotid artery IMT and age, all covariates except age were used to study the association between RAC and carotid artery IMT. The association was weakened but still significant ($r = 0.35$, $P = 0.0032$).

Table 3. Correlation between renal artery calcium and clinical covariates

Covariate	Unadjusted r^c (*P* value)	Model 1[a] r^c (*P* value)	Model 2[b] r^c (*P* value)
Systolic BP *mm Hg*	0.10 (0.3300)	0.04 (0.6986)	0.04 (0.6891)
Diastolic BP *mm Hg*	−0.33 (0.0009)	−0.18 (0.0866)	−0.17 (0.1035)
Hemoglobin A1C %	−0.12 (0.2320)	−0.08 (0.4654)[d]	−0.06 (0.5742)[d]
Urine ACR *mg/g*	0.07 (0.5083)	0.11 (0.2883)	0.11 (0.2989)
GFR *mL/min*	−0.15 (0.1637)	−0.18 (0.0947)[d]	−0.18 (0.1053)[d]
Serum creatinine *mg/dL*	0.16 (0.1173)	0.13 (0.2243)[d]	0.15 (0.1719)[d]
Coronary artery Ca	0.50 (<0.0001)	0.37 (0.0003)	0.36 (0.0006)
Carotid artery Ca	0.58 (<0.0001)	0.45 (<0.0001)	0.45 (<0.0001)
Carotid artery IMT *mm*	0.40 (0.0004)	0.38 (0.0012)[d]	0.35 (0.0032)[d]
Common iliac artery Ca	0.45 (<0.0001)	0.34 (0.0012)	0.33 (0.0021)
Infra-renal aorta Ca	0.70 (<0.0001)	0.55 (<0.0001)	0.55 (<0.0001)

[a]Model 1 adjustments: age, gender, BMI, and smoking (excluding hemoglobin A1C, GFR, serum creatinine, and carotid artery IMT).
[b]Model 2 adjustments: age, gender, BMI, smoking, diabetes duration, HDL cholesterol, and triglycerides (excluding hemoglobin A1C, GFR, serum creatinine, and carotid artery IMT).
[c]*r*, Spearman's rank correlation coefficient.
[d]Because of collinearity with age, age was not included in the multivariate adjustments. All the other covariates listed above for Models 1 and 2 were adjusted.

DISCUSSION

CT scans of major arterial vessels are noninvasive tests that permit quantification of subclinical atherosclerosis in the coronary and carotid circulations. As with carotid artery IMT measured by B-mode ultrasound [1, 2], coronary calcium is an excellent predictor of subsequent cardiovascular morbidity and mortality [3, 4]. This is the first report that we are aware of measuring RAC using CT. We were also able to compare RAC results with coronary and carotid artery calcium and carotid IMT, as well as to assess for association between albuminuria, glomerular filtration rate, and RAC.

Not surprisingly, RAC was strongly correlated with calcium deposition in the coronary, carotid, infra-renal aorta, and common iliac arteries. The presence of coexisting systemic atherosclerosis in patients with renal artery stenosis is well recognized [5–9]. Cardiovascular morbidity and mortality rates are elevated in dialysis patients and chronic renal failure patients manifesting atherosclerotic renovascular disease [14, 15].

The total RAC score, reported as the sum of ostial and main artery RAC, had no association with either renal function or urine ACR. Although there was a trend toward an ostial RAC association with GFR, no association was observed between ostial RAC and urine ACR. Similarly, main renal artery RAC did not have any significant relationship with either GFR or urine ACR.

All diabetic participants in the DHS had severe systemic atherosclerosis, frequently accompanied by hypertension, obesity, hyperlipidemia, and high rates of cigarette smoking. Ninety-eight percent (93/95) and 80% (76/95) of participants in this report, respectively, had measurable coronary artery or carotid artery calcium. Hypertension [16], smoking [17], diabetes mellitus [18], and hyperlipidemia [19] have all been linked with enhanced risk for development of progressive nephropathy. Treatment of these disorders often delays the progression of nephropathy and reduces proteinuria [16, 18, 19]. Although the cardiovascular literature lists similar risk factors for large vessel atherosclerosis (renal, coronary, and carotid artery disease) and small vessel disease (arteriolar nephrosclerosis and glomerulosclerosis) [16], no relationship was observed between atherosclerotic renal artery calcium and either renal function or albuminuria in this cohort of type 2 diabetic patients with fairly well preserved GFRs. However, ostial RAC did demonstrate a weak association with renal function. Markedly reduced GFRs in the presence of hemodynamically significant ostial renal artery stenosis are not uncommon. The nearly significant association observed between ostial RAC and GFR suggests that some of these diabetic subjects may have had reduced renal perfusion with ostial renal artery calcification; however, renal blood flow was not measured. Albuminuria, as is typically observed in hypertensive and diabetic glomerulosclerosis and arteriolonephrosclerosis, did not correlate with any of the CT measures of large vessel renal artery calcium.

