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Diabetic nephropathy and risk factors for peripheral artery disease in Chinese with type 2 diabetes mellitus

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Abstract

The risk for peripheral arterial disease (PAD) is increased in patients with chronic kidney disease. We investigated the effects of renal function on PAD in Chinese with type 2 diabetes mellitus. This study enrolled a total of 2983 (1342 men and 1641 women) Chinese adults with diabetes. The mean age was 63.2 ± 11.9 years. Peripheral arterial disease was diagnosed by an ankle-brachial index less than 0.9. Renal function was evaluated by serum creatinine (SCr), estimated glomerular filtration rate, and urinary albumin-creatinine ratio (ACR). Risk factors for PAD were evaluated using multiple logistic regression analysis. Age, cholesterol, and high-density lipoprotein cholesterol (HDL-C) (inverse association) were significant risk factors in men, whereas age, body mass index (inverse association), low-density lipoprotein cholesterol, and HDL-C (inverse association) were significant risk factors for diabetic women. After adjustment for age, body mass index, blood pressure, glycosylated hemoglobin, cholesterol, HDL-C, low-density lipoprotein cholesterol, and triglyceride levels, we found that SCr levels greater than 1.5 mg/dL, estimated glomerular filtration rate less than 60 mL/min, and urinary ACR greater than 30 mg/g were independent risk factors for PAD in diabetic men and that SCr levels greater than 1.4 mg/dL and urinary ACR greater than 30 mg/g were independently associated with PAD in diabetic women. The risk factors for PAD are somewhat different between men and women with diabetes in Chinese population in Taiwan. Diabetic nephropathy is significantly associated with PAD in this patient population.

1. Introduction

Peripheral arterial disease (PAD), like cardiovascular disease (CVD), is a major arterial disease caused by atherosclerosis. Diabetes mellitus has been shown to be associated with higher risk of PAD in various ethnic groups [1-4]. In Taiwan, 1 study reported that more than half of the diabetic patients who underwent an amputation had PAD [5]. The prognosis of diabetic patients undergoing lower extremity amputation is very poor, as the 5-year survival rate is about 50% [6].

One study, investigating PAD in Asian type 2 diabetes mellitus patients, found that cardiovascular risk factors were significantly different between men and women [7]. We recently reported that Chinese diabetic women were at higher risk for coronary artery disease (CAD) after adjusting for the effect of other cardiovascular risk factors [8]. Previous studies have shown that the risk factors for PAD may differ for men and women [9-11]. If sex contributes to PAD risk factor profile in Chinese diabetic patients, prevention strategies should reflect these differences.

Chronic kidney disease (CKD) is a worldwide public health problem [12]. Many studies have found an association between CKD and increased risk for PAD [13-16]. Compared with whites, Chinese with type 2 diabetes mellitus have a higher risk of developing diabetic nephropathy [17]. The relationship between CKD and PAD, to the best of our knowledge, has never been tested in Chinese diabetic

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population, whose genetic and environmental backgrounds differ from those of other ethnicities. Therefore, this cross-sectional study investigates the sex differences in risk factor profiles for PAD and the association between CKD and PAD among Chinese male and female patients with type 2 diabetes mellitus in Taiwan.

2. Materials and methods

2.1. Population

All patients with type 2 diabetes mellitus who visited the diabetic clinic in the Metabolism Division at Kaohsiung Medical University Hospital and Changhua Christian Hospital between January 2004 and April 2005 were included in this study. We excluded patients with *type 1 diabetes mellitus* (defined as presentation with diabetic ketoacidosis, acute hyperglycemia symptoms with heavy ketonuria [≥3], or the continuous requirement of insulin in the year succeeding diagnosis), patients under dialysis or with estimated glomerular filtration rate (eGFR) less than 15 ml/min, and patients who had received renal transplantation.

The Human Research Ethics Committee at each hospital approved the design, and informed consent was obtained from each patient enrolled in the study. We conducted interviews and a comprehensive assessment with every patient for his or her disease status, complications, and risk factors, including blood and urine analyses; calculated body mass index (BMI); and obtained an average blood pressure as the mean of 3 measurements taken in sitting positions after 10 minutes of rest.

