

strongly associated with risk of coronary heart disease in type 2 diabetic patients. We showed that sTNF-R1 is associated with albuminuria in type 2 diabetic patients (4). To the best of our knowledge, however, it is unclear whether PWV is associated with TNF system activity in type 2 diabetic patients. The aim of the present study, therefore, was to investigate the relationships between PWV and TNF receptors in type 2 diabetic patients.

Eighty-six nonobese Japanese type 2 diabetic patients were enrolled. Their age, BMI, HbA<sub>1c</sub> (A1C), systolic and diastolic blood pressure, and serum creatinine were  $62.8 \pm 1.0$  years,  $22.8 \pm 0.3$  kg/m<sup>2</sup>,  $7.0 \pm 0.1\%$ ,  $136 \pm 2$  mmHg,  $82 \pm 1$  mmHg, and  $0.76 \pm 0.02$  mg/dl, respectively. They had not been treated with insulin. Thirty-four patients were treated with antihypertensive medications. In conjunction with PWV, systolic and diastolic blood pressure, A1C, glucose, lipids, serum creatinine, TNF- $\alpha$ , sTNF-R1, and sTNF-R2 were measured after an overnight fast.

With univariate analysis, PWV was positively correlated to age ( $r = 0.492$ ,  $P < 0.001$ ), diabetes duration ( $r = 0.251$ ,  $P = 0.021$ ), systolic ( $r = 0.595$ ,  $P < 0.001$ ) and diastolic ( $r = 0.248$ ,  $P = 0.022$ ) blood pressure, antihypertensive medication ( $r = 0.268$ ,  $P = 0.013$ ), and the concentrations of sTNF-R1 ( $r = 0.354$ ,  $P = 0.001$ ) and sTNF-R2 ( $r = 0.415$ ,  $P < 0.001$ ). Other variables, including TNF- $\alpha$ , were not associated with PWV. Multiple regression analyses showed that PWV was independently predicted by age ( $F = 15.1$ ), systolic blood pressure ( $F = 31.6$ ), and sTNF-R2 ( $F = 5.2$ ), which explained 49.2% of the variability of PWV. Thus, TNF system activity seems to be associated with atherosclerosis in nonobese Japanese type 2 diabetic patients.

MINAKO OHGUSHI, MD<sup>1</sup>  
 ATARU TANIGUCHI, MD<sup>1</sup>  
 MITSUO FUKUSHIMA, MD<sup>2</sup>  
 YOSHIKATSU NAKAI, MD<sup>3</sup>  
 AKIRA KUROE, MD<sup>1</sup>  
 MICHIOHIRO OHYA, MD<sup>1</sup>  
 YUTAKA SEINO, MD<sup>1</sup>

From the <sup>1</sup>Division of Diabetes and Clinical Nutrition, Kansai-Denryoku Hospital, Osaka, Japan; the <sup>2</sup>Department of Health Informatics Research, Translational Research Informatics Center, Kobe, Japan; and the <sup>3</sup>Karasuma-Nakai Clinic, Kyoto, Japan.

Address correspondence to Ataru Taniguchi, MD, Division of Diabetes and Clinical Nutrition, Kansai-Denryoku Hospital, 2-1-7 Fukushima,

Fukushima-ku, Osaka-city, Osaka 553-0003, Japan. E-mail: taniguchi.ataru@a5.kepco.co.jp.  
 DOI: 10.2337/dc06-0528  
 © 2006 by the American Diabetes Association.

## References

1. Bierman EL: George Lyman Duff Memorial Lecture: Atherogenesis in diabetes. *Arterioscler Thromb* 12:647–656, 1992
2. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG: Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 106:2085–2090, 2002
3. Shai I, Schulze MB, Manson JE, Rexrode KM, Stampfer MJ, Mantzoros C, Hu FB: A prospective study of soluble tumor necrosis factor- $\alpha$  receptor II (sTNF-RII) and risk of coronary heart disease among women with type 2 diabetes. *Diabetes Care* 28:1376–1382, 2005
4. Kawasaki Y, Taniguchi A, Fukushima M, Nakai Y, Kuroe A, Ohya M, Nagasaka S, Yamada Y, Inagaki N, Seino Y: Soluble TNF receptors and albuminuria in non-obese Japanese type 2 diabetic patients. *Horm Metab Res* 37:617–621, 2005

## Divergent Relationships Among Soluble Tumor Necrosis Factor- $\alpha$ Receptors 1 and 2, Insulin Resistance, and Endothelial Function

Inflammation has the capacity to impair flow-mediated vasodilatation, which is regarded as a causal factor in the development of atherosclerosis (1). Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a pro-inflammatory cytokine that is also implicated in the pathogenesis of insulin resistance and endothelium dysfunction linked to this event (2). Contradictory effects of TNF- $\alpha$  on endothelial function have been described in different studies (3). Acute intrabrachial TNF- $\alpha$  infusion impairs endothelium-dependent vasodilatation, but TNF- $\alpha$  also enhances protective mechanism (3).

