

## OBSERVATIONS

## High Prevalence of Hypovitaminosis D in Female Type 2 Diabetic Population

Animal studies have demonstrated lower levels of 1,25(OH)<sub>2</sub>D<sub>3</sub> in a type 2 diabetes model compared with controls (1). Alterations in circulating vitamin D<sub>3</sub> metabolites, such as decreased 1 $\alpha$ -hydroxylase activity and enhanced renal 25-hydroxylase activity, have been found in both experimental and human diabetes. These alterations in vitamin D metabolism may be associated with the deranged mineral homeostasis and skeletal morphology observed in rats and people with chronic insulin deficiency (2). Experimentally, vitamin D deficiency progressively reduces insulin secretion, and this reduction soon becomes irreversible (3). It was also shown that insulin deficiency may be associated with lower vitamin D-binding protein and 1,25(OH)<sub>2</sub>D<sub>3</sub> serum levels in rats. These decreases are somewhat dependent on androgen concentration, but they are counteracted by estrogens (4).

Several studies have demonstrated abnormalities in calcium, phosphate, and vitamin D metabolism in diabetic patients. In particular, Pietschmann et al. (5) evaluated 25(OH)D levels in type 1 and type 2 diabetic patients and found no difference in 25(OH)D levels between type 1 diabetic patients and control subjects, whereas 25(OH)D levels were significantly decreased in type 2 diabetic patients (5).

We conducted an observational study in 799 ambulatory postmenopausal Italian women in order to assess the prevalence of hypovitaminosis D and dietary calcium insufficiency. In all patients, the levels of 25(OH)D<sub>3</sub> (obtained by radioimmunoassay method with double antibody provided by DiaSorin), calcium intake (obtained by a questionnaire filled in by a general practitioner), and several Activity Daily Living (ADL) criteria were assessed. The samples were collected in February and March 2000.

We identified 66 type 2 diabetic pa-

tients based on medical history. Female patients and control subjects were comparable for age and years since menopause, but BMI was significantly higher in diabetic patients. The ADL score was significantly worse in diabetic patients than in control subjects ( $P < 0.01$ ). The 25(OH)D levels (means  $\pm$  SD) were significantly lower in diabetic patients than in control subjects ( $11 \pm 9.8$  vs.  $9 \pm 11.3$  ng/ml,  $P < 0.008$ ), and the prevalence of 25(OH) deficiency ( $<5$  ng/ml) was significantly higher in diabetic patients than in control subjects (39 vs. 25%). Dietary calcium intake was significantly lower in diabetic patients than in control subjects ( $792.9 \pm 400.9$  vs.  $679 \pm 316.9$  mg/day,  $P < 0.020$ ).

The significance of these findings remains unclear. The general recommendation for overweight diabetic patients to lower fat dairy product consumption may explain the lower calcium intake. We have no data that might explain the higher prevalence of hypovitaminosis D among diabetic patients. We believe our results will lead to additional studies on the hypothetical circular relationship among diabetes, vitamin D repletion, and calcium intake and absorption. We believe this relationship leads to both a worsening of diabetes and an increased risk of fractures (6), despite higher bone mineral density levels being found in diabetic subjects (6,7).

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## Plasma Total Homocysteine Levels Are Associated With von Willebrand Factor, Soluble Intercellular Adhesion Molecule-1, and Soluble Tumor Necrosis Factor- $\alpha$ Receptors in Young Type 1 Diabetic Patients Without Clinical Evidence of Macrovascular Complications

Elevated plasma total homocysteine (tHcy) levels are a powerful risk factor for atherosclerotic vascular disease (1), but it is still unclear by which pathophysiological mechanisms tHcy may promote atherothrombosis. In both experimental animal and cell culture studies (2,3), acute hyperhomocysteinemia induces endothelial dysfunction, leading to a low-grade inflammatory state that results in increased leukocyte adher-

ence by upregulation of cell adhesion molecules. Accordingly, an impaired endothelium-dependent flow-mediated dilation was found in nondiabetic subjects with high tHcy when compared with subjects with low tHcy levels (4). In a recent cross-sectional study (5) of both nondiabetic individuals and type 2 diabetic subjects, tHcy was significantly associated with endothelial dysfunction, as estimated from plasma von Willebrand factor (vWF), and with leukocyte adhesion, as estimated from plasma vascular cell adhesion molecule-1. To our knowledge, there is a lack of available data regarding the relationships of tHcy levels with plasma markers of endothelial dysfunction and inflammation in young type 1 diabetic adults. It has been reported in only one previous study (6) that type 1 diabetic patients with higher tHcy levels compared with patients with lower tHcy levels had significantly elevated soluble thrombomodulin, a marker of endothelial function. However, because the group of patients with higher tHcy also had a significantly increased prevalence of microvascular and macrovascular complications, these results should be interpreted with some degree of caution. We have previously demonstrated that young type 1 diabetic patients have significantly higher tHcy levels than healthy control subjects and that smoking itself may be one of the major lifestyle determinants of tHcy (7). In this study, we endeavored to evaluate a selected group of 36 (16 men and 20 women) lean (BMI  $23.6 \pm 0.5$  kg/m<sup>2</sup>), nonsmoking, normotensive (systolic/diastolic blood pressure  $125 \pm 2/80 \pm 1$  mmHg), normolipidemic (total cholesterol and triglycerides  $4.6 \pm 0.1$  and  $0.92 \pm 0.1$  mmol/l, respectively), young (age  $31 \pm 1$  year) type 1 diabetic adults who were without any clinical evidence of macrovascular complications. Their average glycometabolic control was good (HbA<sub>1c</sub>  $6.6 \pm 0.2\%$ ), and their average duration of diabetes was  $15 \pm 1$  years. To exclude the presence of clinical macroangiopathy, a 12-lead resting electrocardiogram, a measurement of the ankle brachial pressure index, and carotid ultrasonography were performed in all of the diabetic patients. We measured plasma levels of tHcy (by an automated high-performance liquid chromatography analyzer with fluorescence detection) (7) and fibrinogen (IL-test-PT-fibrinogen HS; Instrumentation Laboratory, Lexington,