2.2. Diagnosis of PAD

Peripheral arterial disease was diagnosed if the patients had an ankle-brachial index (ABI) of less than 0.9 in either leg. The Fukuda vascular screening system VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan) was used. Subjects rested for at least 5 minutes before the blood pressure in upper arms and ankles was measured to obtain the ABI. To prevent possible misclassification of PAD in patients with medial arterial calcification (a common arterial pathology found in diabetic patients [18]), patients with ABI of at least 1.3 were not included.

2.3. Kidney function tests

We collected an overnight first-void urine sample and fasting venous blood to measure urine albumin and creatinine in the clinic. The albumin-creatinine ratio (ACR) was calculated from urine albumin and urine creatinine levels for each diabetic patent. *Normoalbuminuria* was defined as an ACR of less than 30 mg/g. Patients with an ACR in the range of 30 to 299 mg/g in at least 2 of 3 tests over a period of 6 months were considered to have microalbuminuria. Patients were diagnosed as exhibiting overt proteinuria if ACR was at least 300 mg/g. *Diabetic kidney disease* was defined as presence of either microalbuminuria or overt proteinuria, whereas *nephropathy* was defined as presence of overt proteinuria. We estimated the GFR using the equation recommended by the National Kidney Foundation in the Modified Diet in Renal Disease [19]. *Chronic kidney disease* was defined as eGFR less than 60 mL/min or presence of markers of kidney damage like proteinuria. The 24-hour creatinine clearance was corrected for a standard body surface area of 1.73 m^2.

2.4. Statistical analysis

The clinical and biochemical features of the population were presented as mean ± SD or percentages. Because the distributions of triglycerides (TG) and urinary ACR were highly skewed, these variables were natural log-transformed for all other analyses. All analyses and calculation were performed on the SPSS statistical package, version 10.0 (SPSS, Chicago, IL).We tested differences in mean values of the variables between patients with and without PAD by a Student *t* test and with percentages by a χ^2 test. Multiple logistic regression was used to identify the independent risk factors, and the adjusted odds ratios (ORs) and their 95% confidence interval (CI) for PAD in different subgroups of significant independent variables were estimated from logistic regression. We considered *P* less than .05 as statistically significant.

3. Results

A total of 2983 Chinese with type 2 diabetes mellitus (1342 men and 1641 women) were included in this study. The mean (SD) age of subjects was 63.2 (11.6) years. Among these subjects, 228 (7.6%) were diagnosed as having PAD. Four patients (1.6%) had intermittent claudication, and no patient had rest pain or gangrene. Table 1 reveals baseline characteristics between diabetic men and women. Age, BMI, waist circumference, diastolic blood pressure, cholesterol, high-density lipoprotein cholesterol (HDL-C), and serum creatinine (SCr) differed significantly between the sexes.

Table 2 shows the comparison of the statistically significant risk factors in diabetic patients with and without PAD with regard to sex. Age, cholesterol, TG, low-density lipoprotein cholesterol (LDL-C), and HDL were common significant risk factors for both sexes. Higher glycated hemoglobin (HbA_{1c}) and creatinine were additional risk factors for the diabetic men, whereas lower BMI and higher blood pressure and fasting blood glucose were additional risk factors for diabetic women. Risk factors not listed in Table 2 were not different significantly between the 2 groups.

Table 3 shows the variables for PAD in the multiple logistic regression analysis in each sex. Age, cholesterol, HDL (inverse association), and creatinine of at least 1.5 mg/dL were significant for the diabetic men, whereas age, BMI (inverse association), LDL, HDL (inverse association), and creatinine of at least 1.4 mg/dL were significant for the diabetic women.

