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Hypoadiponectinemia Is Associated with Impaired Endothelium-Dependent Vasodilation

K. C. B. TAN, A. XU, W. S. CHOW, M. C. W. LAM, V. H. G. AI, S. C. F. TAM, AND K. S. L. LAM

Department of Medicine (K.C.B.T., A.X., W.S.C., M.C.W.L., K.S.L.L.), University of Hong Kong; and Department of Diagnostic Radiology (V.H.G.A.) and Clinical Biochemistry Unit (S.C.F.T.), Queen Mary Hospital, Hong Kong

Adiponectin may have an antiatherogenic effect by reducing endothelial activation. We hypothesized that plasma adiponectin levels were correlated with endothelial function.

Plasma adiponectin level was determined by an in-house RIA assay using a rabbit polyclonal antibody in 73 type 2 diabetic patients and 73 controls. Endothelium-dependent and independent vasodilation of the brachial artery was measured by high-resolution vascular ultrasound. Plasma adiponectin level was lower in diabetic patients than in controls (4.73 ± 1.96 *vs.* 7.69 ± 2.80 μg/ml, respectively; $P < 0.001$), and they also had impaired endothelium-dependent (5.6 ± 3.6 *vs.* 8.6 ± 4.5%, respectively; $P < 0.001$) and -independent vasodilation (13.3 ± 4.9 *vs.* 16.5 ± 5.6%, respectively; $P < 0.001$). Plasma adiponectin correlated with endothelium-dependent vasodilation in controls ($P = 0.02$) and diabetic patients ($P = 0.04$). On general linear-model univariate analysis, brachial artery diameter, the presence of diabetes, plasma adiponectin, and high-density lipoprotein were significant independent determinants of endothelium-dependent vasodilation. *In vitro* experiments showed that endothelial cells expressed adiponectin receptors, and adiponectin increased nitric oxide production in human aortic endothelial cells.

In conclusion, low plasma adiponectin level is associated with impaired endothelium-dependent vasodilation, and the association is independent of diabetes mellitus. Adiponectin may act as a link between adipose tissue and the vasculature. (*J Clin Endocrinol Metab* 89: 765–769, 2004)

ADIPONECTIN IS AN adipocyte-specific plasma protein, and recent evidence suggests that adiponectin plays an important role in the regulation of insulin action and energy homeostasis (1, 2). Circulating adiponectin level and adiponectin gene expression in adipose tissue are reduced in subjects with obesity and in those with type 2 diabetes mellitus (3–5). Adiponectin levels in humans are negatively correlated with fasting insulin concentrations and positively correlated with insulin sensitivity, and the relationship between adiponectin and insulin action is independent of body adiposity (5–7). Although the site and mechanisms of adiponectin action on whole-body glucose metabolism remain unknown, available data from *in vitro* and animal studies suggest that adiponectin reduces hepatic glucose production and increases muscle glucose utilization (1, 2).

In addition to its effect on glucose metabolism, adiponectin also appears to affect vascular function. Hypoadiponectinemia has been described in patients with diabetes, hypertension, and coronary artery disease (CAD) and is associated with an increase in C-reactive protein (CRP) levels (5, 8–10). In tissue cultures, adiponectin attenuates TNF-α-induced adhesion molecule expression in endothelial cells (11) and suppresses lipid accumulation in monocyte-derived macrophages through the suppression of macrophage-scavenger receptor expression (12). Animal studies have shown that an adenovirus-mediated supplement of adiponectin attenuates neointimal proliferation in mechanically injured arteries in adiponectin-deficient mice (13). Apolipoprotein E-deficient mice treated with recombinant adenovirus expressing human adiponectin have reduced arteriosclerosis *in vivo* (14). These data suggest that adiponectin has an antiatherogenic effect. Because adiponectin has been shown to suppress adhesion molecule expression in endothelial cells and reduce endothelial activation (10), we postulate that adiponectin may also potentially influence endothelial vasomotor function and a reduced level of adiponectin may be associated with impaired endothelium-dependent vasodilation. Because type 2 diabetes mellitus is frequently associated with hypoadiponectinemia, the aim of this study is to investigate whether plasma adiponectin level is correlated with endothelial dysfunction in patients with type 2 diabetes mellitus and to compare these patients with nondiabetic controls. The effect of adiponectin on endothelial-cell nitric oxide (NO) production *in vitro* is also determined.