KY). By using commercially available enzyme-linked immunosorbent assay kits, we measured interleukin-6 (IL-6), vWF, soluble intercellular adhesion molecule-1 (sICAM-1), P-selectin, and soluble tumor necrosis factor (TNF)- $\alpha$  receptors (i.e., sTNF-R1 and sTNF-R2), which reflect the degree of TNF- $\alpha$  activation more accurately than the measurement of TNF- $\alpha$  itself. The tHcy levels were significantly associated with sICAM-1 ( $r = 0.34$ ,  $P < 0.05$ ), vWF ( $r = 0.45$ ,  $P < 0.01$ ), and sTNF-R1 ( $r = 0.56$ ,  $P < 0.001$ ). The adjustment for potential confounders did not modify these results. The tHcy levels did not significantly correlate with fibrinogen, IL-6, P-selectin, or sTNF-R2 levels. Similarly, when diabetic patients were subdivided into groups according to the median value of the distribution of tHcy, the two groups were comparable for age, sex, BMI, lipids, creatinine, blood pressure, glycometabolic control, diabetes duration, and microvascular complications (i.e., retinopathy and/or microalbuminuria). Nevertheless, plasma levels of sICAM-1 ( $273 \pm 11$  vs.  $241 \pm 7$  ng/ml), vWF ( $122 \pm 8$  vs.  $91 \pm 8\%$ ), and sTNF-R1 ( $2.0 \pm 0.2$  vs.  $1.5 \pm 0.1$  ng/ml) were markedly elevated ( $P < 0.05$  or less) in patients with higher tHcy ( $n = 18$ ,  $12.7 \pm 0.8$   $\mu$ mol/l) versus lower tHcy levels ( $n = 18$ ,  $8.8 \pm 0.2$   $\mu$ mol/l). Fibrinogen concentration tended to be higher in patients with higher tHcy ( $3.53 \pm 0.3$  vs.  $3.06 \pm 0.1$  g/l,  $P = 0.08$ ) but did not achieve statistical significance. No significant differences were found in IL-6, P-selectin, and sTNF-R2 levels between the two groups.

Overall, therefore, these results indicate that in nonsmoking, normotensive, normolipidemic young type 1 diabetic adults with good glycometabolic control and without any clinical evidence of macrovascular complications, there is a significant relationship between tHcy and plasma markers of endothelial dysfunction and inflammation. Although this study is cross-sectional and therefore cannot prove a direct cause-and-effect relationship, our results extend previous observations in nondiabetic and type 2 diabetic individuals, supporting the hypothesis that the pathophysiological link between tHcy and atherothrombosis can, at least in part, be explained by endothelial dysfunction, which leads to an increased endothelial adherence of leuko-

cytes and a low-level chronic inflammatory state.

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that diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction (1). All of these observations indicate the importance of aggressive cholesterol lowering in diabetic patients. We have previously shown that type 2 diabetic Chinese subjects are characterized by impaired endothelial-dependent and -independent brachial arterial vasoactivity when compared with nondiabetic individuals (2). However, we failed to demonstrate that treatment with simvastatin (10 mg daily) had beneficial effects on brachial arterial vasoreactivity in type 2 diabetic subjects, despite a 26–35% reduction in LDL cholesterol levels. Because coronary angiographic trials suggested that more intensive LDL cholesterol lowering (<100 mg/dl) is associated with regression or arrest of progression of coronary lesions compared with moderate LDL cholesterol reduction (3), we tested the hypothesis that aggressive lowering of LDL cholesterol would be associated with more beneficial endothelial vasoreactivity in type 2 diabetic subjects.

We recruited 12 type 2 diabetic subjects with hypercholesterolemia (8 men and 4 women, mean age  $64 \pm 2$  years [mean  $\pm$  SEM], mean HbA<sub>1c</sub>  $8.1 \pm 0.1\%$ ). After  $\geq 6$  weeks on a lipid-lowering dietary advisory period, 20 mg simvastatin every night was prescribed. If a participant's LDL cholesterol concentration still exceeded 100 mg/dl, the dose of simvastatin was doubled 4 weeks later. The total treatment period was 12 weeks. Brachial artery vasoactivity was evaluated as described previously (2). After determination of baseline arterial diameter and blood flow velocity, a blood pressure cuff was inflated to a pressure of 200 mmHg and maintained for 5 min. The brachial artery was scanned before and immediately after cuff deflation and for 20 min thereafter. Twenty minutes later, nitroglycerin (0.6 mg) was administered sublingually and measurement was continued for an additional 20 min.