Table 1
Comparison of characteristics between diabetic men and women

	Male (n = 1342)	Female (n = 1641)	*P* value	Total (N = 2983)
Age (y)	61.43 ± 12.03	64.68 ± 11.50	<.0001	63.22 ± 11.85
BMI (kg/m^2)	25.40 ± 3.51	25.76 ± 3.82	.008	25.60 ± 3.69
Waist (cm)	88.30 ± 39.50	84.41 ± 41.14	.025	86.10 ± 40.47
SBP (mm Hg)	138.74 ± 23.74	137.64 ± 22.53	.792	138.19 ± 23.14
DBP (mm Hg)	78.14 ± 12.10	76.89 ± 11.88	.341	77.52 ± 11.99
HbA_{1c} (%)	7.84 ± 1.97	7.94 ± 4.16	.399	7.90 ± 3.36
Sugar (fasting) (mg/dL)	151.60 ± 56.18	154.73 ± 54.89	.132	153.32 ± 55.49
CHOL (mg/dL)	183.43 ± 42.58	195.06 ± 26.30	<.001	189.82 ± 54.62
Ln (TG) (mg/dL)	2.11 ± 0.25	2.13 ± 0.25	.076	2.12 ± 0.25
LDL-C (mg/dL)	107.27 ± 34.79	109.01 ± 35.19	.177	108.22 ± 35.02
HDL-C (mg/dL)	43.82 ± 11.71	51.08 ± 18.96	<.001	47.82 ± 16.50
Creatinine (mg/dL)	1.24 ± 0.87	1.00 ± 2.07	<.001	1.11 ± 1.65

Data are mean ± SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; CHOL, cholesterol.

Table 4 shows the association between renal function and CAD. After adjusting for risk factors including age, BMI, blood pressure, HbA_{1c}, cholesterol, LDL-C, HDL-C, and TG, we found that SCr of at least 1.5 mg/dL (OR = 2.371 [95% CI, 1.295-4.341], *P* = .005), eGFR less than 60 mL min^{-1} 1.73 m^{-2} (OR = 1.922 [95% CI 1.162-3.180], *P* = .011), and urinary ACR of at least 30 mg/g (OR = 1.784 [95% CI, 1.054-3.020], *P* = .031) were associated with CAD in Chinese men. In diabetic Chinese women and after adjustment for risk factors, SCr of at least 1.4 mg/dL (OR = 2.030 [95% CI, 1.117-3.689], *P* = .020) and urinary ACR of at least 30 mg/g (OR = 1.580 [95% CI, 1.032-2.418], *P* = .035) were associated with PAD.

4. Discussion

Our study found that there was an association between PAD and older age and that male and female diabetic patients may have different risk profiles for PAD. After adjustments for risk factors, we found SCr levels greater than 1.5 mg/dL, eGFR less than 60 mL/min, and urinary ACR greater than 30 mg/g to be independent risk factors for PAD in men with diabetes. In women with diabetes, SCr levels greater than 1.4 mg/dL and urinary ACR greater than 30 mg/g were independently associated with PAD.

Diabetic men with PAD had significantly higher creatinine levels (1.51 ± 1.01 vs 1.23 ± 0.86, *P* = .011) as compared with those without PAD. Diabetic women had nonsignificantly higher creatinine levels (1.16 ± 1.08 vs 0.99 ± 2.14, *P* = .365) as compared with those without PAD (Table 3). However, diabetic men with SCr levels of at least 1.5 mg/dL and women with SCr levels of at least 1.4 mg/d were significantly associated with PAD after adjustment for all independent risk factors (Tables 3 and 4). Thomas et al [20] found that diabetic Chinese with PAD had significantly

Table 2
Comparison of risk factors in diabetic patients with and without PAD with regard to sex

Male	Yes (n = 90)	No (n = 1252)	*P* value
Age	65.83 ± 13.07	61.12 ± 11.89	<.001
HbA_{1c}	8.33 ± 2.48	7.80 ± 1.93	.049
CHOL	202.04 ± 48.82	182.09 ± 41.80	<.001
Ln (TG)	2.19 ± 0.25	2.10 ± 0.25	.001
LDL	121.13 ± 42.29	106.28 ± 33.98	.002
HDL	40.32 ± 11.88	44.07 ± 11.66	.003
Creatinine	1.51 ± 1.01	1.23 ± 0.86	.011
Female	**Yes (n = 138)**	**No (n = 1503)**	***P* value**
Age	68.78 ± 11.86	64.31 ± 11.40	<.001
BMI	24.86 ± 4.04	25.84 ± 3.76	.014
Sugar (fasting)	167.23 ± 61.85	153.62 ± 54.11	.016
CHOL	213.41 ± 58.35	193.38 ± 62.40	<.001
Ln (TG)	2.18 ± 0.28	2.12 ± 0.24	.009
LDL	127.20 ± 41.05	107.36 ± 34.15	<.001
HDL	45.87 ± 15.99	51.56 ± 19.14	.001

Data are mean ± SD.