Patients and Methods

Seventy-three patients with type 2 diabetes mellitus according to World Health Organization criteria were recruited from the diabetes clinics at Queen Mary Hospital (15). Patients on insulin therapy were eligible if they had been controlled previously on diet and an oral agent for at least 1 yr from diagnosis and had no known history of diabetic ketoacidosis. Subjects with overt macrovascular disease were excluded to avoid the confounding effect of preexisting atherosclerosis on endothelial function. Clinical data were obtained from medical records. The mean duration of diabetes was 8.4 ± 5.5 yr. Eighty-six percent of the patients were on oral hypoglycemic agents (sulfonylurea and/or biguanide), and the rest were on insulin therapy. None of the patients was receiving thiazolidinediones. Twenty-one percent of the patients had microalbuminuria, 14% had nonproliferative retinopathy, and 5% had neuropathy. Forty percent of the patients were receiving antihypertensive treatment. Seventy-three healthy nondiabetic controls matched for

Abbreviations: adipR, Adiponectin receptors; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; NO, nitric oxide; TG, triglyceride.

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age, sex, and body mass index (BMI) were recruited from the community by advertisement. In all subjects, fasting blood samples were taken for the measurement of glucose, lipids, hemoglobin A1c (HbA1c), CRP, and adiponectin. Carotid intima-media thickness (IMT) and endothelial function were assessed by high-resolution vascular ultrasound in the fasting state. The study was approved by the Ethics Committee of the University of Hong Kong, and informed consent was obtained from all subjects.

Plasma total cholesterol and triglyceride (TG) were determined enzymatically on a Hitachi 912 analyzer (Roche Diagnostics, GmbH, Mannheim, Germany). High-density lipoprotein (HDL)-cholesterol was measured using a homogenous method, with polyethylene glycol-modified enzymes and α-cyclodextrin. Low-density lipoprotein (LDL)-cholesterol was calculated by the Friedewald equation. HbA1c was measured in whole blood using ion-exchange HPLC with the Bio-Rad Variant Hemoglobin Testing System (Bio-Rad Laboratories, Inc., Hercules, CA). Plasma high-sensitivity CRP was measured by a particle-enhanced immunoturbidimetric assay (Roche Diagnostics) using anti-CRP mouse monoclonal antibodies coupled to latex microparticles.

Plasma adiponectin level was determined by an in-house RIA assay, using a rabbit polyclonal antibody against adiponectin (16, 17). Serum was diluted 1000-fold before assay. A total of 100 μl of diluted serum or standard samples of recombinant human adiponectin were then incubated with ^{125}I-labeled adiponectin tracer and rabbit antiadiponectin polyclonal antibody at room temperature overnight. The immunocomplexes were recovered by polyethylene glycol precipitation. Intra- and interassay coefficients of variation were 5.2% and 5.7%, respectively.

High-resolution B-mode ultrasound (ATL HDI 3000 ultrasound system, Advanced Technology Laboratories, Inc., Bothell, WA) was used to measure the IMT of the carotid artery. The anterior, lateral, and posterolateral projections were used to image longitudinally the right and left common carotid arteries. At each projection, three determinations of IMT were made at 2 cm proximal to the bulb and at the site of greatest thickness. The values at each site were averaged, and the greatest value of the averaged IMT was used as the representative value for each individual. Carotid plaque was defined as the presence of a focal lesion measuring at least twice the thickness of the IMT (18). If a plaque was present in one of the projections, that value was excluded from the analysis, and IMT was averaged on the remaining values.

Endothelium-dependent and endothelium-independent vasodilation of the brachial artery was assessed by high-resolution ultrasound as previously described (see *Patients and Methods*) (19). In brief, diameter measurements of the right brachial artery were taken at rest and then during reactive hyperemia after occlusion by inflation of a pneumatic tourniquet to a pressure of 300 mm Hg for 4.5 min. Twenty minutes were allowed for vessel recovery, and a resting scan was repeated. Sublingual glyceryl trinitrate spray (400 μg) was then administered, and measurement was taken after 5 min. Flow-mediated (endothelium-dependent) and glyceryl trinitrate-induced (endothelium-independent) vasodilation was calculated as the percentage change in diameter compared with baseline.