In response to simvastatin treatment (20 mg in eight subjects and 40 mg in four subjects), total cholesterol decreased from  $229 \pm 9$  to  $158 \pm 4$  mg/dl ( $P < 0.001$ ), LDL cholesterol values decreased from  $144 \pm 9$  to  $75 \pm 4$  mg/dl ( $P < 0.001$ ), fasting plasma triglyceride did not change ( $226 \pm 22$  vs.  $202 \pm 18$  mg/dl,

$P = 0.530$ ), and HDL cholesterol levels increased marginally ( $40 \pm 2$  vs.  $43 \pm 2$  mg/dl,  $P = 0.078$ ). In particular, a significant improvement of peak flow-mediated (endothelium-dependent) brachial arterial dilation was observed ( $5.6 \pm 1.7$  vs.  $13.6 \pm 2.6\%$ ,  $P < 0.028$ ) only in subjects with LDL cholesterol <80 mg/dl ( $n = 6$ , range 57–76 mg/dl) but not in patients ( $4.4 \pm 1.8$  vs.  $8.2 \pm 1.6\%$ ,  $P = 0.173$ ) with a higher LDL cholesterol level ( $n = 6$ , range 81–92 mg/dl) at the end of the study. Endothelium-independent dilation of the brachial artery did not change in either group.

Recent evidence indicated that, in addition to their lipid-lowering effects, statins carry a wide variety of vascular protection effects including vasodilation, antithrombosis, antioxidation, antiproliferation, anti-inflammation, and plaque stabilization (4). Also, previous studies have demonstrated that lipid-lowering therapy beneficially alters endothelial dysfunction in nondiabetic subjects with hypercholesterolemia and coronary atherosclerosis (5). However, we failed to show similar beneficial effects in response to simvastatin treatment in type 2 diabetic subjects (2). Recently, the level of cholesterol, which should be set as a goal of LDL cholesterol lowering, has become a topic of debate. The Post Coronary Artery Bypass Graft Trial demonstrated that subjects with aggressive LDL cholesterol lowering (decreased to  $95 \pm 2$  mg/dl) had significantly less angiographic progression and fewer future combined events than those with less aggressive control (decreased to  $134 \pm 2$  mg/dl) (3). Tamai et al. (6) also showed that a large magnitude reduction of LDL cholesterol by apheresis led to a significant benefit in vasomotor activity. Shechter et al. (7) reported that better dilation of flow-mediated vasoreactivity occurred in coronary heart disease subjects whose LDL cholesterol was <100 mg/dl when compared with those whose LDL cholesterol was >100 mg/dl. Our study demonstrates that aggressive LDL cholesterol lowering to <80 mg/dl by simvastatin led to improvement of endothelial-dependent vasoreactivity in type 2 diabetic subjects with hypercholesterolemia. The magnitude of percent flow-mediated brachial vasoreactivity (14%), as determined by Shechter et al. (7), is very similar to that observed in the present study (13.6%). Our results provide a prelimi-

nary report stating that more aggressive LDL cholesterol lowering is necessary to improve endothelial function in type 2 diabetic subjects. However, it remains to be demonstrated whether lowering LDL cholesterol to <80 mg/dl will result in better cardiovascular outcome in type 2 diabetic individuals.

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## Maternal Mortality in Type 1 Diabetes

The ultimate complication of type 1 diabetes in combination with pregnancy is maternal death, which may result from complications of the pregnancy itself, diabetes and associated diseases, or causes related to neither pregnancy nor diabetes. From the clinical point of view, the greatest reward would be to identify possible preventable causes of maternal death beforehand, especially because these patients are under close surveillance during the entire pregnancy and postpartum period.

The reported incidence of maternal mortality of pregnant type 1 diabetic women has been ~0.5% (1,2), which is 5–20 times higher than that of the general obstetric population. However, these estimates date back prior to 1980, and because of the developments in both the obstetric management and the treatment of diabetes during the past 20 years, we have estimated the risk of death and analyzed the causes of maternal mortality in a large single referral center for all pregnant type 1 diabetic women from Southern Finland.

Between 1975 and 1997, 972 type 1 diabetic women delivered, or intended to deliver, in the Department of Obstetrics and Gynecology at the University Central

Hospital of Helsinki. This is the referral center for all pregnant diabetic women in Southern Finland (population 1.5 million). If the diabetes classification was not evident based on the diagnoses established at pediatric or adult endocrinology units, it was confirmed by the undetectable plasma C-peptide levels. All patients were followed-up for an interval of 1–6 weeks during pregnancy and within 1–2 months after delivery. Maternal deaths (during pregnancy or within 42 days after delivery) were recorded, and the causes of death were determined by a forensic medical autopsy or by clinical findings.