Table 3
Variables in the multiple logistic regression analysis for PAD with regard to sex

	P value	OR	95% CI	
			Lower	Upper
Male				
Age	<.001	1.038	1.017	1.060
HbA_{1C}	.074	1.108	0.990	1.239
CHOL	.023	1.010	1.001	1.019
TG	.930	1.059	0.293	3.824
LDL	.394	1.004	0.995	1.012
HDL	.003	0.961	0.936	0.986
Cre 1.5 group	.041	1.725	1.023	2.909
Female				
Age	<.001	1.033	1.014	1.053
BMI	.008	0.928	0.879	0.981
AC	.169	1.002	0.999	1.006
CHOL	.745	1.000	0.998	1.003
TG	.398	0.677	0.274	1.674
LDL	<.001	1.018	1.012	1.023
HDL	<.001	0.960	0.942	0.977
Cre 1.4 group	.036	1.780	1.040	3.049

Table 4
Unadjusted and adjusted OR and 95% CI of PAD associated with decreased renal function

	P value	OR	95% CI	
			Lower	Upper
Male				
Cr, ≥1.5 mg/dL				
Unadjusted	<.001	3.641	2.085	6.356
Adjusted	.005	2.371	1.295	4.341
GFR, <60				
Unadjusted	<.001	2.758	1.778	4.277
Adjusted	.011	1.922	1.162	3.180
ACR, ≥30				
Unadjusted	.002	2.225	1.351	3.665
Adjusted	.031	1.784	1.054	3.020
Female				
Cr, ≥1.4 mg/dL				
Unadjusted	<.001	3.943	2.31	6.73
Adjusted	.020	2.030	1.117	3.689
GFR, <60				
Unadjusted	.002	1.798	2.576	1.255
Adjusted	.245	1.284	0.842	1.960
ACR, ≥30				
Unadjusted	.012	1.680	1.125	2.510
Adjusted	.035	1.580	1.032	2.418

higher SCr levels than those without PAD. The other large-scale epidemiologic study [21] reported that SCr levels were associated with PAD of Chinese. All these results indicated that Chinese diabetic patients with elevated SCr are at risk of PAD.

In our study, we found that diabetic nephropathy (microalbuminuria and overt proteinuria) was independently associated with PAD in both diabetic women and men. Wattanakit et al [22] found that the presence of albuminuria is an important risk factor for PAD in diabetic but not in nondiabetic subjects. Urinary albumin excretion rate was associated with PAD at baseline but not predictive for new PAD during a mean follow-up of 11 years [23]. Type 2 diabetes mellitus Chinese with PAD were found to have higher urinary ACR than those without PAD in Hong Kong [20]. Recently, Tseng et al [24] reported that urinary ACR was associated with PAD in Chinese. The association between diabetic nephropathy and PAD may or may not be causal. Increasing albumin excretion may lead to increased PAD directly, or it may be a marker of an underlying abnormality such as enhanced platelet aggregation or penetration of the endothelium by atherogenic lipoprotein particles [25,26]. The presence of PAD might imply significant atherosclerosis involving not only vasculatures of the heart and the lower extremity, but also the vasculatures of the kidney.

Many studies revealed that CKD is associated with an increased risk factor for PAD [13-16]. The American Diabetes Association has recommended that GFR be routinely estimated and urinary albumin excretion be routinely measured for proper screening of diabetic nephropathy. However, there was no study to investigate the relationship between CKD and PAD in diabetic Chinese who are at high risk of developing diabetic nephropathy. Our study was the first one and revealed that CKD is independently associated with PAD only in Chinese diabetic men, but not in women.