One potential limitation of this report is that all participants had long-standing type 2 diabetes mellitus. Therefore, the relations observed for RAC in our population may not be relevant in nondiabetic populations. The accelerated rates of systemic atherosclerosis that are typically observed in diabetic subjects would likely magnify the relationships between measures of kidney disease and renal artery calcification. Nonetheless, we believe that the results in these analyses should only be applied to Caucasian diabetic subjects until they are reproduced in other populations.

We also limited the analyses to participants with fairly well preserved renal function. Although progressive atherosclerosis is clearly associated with marked reductions in GFR, our objective was to determine whether relationships existed between renal artery calcium and albuminuria/GFR in those without the need for calcium-containing phosphate binders or supplemental 1,25 dihydroxy vitamin D therapy. We believe that it is likely that the vascular calcium that is often observed in subjects on dialysis and with chronic renal failure may be linked with these therapies [20, 21].

CONCLUSION

Nearly 65% of Caucasian subjects with long-standing type 2 diabetes mellitus have detectable renal artery calcium on helical CT scans. CT is a simple and noninvasive method of identifying renal artery calcium, a surrogate marker for renal artery atherosclerosis. Renal artery calcium is highly correlated with coronary, carotid, common iliac artery, and infra-renal aorta calcium, and with carotid IMT. However, calcification of ostial and main renal arteries is not associated with albuminuria. Ostial renal artery calcium content may be weakly associated with reduced glomerular filtration rate. These findings further support the hypothesis that macrovascular atherosclerosis in the renal arteries, defined by the presence of calcified plaque component, has limited impact on renal function when compared with those processes involving the microvasculature.

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REFERENCES

1. Chambless LE, Heiss G, Folsom AR, *et al*: An association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: The Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol* 146:483–494, 1997
2. O'Leary DH, Polak JF, Kronmal RA, *et al*: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 340:14–22, 1999
3. Raggi P, Callister TQ, Cooil B, *et al*: Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 101:850–855, 2000
4. Arad Y, Spadaro LA, Goodman K, *et al*: Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 36:1253–1260, 2000
5. Harding MB, Smith LR, Himmelstein SI, *et al*: Renal artery stenosis: Prevalence and associated risk factors in patients undergoing routine cardiac catheterization. *J Am Soc Nephrol* 2:1608–1616, 1992
6. Jean WJ, Al-Bitar I, Zwicke DL, *et al*: High incidence of renal artery stenosis in patients with coronary artery disease. *Catheter Cardiovasc Interv* 32:8–10, 1994
7. Gross CM, Kramer J, Waigand J, *et al*: Relation between arteriosclerosis in the coronary and renal arteries. *Am J Cardiol* 80:1478–1481, 1997
8. Olin JW, Melia M, Young JR, *et al*: Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. *Am J Med* 88:1-46N–1-51N, 1990
9. Kuroda S, Nishida N, Uzu T, *et al*: Prevalence of renal artery stenosis in autopsy patients with stroke. *Stroke* 31:61–65, 2000
10. Greco BA, Breyer JA: Atherosclerotic ischemic renal disease. *Am J Kidney Dis* 29:167–187, 1997
11. Wagenknecht LE, Bowden DW, Carr JJ, *et al*: Familial aggregation of coronary artery calcium in families with type 2 diabetes. *Diabetes* 50:861–866, 2001
12. Lange LA, Bowden DW, Langefeld CD, *et al*: Heritability of carotid artery intima-medial thickness in type 2 diabetes. *Stroke* 33:1876–1881, 2002
13. Carr JJ, Langefeld CD, Shi R, *et al*: Coronary and carotid vascular calcium are inversely associated with thoracic bone mineral density in type 2 diabetic families—The Diabetes Heart Study. *Circulation* 105:86E, 2002
14. Appel RG, Bleyer AJ, Reavis S, Hansen KJ: Renovascular disease in older patients beginning renal replacement therapy. *Kidney Int* 48:171–176, 1995
15. Wright JR, Shurrab AE, Cheung C, *et al*: A prospective study of the determinants of renal functional outcome and mortality in atherosclerotic renovascular disease. *Am J Kidney Dis* 39:1153–1161, 2002
16. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC report. *JAMA* 289:2560–2572, 2003
17. Bleyer AJ, Shemanski LR, Burke GL, *et al*: Tobacco, hypertension and vascular disease: Risk factors for renal functional decline in an older population. *Kidney Int* 57:2072–2079, 2000
18. Reichard P, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 329:304–309, 1993
19. Bianchi A, Bigazzi R, Caiazza A, Campese VM: A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. *Am J Kidney Dis* 41:565–570, 2003
20. Reslerova M, Moe SM: Vascular calcification in dialysis patients: Pathogenesis and consequences. *Am J Kidney Dis* 41(Suppl 1):S96–S99, 2003
21. Goodman WG: Vascular calcification in end-stage renal disease. *J Nephrol* 15(Suppl 6):S82–S85, 2002