Of the 972 women, 5 (0.51%, 95% CI 0.17–1.20) died during pregnancy or in the postpartum period (Table 1). Four of these women had a duration of diabetes >20 years; two of the deaths were caused by hypoglycemia and one by ketoacidosis. Patient 1 suffered a brain stem infarction the night after cesarean section. The diagnosis was made by neurological senior consultants on the basis of clinical findings. She never regained consciousness. Patient 2 died from the complications of a massive unintentional spinal anesthesia for an elective cesarean section. She could not be intubated because of severe rheumatoid arthritis, and a tracheostomy was performed too late. Patient 3 was found unconscious at her home at 14 weeks of gestation. At that time, she was hypoglycemic and had cardiac ventricular fibrillation. She died from anoxic brain damage at 24 weeks of gestation. Patient 4 had labile diabetes with wide fluctuations in blood glucose levels and frequent episodes of hypoglycemia. She was found dead at her home at 10 weeks of gestation, and, after combining the clinical data and the findings of a forensic autopsy, the cause of her death was assigned to severe hypoglycemia. Patient

5 had dilatation and curettage for a missed abortion at 9 weeks of gestation. Thirteen days later, she became disoriented and suddenly lost consciousness, and when an emergency team arrived, she was already dead. A forensic chemical investigation revealed ketoacidosis and intoxication by trimipramine, ethylmorphine, and temazepam.

The relative death rate of type 1 diabetic Finnish women increases with the duration of diabetes and is highest at 30–34 years of age (3). In Finnish women with a duration of type 1 diabetes between 20 and 25 years, the relative death rate was 8.9 times higher than in nondiabetic Finnish women of the same age (3). On the other hand, the maternal mortality in Finland during the 1980s was 4.7 deaths per 100,000 births. Based on these data and this study, the mortality of type 1 diabetic mothers was 109 times greater than the general population and 3.4 times greater than nonpregnant type 1 diabetic women when calculated in person-years (each diabetic pregnancy was considered as 1 person-year).

None of the deaths were definitely associated with unsuspected diabetic complications that have a high maternal mortality rate, such as ischemic heart disease, although vascular disease might have been a contributing factor in the death of one of our patients (Patient 1). As reported in previous studies (1), anesthetic complications are an important cause of maternal death in diabetes. Other directly obstetrical deaths were not observed in our study.

The tight metabolic control of diabetes during pregnancy that is mandatory for the normal development of the fetus may expose the mother to life-threatening cases of hypoglycemia. Two deaths in our study could be assigned to “dead-in-bed

**Table 1—Maternal deaths in 972 pregnant type 1 diabetic women followed at the Department of Obstetrics and Gynecology, University Central Hospital of Finland, between 1975 and 1997**

Patient	Age (years)	Parity	Type 1 diabetes onset (years)	Type 1 diabetes duration (years)	Last HbA <sub>1c</sub> (% [±SD])	Time of death (week + day of pregnancy)	Cause of death
1	32	G3P1	4	29	6.1 (+2)	Postpartum	Spinal anesthesia
2	38	G5P3	14	24	NA	Postpartum	Brain stem infarction
3	24	G1P0	21	3	8.0 (+6)	14 + 5	Hypoglycemia
4	29	G2P0	9	21	8.6 (+7)	10 + 1	Dead-in-bed syndrome
5	33	G7P3	9	25	6.7 (+3)	After spontaneous abortion	Ketoacidosis and intoxication

For parity, G = number of pregnancies, P = number of parturitions. Patients 1–3 had uncomplicated type 1 diabetes (except a few had fundus microaneurysms), and patients 5 and 6 had diabetic nephropathy. NA, not available.



of healthcare utilization are increased among patients who are noncompliant with CBG monitoring, and 4) pain and soreness are the most common reasons for noncompliance with CBG monitoring. Clear guidelines should be developed for CBG monitoring frequency in patients with diabetes so that a consistent message is delivered by diabetes care providers. Moreover, compliance with CBG monitoring should be assessed at patient visits, and its importance should be reinforced. Strategies to improve compliance with CBG monitoring, including reducing the pain or perceived pain associated with the procedure, should be developed and implemented with the aim of improving the acceptability of this essential component of diabetes management. Finally, needleless methods of blood sampling for CBG monitoring may also improve compliance in patients with needle phobia (5).

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## Seasonal Variation of Glycemic Control in Type 2 Diabetic Patients

Medical nutrition therapy is integral to diabetes care and management (1). Balance between dietary intake and energy consumption through daily physical activities is the most influential factor in the glycemic control of type 2 diabetic patients. The nutritional prescription made for a diabetic individual is usually determined by taking into consideration the expected physical activity, diabetes complication(s), and age. The dietary advice based on this prescription seems to be valid in many cases for at least a few years; for some diabetic patients, its validity is lifelong. Such a dietary prescription is made by an implied understanding that eating habits and physical activity do not change throughout the year. Here, we show a seasonal variation of HbA<sub>1c</sub> levels in type 2 diabetic patients.