The prevalence of PAD in our study population was 7.6%. Previous studies reported interethnic variations in the prevalence of PAD. Its prevalence in diabetic patients has been reported to be as high as 42.0% and 61.4% in previous studies [2,27]. Recently, Allison et al [28] have found that ethnicity is significantly associated with PAD after adjustment for other risk factors and that the Chinese have a lower risk for PAD than whites. Tseng [29] has estimated the prevalence of PAD to be 10.0% in diabetic Chinese in Taiwan. Thomas et al [20] have found that the prevalence of PAD is 6.5% in diabetic Chinese in Hong Kong. However, 2 other studies have found that the prevalence of PAD was 25.4% in Chinese with high cardiovascular risk [21] and 32.2% in Chinese with type 2 diabetes mellitus [30] in China. Our study enrolled diabetic Chinese in Taiwan. Because of differences in socioeconomic status, literacy, and access to health care, the Taiwanese of Chinese heritage may have other differences not found in Chinese population in other parts of the world.

Aging has been shown to be an important risk factor for PAD [31,32]. The present study suggested that PAD is basically a clinical problem associated with aging in diabetic Chinese. Age remained as an independent risk factor for both sexes in the multiple logistic regression analysis. Age itself might be associated with progression of renal function, and the association of renal dysfunction with PAD might simply reflect this. We had enrolled 2349 diabetic Taiwanese and found that the prevalence of diabetic nephropathy was 37.4% and that age was not associated with nephropathy (unpublished data). Moreover, decreased renal function was significantly associated with PAD after adjustment for age in our study (Tables 3 and 4).

Although obesity is an important risk for CAD [33], our results revealed that low BMI was associated with PAD in diabetic women. The PAD-SEARCH (peripheral arterial disease, screening and evaluation of diabetic patients in Asian regions characterized by high risk factors) Study Group [7] reported that PAD subjects had a significantly lower BMI than non-PAD subjects in Asian type 2 diabetes mellitus patients. In the United Kingdom Prospective Diabetes Study, PAD was also linked to lower BMI [34]. Recently, Sritara et al [35] found that overweight was significantly associated with PAD as a protective factor in Thai population. Previous studies suggested that underweight patients demonstrate higher metabolic rate, lower antioxidant capacity in skeletal muscles, and increased inflammatory response, which may contribute to excess morbidity [36,37]. Malnutrition may be associated with the development of arteriosclerosis [38]. The cause-effect relation between lower BMI and PAD remained to be clarified. However, the present study indicated that the risk of PAD should not be neglected in diabetic women with lower BMI.

In the present study, we found that more Chinese women than men had PAD (8.4% vs 6.7%). This was inconsistent with other studies in white populations [39-41]. However, the PAD-SEARCH Study Group [7] reported that Asian diabetic women are at higher risk for PAD. Two Chinese studies [21,30] have also found the prevalence of PAD to be higher in women than in men. All of these findings might suggest that Chinese diabetic women require more aggressive PAD screening and prevention measures.

Of lipid parameters, we found that only HDL was significantly associated with PAD in both sexes by multivariate logistic regression analyses. Recently, we found that only HDL was associated with CAD in diabetic Chinese, whereas total cholesterol, TG, and LDL were not [8]. Pan and Chiang [42] reported that, in Taiwanese, HDL was a more important risk factor for CAD than were total cholesterol and LDL. Tseng et al [43] found that, among lipid profiles, only HDL was an independent risk factor for CAD in Taiwanese with type 2 diabetes mellitus. Results of our study and of other studies conducted in Taiwan on diabetic patients have demonstrated that HDL might play an important role in the development of CVDs including PAD.

Our study has several limitations. First, the cross-sectional design allows us to establish association only, without reliably defining the underlying cause-effect relationship. We could not assess temporal relationships between PAD and renal insufficiency, and could not determine which came before the other. A large prospective study is needed to clarify this point. Second, we used the VS-1000 to measure ABI as in the PAD-SEARCH study [7]. Although this method is not the criterion standard, the American Diabetes Association consensus stated that ABI can be used to estimate the prevalence of PAD in diabetic patients [44]. The ABI has been validated against angiographically confirmed disease and found to be 95% sensitive and almost 100% specific [45]. Third, we have not examined the contribution of novel cardiovascular risk factors such as apolipoprotein (apo) B and apo A1, which are not routinely measured in our daily clinical practice. Apolipoprotein B and apo A1 have been found to be better predictors of CVD risk than LDL-C [46,47]. However, other studies [48,49] revealed that apo B and apo A1 did not outperform LDL-C as risk predictors. Recently, Inglesson et al [50] reported that they did not support the need for measuring apo B or apo A1 in clinical practice when traditional lipid measurements are obtained routinely. Fourth, our study was hospital based, making selection bias a potential confounding factor. However, there is no strict transferring system of medical care in Taiwan, meaning that the characteristics of patients visiting hospital and local clinics do not differ significantly. Nevertheless, we believe that the patients in our study, coming from 2 medical centers in different areas of Taiwan, constitute a reliable sample of the diabetic population in Taiwan. Despite its limitations, we believe that our study is useful. To date, there have been few studies [20,24] evaluating the relationship between renal insufficiency and PAD in diabetic Chinese. Our study extends the observation of a link between PAD and renal insufficiency in diabetic patients to Chinese population that is otherwise characterized by a relatively lower risk for CVD and a higher risk for diabetic nephropathy.