Results were expressed as mean and SD or median and interquartile range if the data were not normally distributed. We used a criterion for defining hypoadiponectinemia similar to that used in a study by Kumada *et al.* (9). Hypoadiponectinemia and impaired endothelial function were therefore defined as plasma levels of adiponectin and endothelium-dependent vasodilation below the cutoff points of the lowest quartile of the healthy controls (<5.49 μg/ml and <5.41%, respectively). Comparisons between two different groups were done using independent sample Student's *t* test, and skewed data were logarithmically transformed before analysis. Pearson's correlations were used to test the relationship between variables. General linear model univariate analysis was used to assess the relationships between vasomotor function and various variables simultaneously. All analyses were performed using SPSS 11.0 for Windows (SPSS Inc., Chicago, IL).

In vitro experiments were performed to determine whether adiponectin influenced endothelial cell NO production and whether endothelial cells expressed adiponectin receptors (adipR) (20). Human aortic endothelial cells (Clonetics Corp., San Diego, CA) were grown in M199 medium supplemented with growth supplement, fetal bovine serum, and hydrocortisone. At 90% cell confluence, cells were starved for 18 h and then stimulated with a physiological concentration of human adiponectin (30 μg/ml) (16, 17). The cells were then incubated at 37 C for 24 h, and the amount of total NO produced was determined by measuring its metabolites using the Nitrate/Nitrite Fluorometric Assay Kit (Cayman Chemical, Ann Arbor, MI). Nitrate was first converted to nitrite using nitrate reductase. Then, 2,3-diaminonaphthalene was added, followed by NaOH, which converted nitrite into a fluorescent compound. Data are presented as mean ± SD determined from three independent experiments.

adipR expression was determined by RT-PCR. Total cellular RNA was isolated from human aortic endothelial cells using TRIzol (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. Two micrograms of total RNA was reverse-transcribed to synthesize cDNA using SuperScript First Strand Synthesis System (Invitrogen). cDNA was PCR-amplified using primers specific to human adipR as follows: human adipR1 (NM_015999): sense, GTCAGGGATCCGCTGAAGCTGCAGGGTATTC; antisense, GATCACTCGAGCTGAAGCTTGGTTGGTACTG; human adipR2 (NM_024551): sense, GACTAGAATTCATGG AAAAAATGGAAGAATTTG; antisense, GATCGCTCGAGCTGGC ATCAGTAGCCAGCAG.

Results

The diabetic patients had similar BMI as the controls, but they had significantly higher waist circumference and waist-hip ratios (Table 1). They also had higher plasma TG, CRP, and systolic blood pressure than the controls. Plasma adiponectin level was reduced ($P < 0.001$) in the diabetic patients compared with controls. On univariate analysis, adiponectin levels correlated with BMI, waist circumference, and waist-hip ratios in the nondiabetic controls but only with BMI in the diabetic patients (Table 2). Adiponectin levels significantly correlated positively with HDL and inversely with log(TG) and log(CRP) in both groups.

Carotid IMT was similar in the diabetic patients and controls (0.58 ± 0.01 *vs.* 0.57 ± 0.02 mm, respectively). Twelve of the controls and 14 of the diabetic patients had evidence of carotid plaques. Baseline brachial artery diameter and the peak hyperemic velocity were similar in the controls and diabetic patients, whereas both endothelium-dependent and -independent vasodilation were significantly impaired in the diabetic patients (Table 3). The relationships between plasma adiponectin levels and endothelium-dependent vasodilation are shown in Fig. 1, A and B. Plasma adiponectin levels

TABLE 1. Clinical characteristics of controls and diabetic patients

	Controls (n = 73)	DM (n = 73)
M/F (%)	49/51	49/51
Age (yr)	49.6 ± 6.4	50.0 ± 7.5
Smokers (%)	8%	9%
BMI (kg/m^2)	24.9 ± 3.4	25.3 ± 3.5
Waist (cm)	80.8 ± 9.4	86.3 ± 8.1^b
Waist/hip ratio	0.85 ± 0.06	0.89 ± 0.06^b
HbA1c (%)	5.8 ± 0.4	7.8 ± 1.3^b
TC (mmol/liter)	5.5 ± 0.9	5.3 ± 1.1
TG (mmol/liter)	1.2 (0.8–1.7)	1.5 (0.9–2.2)^a
LDL (mmol/liter)	3.5 ± 0.8	3.3 ± 0.9
HDL (mmol/liter)	1.3 ± 0.4	1.2 ± 0.4
Systolic BP (mm Hg)	122 ± 20	131 ± 15^a
Diastolic BP (mm Hg)	78 ± 11	79 ± 9
CRP (mg/liter)	0.86 (0.47–1.76)	1.58 (0.86–2.69)^b
Adiponectin (μg/ml)	7.69 ± 2.80	4.73 ± 1.96^b

Values are mean ± SD or median (interquartile range). DM, Diabetes mellitus; M, male; F, female; TC, total cholesterol; BP, blood pressure.