After binding of TNF- $\alpha$  to TNF- $\alpha$  receptors (TNFR1 and TNFR2), a proteolytic cleavage of the extracellular parts of these receptor elicits the soluble forms, named sTNFR1 and sTNFR2 (4).

We aimed to evaluate brachial artery vascular reactivity (high-resolution external ultrasound) and insulin sensitivity (minimal model analysis [5]) in relation with plasma sTNFR1 and sTNFR2 levels (commercially available solid-phase enzyme-amplified sensitivity immunoassays [EASIA]; Medgenix, Biosource Europe, Fleunnes, Belgium) in 100 consecutive, apparently healthy, Caucasian men, 70 with normal glucose tolerance (NGT) and 30 with impaired glucose tolerance (IGT), enrolled in a prospective study of insulin sensitivity in Northern Spain.

In multiple regression analysis, serum sTNFR1 independently contributed to endothelium-dependent vasodilatation (EDVD) in subjects with NGT, after adjusting for age, BMI, smoking status, systolic and diastolic blood pressure, and insulin sensitivity ( $\beta = 0.414$ ,  $P = 0.002$ ). In fact, we observed a positive correlation between sTNFR1 levels and endothelium-dependent vasodilatation ( $r = 0.291$ ,  $P = 0.02$ ) (Table 1).

In all subjects as a whole, circulating sTNFR2 was negatively associated with insulin sensitivity ( $r = -0.20$ ,  $P = 0.04$ ) and a trend was observed with EDVD ( $r = -0.190$ ,  $P = 0.058$ ). In IGT subjects, serum sTNFR2 levels correlated negatively with EDVD ( $r = -0.366$ ,  $P = 0.047$ ) (Table 1). The relationship, however, was not significant after adjusting for confounding variables. No association was found between endothelium-independent vasodilatation and circulating sTNFR1 or sTNFR2 levels (Table 1).

This study shows divergent relationships between circulating sTNFRs levels and endothelial function. While sTNFR1 was positively associated with EDVD, opposite relationships regarding sTNFR2 were observed, mainly in subjects with IGT.

Shedding of TNFR1 leads to increased sTNFR1, which antagonizes TNF- $\alpha$  (6). Increased sTNFR1 expression reduced TNF- $\alpha$  bioactivity and protected the myocardium from infarction following ischemia and reperfusion in animal models (7). sTNFR1 might have other protective roles through the stimulation of endothelial cell growth. These antiatherosclerotic mechanisms induced by sTNFR1 are in line with our findings. On the other hand, sTNFR2 levels have been linked to coronary artery disease (8), insulin resistance, and hypertension (5) in concordance with the inverse association between sTNFR2 levels and endothelium

Table 1—Simple correlation analysis between endothelium-dependent and independent vasodilatation and sTNFR1 and sTNFR2

|                                  | EDVD (%)               |                          |                          | EIVD (%)              |                       |                       |
|----------------------------------|------------------------|--------------------------|--------------------------|-----------------------|-----------------------|-----------------------|
|                                  | NGT                    | IGT                      | Total                    | NGT                   | IGT                   | Total                 |
| n                                | 70                     | 30                       | 100                      | 70                    | 30                    | 100                   |
| Log <sub>10</sub> sTNFR1 (ng/ml) | r = 0.291,<br>P = 0.02 | r = -0.043,<br>P = NS    | r = 0.107,<br>P = NS     | r = -0.132,<br>P = NS | r = -0.313,<br>P = NS | r = -0.178,<br>P = NS |
| Log <sub>10</sub> sTNFR2 (ng/ml) | r = -0.028,<br>P = NS  | r = -0.366,<br>P = 0.047 | r = -0.190,<br>P = 0.058 | r = -0.013,<br>P = NS | r = 0.171,<br>P = NS  | r = -0.065,<br>P = NS |

vasodilatation in subjects with IGT described here.

Sustained upregulation of human TNFR2 in transgenic mice leads to a chronic accumulation of cell surface and plasma receptor (9), providing them the capacity to be hyperresponders to circulating TNF- $\alpha$ . It is tempting to speculate that similar findings in subjects with IGT may contribute to both insulin resistance and endothelial dysfunction induced by TNF- $\alpha$ .

In summary, we found divergent associations between both sTNFR and endothelium vasodilatation. The knowledge of how these interactions occur may have therapeutic implications.