In conclusion, the risk factors for PAD were different between men and women in a Chinese diabetic population in Taiwan. Diabetic nephropathy was significantly associated with PAD in both sexes. Because Chinese diabetic patients tend to have a relatively higher frequency of nephropathy than whites with diabetes, these patients with decreased renal function may need aggressive interventions to prevent and treat PAD.

References

[1] Cheng SW, et al. Epidemiology of atherosclerotic peripheral arterial occlusive disease in Hong Kong. World J Surg 1999;23:202-6.

[2] Al Zahrani HA, et al. The distribution of peripheral arterial disease in a defined population of elderly high-risk Saudi patients. Int Angiol 1997; 16:123-8.

[3] Novo S, et al. Prevalence of risk factors in patients with peripheral arterial disease. A clinical and epidemiological evaluation. Int Angiol 1992;11:218-29.

[4] Fowkes FG, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol 1992;135:331-40.

[5] Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia. The Global Lower Extremity Amputation Study Group. Br J Surg 2000;87:328-37.

[6] Tseng CH, et al. Mortality in diabetic patients after lower extremity amputations. J Formos Med Assoc 1994;93:842-8.

[7] Rhee SY, et al. Multi-country study on the prevalence and clinical features of peripheral arterial disease in Asian type 2 diabetes patients at high risk of atherosclerosis. Diabetes Res Clin Pract 2007;76: 82-92.

[8] Hsieh MC, et al. Chronic kidney disease as a risk factor for coronary artery disease in Chinese with type 2 diabetes. Am J Nephrol 2008;28: 317-23.

[9] Tseng CH. Sex difference in the distribution of atherosclerotic risk factors and their association with peripheral arterial disease in Taiwanese type 2 diabetic patients. Circ J 2007;71:1131-6.

[10] Crouse III JR. Gender, lipoproteins, diet, and cardiovascular risk. Sauce for the goose may not be sauce for the gander. Lancet 1989;1: 318-20.

[11] Cheng SW, et al. Survival in patients with chronic lower extremity ischemia: a risk factor analysis. Ann Vasc Surg 2000;14:158-65.

[12] National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. US renal data system. USRDS; 1998.

[13] O'Hare AM, et al. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999-2000. Circulation 2004;109: 320-3.

[14] Leskinen Y, et al. The prevalence of peripheral arterial disease and medial arterial calcification in patients with chronic renal failure: requirements for diagnostics. Am J Kidney Dis 2002;40:472-9.

[15] O'Hare AM, et al. Renal insufficiency and the risk of lower extremity peripheral arterial disease: results from the Heart and Estrogen/ Progestin Replacement Study (HERS). J Am Soc Nephrol 2004;15: 1046-51.