^{a} $P < 0.05$; ^{b} $P < 0.001$.

TABLE 2. Correlations between plasma adiponectin and clinical parameters

	Controls	DM	All
BMI	−0.40[b]	−0.30[b]	−0.34[b]
Waist	−0.51[b]	−0.17	−0.46[b]
Waist-hip	−0.40[b]	−0.13	−0.40[b]
HbA1c	−0.17	−0.01	−0.33[b]
TC	0.09	0.03	0.09
Log(TG)	−0.46[b]	−0.37[b]	−0.43[b]
LDL	0.02	−0.05	0.06
HDL	0.63[b]	0.34[b]	0.46[b]
Systolic BP	0.08	0.21	−0.01
Diastolic BP	−0.15	−0.07	−0.12
Log(CRP)	−0.23[a]	−0.30[b]	−0.34[b]

TC, Total cholesterol; BP, blood pressure; DM, diabetes mellitus.
[a] $P < 0.05$; [b] $P < 0.01$.

TABLE 3. Vasomotor function in controls and diabetic patients

	Controls (n = 73)	DM (n = 73)
Baseline brachial artery diameter (mm)	3.9 ± 0.7	3.9 ± 0.7
Baseline flow velocity (cm/sec)	52.6 ± 19.0	53.9 ± 16.0
Peak hyperemic velocity (cm/sec)	60.8 ± 23.9	64.2 ± 16.9
Endothelium-dependent vasodilation (%)	8.6 ± 4.5	5.6 ± 3.6[a]
Endothelium-independent vasodilation (%)	16.5 ± 5.6	13.3 ± 4.9[a]

DM, Diabetes mellitus.
[a] $P < 0.001$.

correlated with endothelium-dependent vasodilation in both groups, whereas no significant relationship between plasma adiponectin and endothelium-independent vasodilation was found in either the controls ($r = 0.22$; $P = 0.06$) or diabetic subjects ($r = 0.15$; $P = 0.2$).

To find the important determinants of endothelial dysfunction, general linear model univariate analysis was performed. Age, gender, smoking status, the presence of diabetes or hypertension, and continuous variables that showed an association with endothelium-dependent vasodilation [brachial artery diameter, adiponectin, log(CRP), and HDL] were entered into the model, and the results are shown in Table 4. Only brachial artery diameter, the presence of diabetes, plasma adiponectin level, and HDL were significant independent determinants of endothelium-dependent vasodilation. The analyses were repeated in the diabetic cohort alone to determine whether adiponectin remained a significant determinant of endothelial function in these patients. Brachial artery diameter ($P = 0.007$), plasma HDL ($P = 0.020$), and adiponectin level ($P = 0.023$) were the main independent determinants.

Results from the *in vitro* experiments showed that human adiponectin caused a significant increase in NO production. Total nitrite concentration was increased in adiponectin-treated endothelial cells compared with untreated cells (1.49 ± 0.09 μmol/liter *vs.* 1.22 ± 0.05 μmol/liter, respectively; $P = 0.02$). Endothelial cells expressed both isoforms of adiponectin receptors (Fig. 2). The identities of the amplified fragment as human adipR1 and adipR2 were confirmed by DNA sequencing analysis.