Fukushima province is a large agricultural area surrounded by mountains, and it has a relatively low population density compared with central Japan. The climate is typical of any valley area; the people experience very warm and humid Asian summers (>34°C) and icy cold winters from January to early March. Generally, the people here are active outdoors, with some patients engaging in field work from spring to fall, but not as frequently during winter. During winter, when it gets dark around 4:00 P.M. and the roads are icy and slippery, the people customarily enjoy salty meals prepared in a pot and alcoholic beverages.

We calculated the mean HbA<sub>1c</sub> levels of 39 type 2 diabetic patients (27 women and 12 men, mean age 65.6 years) in each month. The mean HbA<sub>1c</sub> level was elevated by ~0.5% in winter compared with the period between spring and autumn, ranging from 6.42 ± 0.65% (mean ± SD) in July to 6.96 ± 0.90% in March, *P* < 0.01.

This observed seasonal variation in HbA<sub>1c</sub> levels is likely caused by an increased dietary calorie intake and decreased physical activity during the cold winter months. It is rare for doctors to prescribe different nutritional prescriptions in winter, and we did not find any diabetes textbook that discussed this seasonal change in lifestyle. It seems reasonable for diabetologists and dietitians to modify the nutritional prescription for those diabetic patients whose opportunities for physical exercise are reduced during the winter months.

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## Is There a Predisposition to Intestinal Parasitosis in Diabetic Patients?

Although intestinal parasites usually create benign diseases, sometimes they may cause complications with high mortality and morbidity (1,2). It is known that diabetic patients are more susceptible to bacterial infections. Decreased arterial perfusion, neuropathy, and suppressed immune response in diabetes aggravate the frequency and severity of infectious diseases (3). Lymphocyte and polymorphonuclear leukocyte functions are altered (4). The most prominent alteration is the phagocytic functions of polymorphonuclear leukocytes (5,6). It has also been reported that candidal infections occur more frequently in diabetic

patients than in nondiabetic control subjects (7,8). Is a similar kind of predisposition present against parasitic infections, particularly against the intestinal parasites in diabetic patients? There is no adequate study about this subject. Therefore, we assessed whether there is a predisposition against intestinal parasites in the diabetic population by comparing their prevalence in diabetic and nondiabetic individuals living in the Sanliurfa province, which lies in southeast Anatolia. Here, intestinal parasites are very common because of the hot climate, agricultural usage of sewage, and inadequate purified drinking water.

A total of 200 diabetic (16 type 1 and 184 type 2) and 1,024 nondiabetic individuals who were consecutively recruited to endocrinology and internal medicine outpatient clinics were included in the present study. The diabetic group comprised 72 male and 128 female patients (mean age 45.2 years, range 15–79). Of the 200 diabetic patients, 26 were on insulin therapy, 106 were on oral antidiabetic agents, 21 were on diet alone, and 47 were not on therapy. The nondiabetic group comprised 344 male and 680 female patients (mean age 40.0 years, range 15–74). Fresh stool samples were examined macroscopically, followed by microscopic examination by native, lugol, and flotation methods under 10 $\times$  and 40 $\times$  magnification. The differences between the categorical variables under consideration were analyzed by  $\chi^2$  test.  $P < 0.05$  was considered statistically significant.

Intestinal parasitosis was diagnosed in 94 of 200 patients (47%) in the diabetic group (61 women and 33 men). The distribution of the parasites found was: 57.5% *Ascaris lumbricoides*, 14.2% *Trichuris trichura*, 13.3% *Entamoeba histolytica*, 11.7% *Giardia intestinalis*, and 3.3% tenias (*T. saginata* or *Hymenolepis nana*). In 15 patients, two or more kinds of parasites were found. There were no statistically significant differences with regard to incidences of intestinal parasites between male and female patients (45.8 and 47.6%, respectively) and between therapy groups. In the control subject group, 380 of 680 women (55.9%) and 184 of 344 men (53.4%) had intestinal parasites, and 72 people had more than one kind of parasite. The prevalence of the parasites did not show significant differences between sex parasites. *Ascaris lumbricoides*

was the most common intestinal parasite in both groups ( $P < 0.05$ ). Intestinal parasite prevalence in the diabetic group was found to be significantly lower than in the control subject group (47 vs. 55%,  $P < 0.05$ ).

It has been reported that certain medications and diabetes affect immune mechanisms in AIDS-infected patients. The patient's immune status is relevant in determining which parasitic infections need to be considered. In patients infected with HIV, specific protozoan diseases may develop opportunistically (9). Patients with hypogammaglobulinemia or cystic fibrosis may develop refractory giardiasis. In patients developing symptoms of enterocolitis while receiving glucocorticoids, the possibility of an exacerbation of unsuspected strongyloidiasis or amebic colitis should be considered (10). Although several defects in the immune system have been reported in diabetic patients (3,4), there are insufficient data in the literature about concordance of diabetes and intestinal parasitic diseases. In a study by Abaza et al. (11), the frequency of opportunistic intestinal parasites was explored in four groups with immunocompromised hosts and was found in 31.7% of patients under corticosteroid therapy, in 28.8% of patients suffering renal failure, in 25.7% of patients with malign neoplasm, and in 8% of diabetic patients. In our study, no significant predisposition to intestinal parasitosis was observed in diabetic patients. Moreover, diabetic patients had less intestinal parasites compared with the general population in our endemic region. Because of similar frequencies of parasites in all groups, the lower prevalence of intestinal parasitic disease in diabetic patients did not depend on the antidiabetic agents used (i.e., insulin, oral antidiabetic agents, diet alone, or no treatment). This low frequency of parasites in diabetic patients may be a result of the fact that, because of their illness, they undergo physical examinations and laboratory tests more frequently than the general population in our region. The greater number of physician visits incurred by diabetic patients may cause this lower frequency of parasitosis.