EDUARDO ESTEVE, MD, PHD<sup>1</sup>

ANTONI CASTRO, MD, PHD<sup>2</sup>

ABEL LÓPEZ-BERMEJO, MD, PHD<sup>1</sup>

JOAN VENDRELL, MD, PHD<sup>3</sup>

WIFREDO RICART, MD<sup>1</sup>

JOSE-MANUEL FERNÁNDEZ-REAL, MD, PHD<sup>1</sup>

From the <sup>1</sup>Unit of Diabetes, Endocrinology and Nutrition, Hospital de Girona "Dr. Josep Trueta," Girona, Spain; the <sup>2</sup>Department of Internal Medicine, Hospital de Girona "Dr. Josep Trueta," Girona, Spain; and the <sup>3</sup>Unit of Diabetes, Endocrinology and Nutrition, Hospital de Tarragona "Joan XXIII," Tarragona, Spain.

Address correspondence to J.-M. Fernández-Real, MD, PhD, Unit of Diabetes, Endocrinology and Nutrition, Hospital de Girona "Dr Josep Trueta," Ctra. França s/n, 17007 Girona, Spain. E-mail: uden.jmfernandezreal@htrueta.scs.es.

DOI: 10.2337/dc06-0423

© 2006 by the American Diabetes Association.

## References

- Hansson GK: Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 352:1685–1695, 2005
- Fernández-Real JM, Ricart W: Insulin resistance and chronic cardiovascular inflammatory syndrome. *Endocr Rev* 24: 278–301, 2003
- Chia S, Qadan M, Newton R, Ludlam C, Fox KA, Newby DE: Intra-arterial tumor necrosis factor- $\alpha$  impairs endothelium-dependent vasodilatation and stimulates local tissue plasminogen activator release

in humans. *Arterioscler Thromb Vasc Biol* 23:695–701, 2003

- Aderka D, Engelmann H, Maor Y, Brakebusch C, Wallach D: Stabilization of the bioactivity of tumor necrosis factor by its soluble receptors. *J Exp Med* 175:323–329, 1992
- Fernández-Real JM, Lainez B, Vendrell J, Rigla M, Castro A, Peñarroja G, Broch M, Perez A, Richart C, Engel P, Ricart W: Shedding of TNF- $\alpha$  receptors, blood pressure, and insulin sensitivity in type 2 diabetes mellitus. *Am J Physiol Endocrinol Metab* 282:952–959, 2002
- Selinsky CL, Boroughs KL, Halsey WA, Howel MD: Multifaceted inhibition of anti-tumor immune mechanisms by soluble tumor necrosis factor receptor type I. *Immunology* 94:88–93, 1998
- Sugano M, Hata T, Tsuchida K, Suematsu N, Oyama J, Satoh S, Makino N: Local delivery of soluble TNF- $\alpha$  receptor 1 gene reduces infarct size following ischemia/reperfusion injury in rats. *Mol Cell Biochem* 266:127–132, 2004
- Benjafield AV, Wang XL, Morris BJ: Tumor necrosis factor receptor 2 gene (TNFRSF1b) in genetic basis of coronary artery disease. *J Mol Med* 79:109–115, 2001
- Douni E, Kollias G: A critical role of the p75 tumor necrosis factor receptor (p75TNFR) in organ inflammation independent of TNF, lymphotoxin  $\alpha$ , or the p55TNFR. *J Exp Med* 188:1343–1352, 1998

## COMMENTS AND RESPONSES

### Race Differences in Long-Term Diabetes Management in an HMO

Response to Adams et al.

Adams et al. (1) examined longitudinal differences in HbA<sub>1c</sub> (A1C) between black and white diabetic members of an HMO. They found a small,

but persistent, increase in A1C values in black subjects; however, there is an important omission in their study. There is no indication that the authors considered the potential effect of the presence of variant hemoglobins in the study subjects. Eight percent of black individuals are carriers of hemoglobin S (2) and are thus heterozygotes for an amino acid substitution in the hemoglobin  $\beta$  chain, which can alter A1C test results. The prevalence of this hemoglobinopathy in white Americans is much lower (3). A1C can give an inaccurate assessment of glycemia in patients with sickle hemoglobin. The magnitude of this perturbation is method dependent and is not linear over the entire glycohemoglobin range (4). The possible contribution of this effect to the observed differences in A1C described between black and white patients should have been considered. Failure to be aware of this can result in overtreatment of these patients, placing them at increased risk of hypoglycemia.

There are some test kits in commercial use that may eliminate interference by hemoglobin variants (5). The authors have not indicated, however, which assay method they used. Without this information and with no correlating blood glucose data, the presumption of racially based "psychosocial barriers to therapy intensification among patients and clinicians" (1) may be unwarranted.

Our efforts to achieve the best possible clinical outcome for our patients with diabetes by near normalization of blood glucose often focus on maintaining A1C levels as near normal as possible without undue hypoglycemia. While A1C is a valuable surrogate for glycemic control, current American Diabetes Association Clinical Practice Recommendations remind us that "[g]lycemic control is best judged by the combination of the results of the patient's SMBG testing and the current A1C result" (6).

CELESTE B. HART, MD