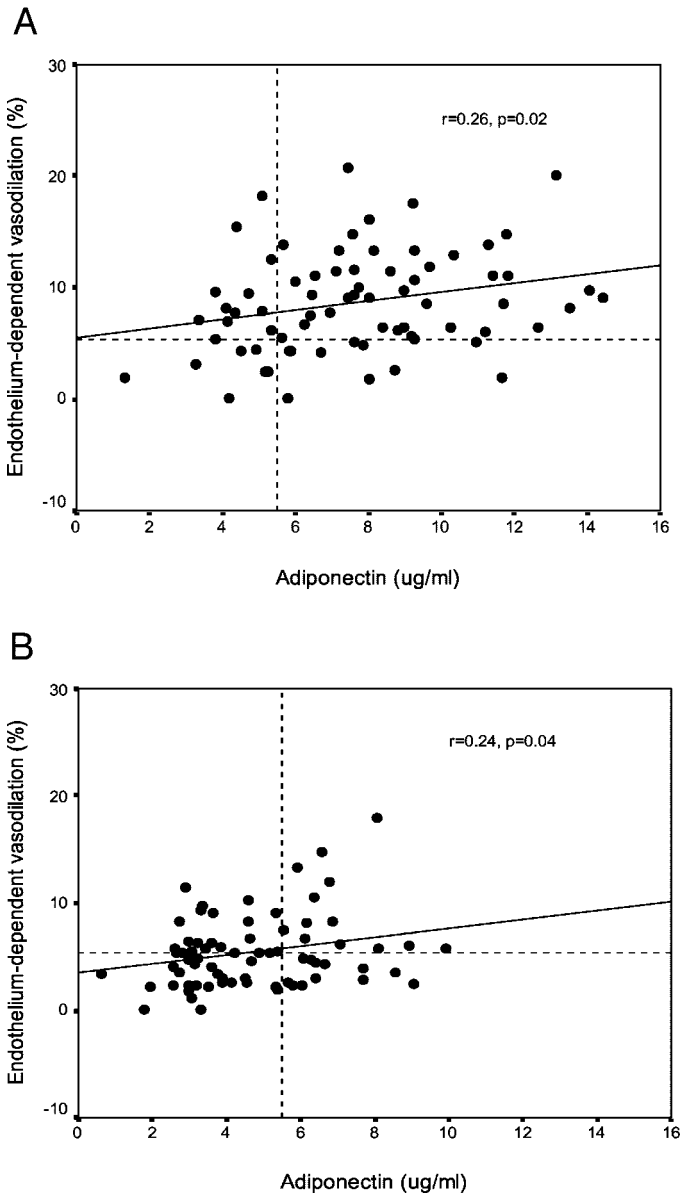

FIG. 1. Pearson's correlation between plasma adiponectin level and endothelium-dependent vasodilation in controls (A) and diabetic patients (B). *Dotted lines* represent the cutoff points for defining hypoadiponectinemia and impaired endothelial function.

Discussion

Recent studies have shown that subjects with type 2 diabetes mellitus have decreased levels of plasma adiponectin (4, 5). Hotta *et al.* (4) have reported that diabetic patients with macroangiopathy have the lowest plasma adiponectin concentrations, whereas the presence of microangiopathy does not affect plasma adiponectin levels. Plasma adiponectin levels are also reduced in subjects with CAD, and Kumada *et al.* (9) have demonstrated that hypoadiponectinemia is significantly associated with the prevalence of CAD. In their cohort of Japanese men, those with hypoadiponectinemia (<4.0 μg/ml) had a significant 2-fold increase in CAD prevalence independent of well-known CAD risk factors, including diabetes mellitus. Recent studies have shown that hy-

TABLE 4. General linear model univariate analysis with endothelium-dependent vasodilation as the dependent variable

	Regression coefficient	SE of regression coefficient	*P*
Intercept	13.439	4.024	0.001
Age	−0.002	0.048	0.958
Sex	1.796	0.957	0.063
Diabetes, yes/no	2.569	0.841	0.003
Smoker, yes/no	0.412	0.508	0.419
Hypertension, yes/no	0.695	0.936	0.459
Brachial artery diameter	−25.359	6.024	<0.001
HDL	−2.510	0.980	0.012
Adiponectin	0.421	0.171	0.015
Log(CRP)	0.129	0.725	0.859

R^2 of model = 44%.