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## Serum Nonesterified Fatty Acids Are Related With Carotid Atherosclerotic Plaque in Nonobese Nonhypertensive Japanese Type 2 Diabetic Patients

The occurrence of coronary heart disease (CHD) and other manifestations of atherosclerotic vascular disease are substantially increased in patients with type 2 diabetes. Mortality from CHD and the incidence of nonfatal CHD events are two to four times higher in patients with type 2 diabetes than in age-matched nondiabetic subjects (1,2). It has been demonstrated that lipoprotein lipase (LPL), a secretory product of macrophage in the arterial wall, contributes to the development and progression of atherosclerosis (3). Michaud et al. (4) recently demonstrated that fatty acids enhance LPL production in human macrophages. Type 2 diabetic patients frequently have higher serum nonesterified fatty acids (NEFAs) (5). From these reports, it may be suggested that fatty acids participate in the development and progression of atherosclerosis in type 2 diabetic patients. To the best of our knowledge, however, the relationship between serum fatty acids and the degree of atherosclerosis has not been fully clarified in type 2 diabetic patients.

Plasma glucose level per se seems to enhance LPL production in human macrophage (6). Moreover, it is well recognized that obesity and/or hypertension per se causes atherosclerosis in type 2 diabetic patients. We therefore recruited nonobese nonhypertensive well-controlled unique type 2 diabetic patients after taking into account these confounding risk factors. The degree of atherosclerosis can be evaluated by high-resolution B-mode ultrasound scan. This is a reliable noninvasive method for the assessment of carotid atherosclerosis (7). Carotid atherosclerosis is important in view of its relation to cerebrovascular ischemic diseases and coronary atherosclerosis (8).

A total of 54 nonobese nonhypertensive Japanese type 2 diabetic patients who visited Kansai-Denryoku Hospital were

enrolled in the study. Type 2 diabetes and hypertension were diagnosed based on the criteria of World Health Organization (9,10). The patients were treated with diet alone (27 patients) or diet in combination with sulfonylurea (27 patients). No patients were treated with insulin or antihypertensive medications. All subjects had ingested at least 150 g of carbohydrate for the 3 days preceding the study. None of the subjects had significant renal, hepatic, or cardiovascular disease. They did not receive any medications affecting lipid metabolism. They did not consume alcohol or perform heavy exercise for  $\geq 1$  week before the study.

Blood was drawn in the morning after a 12-h fast. Plasma glucose was measured with the glucose oxidase method and serum insulin was measured using a two-site immunoradiometric assay (Insulin Riabead II; Dainabot, Osaka City, Japan). Coefficients of variation (CVs) were 4% for insulin  $>25 \mu\text{U/ml}$  and 7% for insulin  $<25 \mu\text{U/ml}$ , respectively. The triglycerides, total cholesterol, and HDL cholesterol were also measured. LDL cholesterol was calculated using the Friedewald formula (11). Serum NEFAs were measured in duplicate using enzymatic method (NEFA HR kit; Wako Chemicals, Osaka, Japan), and the mean of the two values was used (12). The CV for NEFA was 2%. Blood pressure was measured twice in the sitting position, and the average was taken.

A carotid sonography was performed with high-resolution B-mode scanning equipment (Logic 400 GE; GE Yokogawa, Milwaukee, WI) with a 7.5-MHz sector scanner probe. The common carotid arteries of both sides were examined with longitudinal and transverse scans, because we could not fully analyze the internal and external carotid arteries in all patients. The CV for interobserver variability was found to be 8.5% and the CV for intraobserver variability was 6.0%. The intimal plus medial thickness (IMT) of the common carotid artery was measured in plaque-free segments as the distance from the leading edge of the first echogenic line corresponding to the lumen-intimal interface to the second echogenic line corresponding to the collagen-containing upper layer of tunic adventitia (13). The mean of IMT in plaque-free segments of bilateral common carotid arteries was used for the analysis. The degree of stenosis was also measured in the

plaque segments of bilateral common carotid arteries. It was calculated as a percentage ratio between the area of the plaque and that of the lumen using the formula  $(\text{lumen area} - \text{residual lumen}) \times 100$  (14). Both of the areas were automatically measured by the system on a frozen transverse scanning plane at the site of maximal narrowing. When two or more plaques were present in the vessel, only the one causing the greatest degree of stenosis was considered for analysis.

The statistical analyses were conducted using the StatView 5 system (Statview, Berkeley, CA). Simple (Spearman's rank) correlation coefficients between the degree of carotid atherosclerosis (IMT and carotid stenosis) and measures of variables were calculated, and a stepwise multiple regression analysis was then used to evaluate the independent association of these variables with the degree of carotid atherosclerosis. Data were presented as means  $\pm$  SEM unless otherwise stated.  $P < 0.05$  was considered significant. In multivariate analysis,  $F \geq 4$  was considered significant.