[16] Wattanakit K, et al. Kidney function and risk of peripheral arterial disease: results from the Atherosclerosis Risk in Communities (ARIC) Study. J Am Soc Nephrol 2007;18:629-36.
[17] Chi ZS, et al. Vascular disease prevalence in diabetic patients in China: standardised comparison with the 14 centres in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44:S82-S86.
[18] Dieter RS, et al. The significance of lower extremity peripheral arterial disease. Clin Cardiol 2002;25:3-10.
[19] Levey AS, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137-47.
[20] Thomas GN, et al. Peripheral vascular disease in type 2 diabetic Chinese patients: associations with metabolic indices, concomitant vascular disease and genetic factors. Diabet Med 2003;20:988-95.
[21] Hasimu B, et al. Ankle brachial index as a marker of atherosclerosis in Chinese patients with high cardiovascular risk. Hypertens Res 2006;29:23-8.
[22] Wattanakit K, et al. Albuminuria and peripheral arterial disease: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 2008.
[23] Kallio M, et al. Development of new peripheral arterial occlusive disease in patients with type 2 diabetes during a mean follow-up of 11 years. Diabetes Care 2003;26:1241-5.
[24] Tseng CH, et al. The association between urinary albumin excretion and ankle-brachial index in elderly Taiwanese patients with type 2 diabetes mellitus. Age Ageing 2008;37:77-82.
[25] Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000;356:147-52.
[26] Gerstein HC, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421-6.
[27] Katsilambros NL, et al. Risk factors for lower extremity arterial disease in non–insulin-dependent diabetic persons. Diabet Med 1996;13:243-6.
[28] Allison MA, et al. The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol 2006;48:1190-7.
[29] Tseng CH. Prevalence and risk factors of peripheral arterial obstructive disease in Taiwanese type 2 diabetic patients. Angiology 2003;54:331-8.
[30] Li J, et al. Risk factors of peripheral arterial disease and relationship between low ankle-brachial index and mortality from all-cause and cardiovascular disease in Chinese patients with type 2 diabetes. Circ J 2007;71:377-81.
[31] Premalatha G, et al. Prevalence and risk factors of peripheral vascular disease in a selected South Indian population: the Chennai Urban Population Study. Diabetes Care 2000;23:1295-300.
[32] Meijer WT, et al. Determinants of peripheral arterial disease in the elderly: the Rotterdam study. Arch Intern Med 2000;160:2934-8.
[33] Meigs JB, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J Clin Endocrinol Metab 2006;91:2906-12.
[34] Adler AI, et al. UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. Diabetes Care 2002;25:894-9.
[35] Sritara P, et al. Prevalence and risk factors of peripheral arterial disease in a selected Thai population. Angiology 2007;58:572-8.
[36] Stump CS, et al. The metabolic syndrome: role of skeletal muscle metabolism. Ann Med 2006;38:389-402.
[37] Imbeault P, et al. Weight loss–induced rise in plasma pollutant is associated with reduced skeletal muscle oxidative capacity. Am J Physiol Endocrinol Metab 2002;282:E574-9.
[38] Pecoits-Filho R, et al. Genetic approaches in the clinical investigation of complex disorders: malnutrition, inflammation, and atherosclerosis (MIA) as a prototype. Kidney Int Suppl 2003:S162-7.
[39] Barzilay JI, et al. Prevalence of clinical and isolated subclinical cardiovascular disease in older adults with glucose disorders: the Cardiovascular Health Study. Diabetes Care 2001;24:1233-9.
[40] Orchard TJ, Strandness Jr DE. Assessment of peripheral vascular disease in diabetes. Report and recommendations of an international workshop sponsored by the American Diabetes Association and the American Heart Association 18-20 September 1992, New Orleans, Louisiana. Circulation 1993;88:819-28.
[41] Resnick HE, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation 2004;109(Suppl 2):733-9.
[42] Pan WH, Chiang BN. Plasma lipid profiles and epidemiology of atherosclerotic diseases in Taiwan—a unique experience. Atherosclerosis 1995;118:285-95.
[43] Tseng CH, et al. Independent association between triglycerides and coronary artery disease in Taiwanese type 2 diabetic patients. Int J Cardiol 2006;111:80-5.
[44] Peripheral arterial disease in people with diabetes. Diabetes Care 2003;26:3333-41.
[45] Bernstein EF, Fronek A. Current status of noninvasive tests in the diagnosis of peripheral arterial disease. Surg Clin North Am 1982;62:473-87.
[46] Lamarche B, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec cardiovascular study. Circulation 1996;94:273-8.
[47] Walldius G, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 2001;358:2026-33.
[48] Ridker PM, et al. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA 2005;294:326-33.
[49] van der Steeg WA, et al. Role of the apolipoprotein B–apolipoprotein A-I ratio in cardiovascular risk assessment: a case-control analysis in EPIC-Norfolk. Ann Intern Med 2007;146:640-8.
[50] Ingelsson E, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. JAMA 2007;298:776-85.