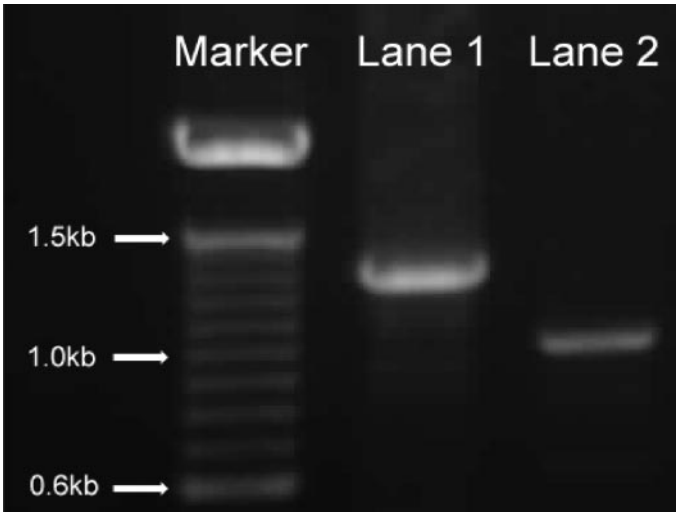

FIG. 2. Both isoforms of adipR are expressed in human aortic endothelial cells. The cDNA template was generated by reverse transcription of 2 μg total RNA purified from human aortic endothelial cells. PCR amplification was conducted using a pair of primers specific to adiponectin receptor1 (lane 1) or to adipR 2 (lane 2).

poadiponectinemia is closely linked to endothelial dysfunction in nondiabetic Japanese men and in those with hypertension (21, 22). We have shown further that hypoadiponectinemia is associated with impaired endothelium-dependent vasodilation in subjects with or without diabetes mellitus, and the association between plasma adiponectin and endothelium-dependent vasodilation is independent of diabetes status. Our study is limited by its cross-sectional nature, and we could demonstrate only associations and not causal relations. The correlation between plasma adiponectin level and endothelium-dependent vasodilation is weaker in patients with type 2 diabetes than in nondiabetic controls. This is probably because endothelial dysfunction in patients with diabetes is multifactorial (23, 24), and hypoadiponectinemia only partly contributes to the abnormal function of endothelial cells in these patients.

Endothelial cells cause vasodilation by releasing a number of vasodilating substances. Generally, NO has been considered to be the principal mediator of this vasodilation, and impaired endothelium-dependent vasodilation is frequently associated with reduced bioavailability of NO (25). The mechanism(s) whereby adiponectin affects endothelium-dependent vasodilation have not been studied, and we speculate that there may be several potential mechanisms. Firstly, adiponectin might have a direct effect on vessel walls. Plasma adiponectin has been shown to accumulate rapidly in the subendothelial space of the injured human artery (26). adipR has recently been cloned (20), and we have shown for the first time that endothelial cells express both isoforms of adipRs and that adiponectin is able to stimulate NO production in endothelial cell culture. Chen *et al.* (27) have also reported that adiponectin stimulates phosphorylation and activation of endothelial NO synthase via phosphatidylinositol 3-kinase-dependent pathways and increases NO production in vascular endothelial cells. Hence, adiponectin might act as an endogenous modulator of endothelial cell function. Secondly, adiponectin may indirectly cause impaired endothelial vasomotor function through insulin resistance and its associated metabolic abnormalities (28). Thirdly, adiponectin may serve as an antiinflammatory molecule for vascular walls, and therefore low levels of adiponectin predispose patients to endothelial dysfunction. We have found an inverse relationship between plasma CRP and adiponectin levels in both our controls and diabetic patients. A similar inverse relationship between circulating CRP and adiponectin levels has also been described in subjects with CAD, and Ouchi *et al.* (10) have reported a reciprocal association between CRP and adiponectin mRNA levels in human adipose tissue. Therefore, it has been suggested that adiponectin might directly counteract the proinflammatory effects of TNF-α in vascular cellular components and adipose tissues (11, 29) or might indirectly influence IL-6 and CRP production through modulating the action of TNF-α.

In conclusion, low plasma adiponectin level is associated with impaired endothelium-dependent vasodilation in subjects with or without type 2 diabetes mellitus. In addition to its role in glucose metabolism, adiponectin may act as a link between adipose tissue and the vasculature. There is already some prospective data available suggesting that plasma adiponectin level is an inverse predictor of cardiovascular outcomes among patients with end-stage renal disease (30). Additional prospective studies are necessary to determine whether low plasma level of adiponectin can be considered as a cardiovascular risk factor.

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Address all correspondence and requests for reprints to: Dr. Kathryn Tan, Department of Medicine, University of Hong Kong, Queen Mary Hospital, 120 Pokfulam Road, Hong Kong. E-mail: kcbtan@hkucc.hku.hk.

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