The subjects studied were 54 nonhypertensive Japanese type 2 diabetic patients (41 men and 13 women) with an age of  $59.8 \pm 1.4$  years and a BMI of  $22.6 \pm 0.3 \text{ kg/m}^2$ . They all were nonobese (BMI  $<27.0 \text{ kg/m}^2$ ) (15). The duration of diabetes was  $9.5 \pm 1.0$  years. Systolic and diastolic blood pressure was  $124 \pm 2 \text{ mmHg}$  (range 92–155) and  $72 \pm 1$  (58–90), respectively. Fasting plasma glucose was  $153 \pm 5 \text{ mg/dl}$  and HbA<sub>1c</sub> was  $7.0 \pm 0.2\%$ . Fasting insulin level was  $6.4 \pm 0.4 \mu\text{U/ml}$ . Serum triglycerides, total cholesterol, and HDL cholesterol levels were  $119 \pm 8$ ,  $190 \pm 4$ , and  $51 \pm 2 \text{ mg/dl}$ , respectively. LDL cholesterol level was  $115 \pm 3 \text{ mg/dl}$ . Serum NEFA level was  $0.61 \pm 0.03 \text{ mEq/l}$ . Mean IMT in plaque-free segments and the degree of carotid stenosis (% stenosis) was  $0.71 \pm 0.02 \text{ mm}$  and  $8.1 \pm 2.1\%$ , respectively.

Spearman's rank correlations of mean IMT in plaque-free segments or the degree of carotid stenosis with measures of variables were calculated for all of our diabetic patients. IMT in plaque-free segments was positively correlated with age ( $r = 0.502$ ,  $P = 0.0003$ ) and NEFA ( $r = 0.378$ ,  $P = 0.0096$ ). The degree of stenosis was positively correlated to age ( $r = 0.431$ ,  $P = 0.0017$ ), duration of diabetes ( $r = 0.307$ ,  $P = 0.0255$ ), and NEFA ( $r = 0.544$ ,  $P = 0.0001$ ).

Next, multiple regression analyses were carried out using the stepwise procedure. The analysis included IMT or the degree of stenosis as a dependent variable and candidate risk factors as independent variables. IMT in plaque-free segments was independently predicted by age ( $F = 16.5$ ), which explained 24.8% of the variability of IMT in our diabetic patients. In contrast, the degree of stenosis was independently associated with NEFA ( $F = 10.5$ ), which explained 16.8% of the variability of the carotid stenosis in our type 2 diabetic patients. Other variables, including BMI and lipid profile, were not associated with either IMT in plaque-free segments or the degree of carotid stenosis in our patients.

It is generally accepted that atherosclerosis and related vascular disorders are the leading cause of death in type 2 diabetic patients. Several factors are associated with atherosclerosis in diabetes. Bierman (16) previously estimated that typical risk factors, including smoking, cholesterol, and blood pressure, can account for no more than 25–30% of excess cardiovascular risk factors in diabetic patients. This suggests that other factors might play a key role in the progression of atherosclerosis in diabetes. One of them is the disturbance of lipid metabolism. Atherothrombotic changes and high serum NEFA frequently accompany type 2 diabetic patients (5).

Some previous investigators emphasized the importance of the relationship between fatty acids and atherosclerosis. Hoak et al. (17) found thrombosis to be associated with the mobilization of fatty acids. Botti et al. (18) found that long-chain saturated fatty acids promote clotting. Connor et al. (19) reported the induction of fatal occlusive thrombi within minutes of infusing fatty acids. Michaud et al. (4) recently demonstrated that fatty acids enhance LPL production in human macrophage. It has been demonstrated that LPL secreted from macrophage contributes to the development and progression of atherosclerosis (3). Thus, fatty acids seem to participate in the development and progression of atherosclerosis in type 2 diabetic patients. To the best of our knowledge, however, the relationship between serum NEFA and atherosclerosis has not been examined in diabetic patients. In this respect, a major problem is that plasma glucose per se enhances LPL production in human mac-

rophage and is also associated with atherosclerosis (6). In addition, it is well known that the degree of overweight and/or hypertension per se affects atherosclerosis. Therefore, we investigated NEFA level in nonobese nonhypertensive well-controlled unique type 2 diabetic patients (mean HbA<sub>1c</sub> 7.0%) and studied the relationship between atherosclerosis and serum NEFA level. As an index of atherosclerosis, we evaluated IMT in the plaque-free segments and carotid stenosis (% stenosis) in the segments of plaque using high-resolution B-mode ultrasound scan. This is the first description of the effect of serum NEFA on carotid atherosclerosis in type 2 diabetic patients.

In this study, we first demonstrated that serum NEFA is associated with both IMT in plaque-free segments and the degree of carotid stenosis in plaque segments in type 2 diabetic patients. However, the effect of NEFA on IMT in plaque-free segments and the degree of carotid stenosis were different. Whereas age was independently associated with IMT in plaque-free segments, NEFA was independently associated with the degree of atherosclerotic plaque. Thus, levels of circulatory NEFA may predict the degree of carotid atherosclerotic plaque in nonobese nonhypertensive well-controlled unique Japanese type 2 diabetic patients.

Presently, the mechanism by which serum NEFA level affects the degree of carotid atherosclerotic plaque in our unique Japanese type 2 diabetic patients is unknown. Although macrophages are able to use glucose, glutamine, and fatty acids as energy sources (20), complete oxidation of glucose and glutamine is limited in macrophages. Thus, fatty acids may constitute the crucial fuel for activated macrophage energy expenditure in the energy-limited environment of the atherosclerotic plaque.

Coagulation abnormalities are proposed as a further potentially important pathophysiological link between type 2 diabetes and atherosclerosis. In this respect, the study by Didisheim et al. (21), who showed that saturated long-chain fatty acids activate Hageman factor (factor XII), is very interesting. Hageman factor initiates the cascade sequence of enzymatic reactions, culminating in the production of thrombin and the conversion of fibrinogen to fibrin. Thrombin also induces an increase in fibrinogen biosynthesis. Pilgeram and Pickart (22) have

shown that free fatty acids (FFAs), which are unbound by protein, stimulate the rate of biosynthesis of fibrinogen in vitro. Thereafter, Schneider et al. (23) demonstrated that FFAs had synergistic effects on insulin-stimulated increase in plasminogen activator inhibitor 1 (PAI-1) in the blood of type 2 diabetic patients. Decreased fibrinolytic capacity caused by overexpression of PAI-1 may also be related to NEFA-induced atherosclerosis in our diabetic patients. Kwok et al. (24) recently reported that linoleic acid and oleic acid increased the endothelin-1 binding and action in cultured rat aortic smooth muscle cells.

Finally, we could not find an association between carotid atherosclerosis and conventional risk factors, including LDL cholesterol, in our unique populations. The reason is unclear, but it may mean that the diabetic state per se is such a powerful factor on the carotid atherosclerosis that the effect of other risk factors is masked (25). Alternatively, it could be the result of the selection of diabetic subjects, because we excluded patients with known obesity, hypertension, cardiovascular disease, or ischemic stroke (26). Mohan et al. (25) recently demonstrated that diabetes and age, but not conventional risk factors associated with increased IMT in South Indian diabetic patients with a BMI of 24.5 kg/m<sup>2</sup>.

In summary, although our cross-sectional study was performed with a limited number of patients ( $n = 54$ ), it can be concluded that levels of serum NEFAs may predict the degree of carotid atherosclerotic plaque in nonobese nonhypertensive well-controlled unique type 2 diabetic patients. Prospective studies should be undertaken to confirm the validity of our findings.

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## COMMENTS AND RESPONSES

### Increased Prevalence of Significant Coronary Artery Calcification in Patients With Diabetes

In a recent issue of *Diabetes Care*, Schurigin et al. (1) demonstrated a twofold increased prevalence of coronary artery calcification in diabetic patients versus age- and risk-matched nondiabetic patients. This finding suggests two important questions that relate to whether such a finding fully correlates with potential coronary artery stenosis in diabetic patients: 1) does electron beam-computed tomography distinguish between intimal (i.e., plaque) calcification and medial calcification? and 2) if such a distinction is possible, then what fraction of the observed densities in diabetic patients was found to be intimal versus medial?

It has long been known (2) that medial calcification (Moenckeberg's Atherosclerosis [MA]) is ubiquitous among diabetic patients and is possibly unique to diabetes. Primarily, it has been studied in the lower extremities, where it is inevitably associated with neuropathy. I have found no reports that speculate on or demonstrate the cause of this condition, but I



During that period, diabetes increased from 5.2 to 8.5% among AI/AN, a 63.5% increase in 8 years. These rates are likely an underestimate of the true rates among this ethnic group. Previous Centers for Disease Control and Prevention studies conducted among AI/AN reported a much higher rate of diabetes. Will et al. (2) reported an age-adjusted prevalence of 22.9% for diabetes among Navajo adults aged  $\geq 20$  years. In a recent study, Burrows et al. (3) reported that the age-adjusted rate of diagnosed diabetes among AI/AN increased from 6.2% in 1990 to 8.0% in 1997, a 29% increase. Clearly, this increase results in serious health challenges for AI/AN populations, as discussed in another recent publication (4).

In conclusion, diabetes is a critical public health problem among all people in the U.S., including AI/AN. To reduce the burden of diabetes among all groups, it is imperative to increase current efforts in diabetes prevention, quality diabetes

care, and patient education. New initiatives may also be required, such as aggressive campaigns to decrease the likelihood of developing diabetes, especially among youth. The development of culturally sensitive programs to facilitate weight reduction among people with diabetes, using a balanced diet and increased physical activity, is also a high public health priority (5).

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## Erratum

Armstrong DG, Nguyen HC, Lavery LA, van Schie CHM, Boulton AJM, Harkless LB: Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care* 24:1019–1022, 2001

The degrees of Drs. Armstrong, Nguyen, Lavery, and Harkless were listed incorrectly in the author list. The correct degrees are as follows:

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