OBSERVATIONS

Progression of the Carotid Artery Intima-Media Thickness in Young Patients With Type 1 Diabetes

Cross-sectional studies of the combined intima-media wall thickness (IMT) of the carotid arteries performed in type 1 diabetic patients show partly contradictory results with regard to variables that are associated with the IMT. Therefore, we observed the IMT progression in a longitudinal study with two follow-ups: *1*) after 2–3 years (mean 2.5 ± 0.4); and *2*) after 4–8 years (mean 6.3 ± 1.4).

A total of 65 type 1 diabetic patients (24 men, 41 women) with ≤40 years of age and a diabetes duration of ≥2 years at baseline were included. Recruitment, characteristics of patients at baseline and the methods used, including ultrasound procedures, have been reported elsewhere (1).

The annual progression rate (APR) of each patient was calculated using the difference of the IMT values at the baseline and the follow-up examinations, divided by the time (in years) between these examinations.

The IMT was significantly higher at both follow-up examinations (0.65 ± 0.14 and 0.70 ± 0.19 mm, respectively) than the baseline measurement (0.57 ± 0.13 mm; mean ± SD; $P < 0.001$). The mean APR was 0.036 mm/year until the first follow-up and 0.020 mm/year until the second follow-up, and it was significantly correlated with these baseline parameters: age, hypertension, systolic blood pressure, ACE inhibitor therapy (all $P < 0.001$), albumin excretion rate, nephropathy (stage IV and overall), and smoking ($P < 0.05$). In a multiple linear regression analysis, besides age, only hypertension as a categorical variable was an independent predictor of IMT progression. This was also the case for women when both sexes were analyzed separately, but in men the only independent predictor of APR was nephropathy stage IV.

Compared with the baseline examination, the HbA_{1c} value was significantly lower (7.9 ± 1.8 vs. 8.8 ± 2.5%, $P < 0.05$) at the time of the second follow-up, and systolic (131 ± 19 vs. 122 ± 16 mmHg, $P < 0.01$) and diastolic blood pressure (83 ± 12 vs. 75 ± 11 mmHg, $P < 0.001$) were significantly higher. The lipids remained unchanged, except for HDL cholesterol, which increased significantly (63 ± 21 vs. 51 ± 18 mg/dl, $P < 0.05$). Significantly more patients presented with hypertension at the second follow-up (34 vs. 13%, $P < 0.05$), compared with the baseline examination, and the frequency of nephropathy (35 vs. 25%), retinopathy (49 vs. 31%), and plaques (34 vs. 21%) also increased without reaching significance.

For young type 1 diabetic patients, diabetes seems not to be the main risk for IMT progression (while a better metabolic control could have a retarding effect on it). Hypertension plays a major role, especially in women, whereas advanced nephropathy as a diabetes-specific risk was confirmed in men only. These results are in concordance with our previous findings (2) but still have to be regarded with caution because of the relatively small number of included patients.

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Inflammatory Parameters Are Independent Predictors of Severe Epicardial Coronary Stenosis in Asymptomatic Diabetic Patients With Silent Myocardial Ischemia

Inflammatory markers (IM) have been associated with the risk of development of coronary artery disease (CAD) in nondiabetic patients (1). So far, no data are available concerning the relationship between angiographically documented CAD and inflammation in the diabetic population. Moreover, recently it has been suggested that in patients with silent myocardial ischemia (SMI), a condition frequently observed in diabetic populations (2), there is a higher production of anti-inflammatory cytokines (3), which suggests that the commonly described association between IM and CAD might not be found in patients with SMI. Therefore, we investigated these markers in diabetic patients who screened positive for SMI and who underwent coronary angiography.

All asymptomatic diabetic patients admitted to our department between January 1999 and April 2001 were considered for SMI screening using exercise-stress and/or dipyridamol 99Tcm-MIBI scintigraphy if they had at least two other major cardiovascular risk factors. A total of 422 patients were screened; 174 had a positive test, and 85 (83% with type 2 diabetes) had a coronary angiography performed by the same angiographer in our hospital. High-sensitivity C-reactive protein, fibrinogen, and leukocyte counts were measured in these 85 patients. Of the 85, 20 patients had no coronary stenoses, 19 had moderate stenosis (<70%), and 46 had severe stenosis (≥70%). The 46 patients with severe stenosis in at least one vessel showed higher levels of fibrinogen than the 20 patients without coronary stenosis and the 19 patients with moderate stenosis (4.10 ± 0.14, 3.40 ± 0.21, 3.49 ± 0.23 g/l; $P = 0.004$ and $P =$

0.03, respectively). A greater proportion of patients with severe stenosis were in the third tertile of CRP levels (i.e., >4.9 mg/l) in comparison with patients with moderate or no stenoses (42.9, 26.3, and 10.5%, respectively, $P = 0.036$). The same trend was noted for leukocyte counts. Among potential confounders (age, sex, smoking, type of diabetes, diabetes duration, HbA_{1c}, hypertension, retinopathy, nephropathy, calculated creatinine clearance, and dyslipidemia), hypertension and albuminuria were the only ones to be significantly associated with CAD ($P = 0.002$ and $P = 0.056$, respectively). However, the associations between IM and severity of CAD remained significant when taking into account these variables.

These data provide evidence that severe epicardial stenosis is associated with a systemic inflammatory profile, even in diabetic patients with SMI (in the absence of unstable coronary syndrome). Further investigations are required to verify these observations and to subsequently determine whether these markers can be a useful tool to select a high-risk subgroup of asymptomatic diabetic patients with SMI who are likely to benefit from coronary angiography and subsequent revascularization.

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Spending in the U.S. on Advertising for Fast Foods, Sodas, and Automobiles

Food for thought regarding the type 2 diabetes epidemic

Type 2 diabetes is approaching epidemic proportions, mostly because of a sharp increase in the prevalence of obesity and the associated insulin resistance (1). Important risk factors in the pathogenesis of type 2 diabetes (sedentary lifestyle, poor diet, and changes in body composition) are essentially modifiable risks related to profound social and cultural changes that have taken place recently in our society. Several reports suggest that our more hectic pace of life, longer working hours, and changes in family roles all reward convenience in eating habits and limit time available for recreation and outside activities (2–10). Greater use of labor-saving devices, including the automobile, further reduce habitual activity levels. Widespread access to mass-produced high-calorie foods that are relatively inexpensive and widely advertised is reported. However, research in this area is in its infancy and more data are needed to support and clarify these assertions.

We focused on the issue of daily exposure to advertising and examined U.S. spending in 2001 on brand advertising via TV, print, outdoor billboard, and radio media that aimed to promote consumption of fast foods, sodas, and confectionery and the use of automobiles. Data were abstracted from an annual report on advertising statistics from TV, newspaper, magazine, outdoor billboard, and radio media in 10 categories and focused on the top 200 U.S. brands (11). Results showed advertising spending for the fast-food category involving nine brands was $3.5 billion. Spending in the separate food, confectionery, and beverages category was an additional $5.8 billion (including $785.5 million for the top five soda brands). Another $15.5 billion was spent in the automobile category. The magnitude of this advertising onslaught on U.S. adults and children in order to promote consumption of products that could be argued to directly and indirectly promote obesity is alarming. By comparison, the total administrative budgets in 2001 for the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) were $5.1 billion and $1.3 billion, respectively.

As a research community, we need to more systematically investigate the societal and cultural forces shaping our eating and exercise habits, including the use of advertising and marketing. Public health strategies, population-based educational programs, and political initiatives could build from this work. The current research focus in type 2 diabetes is on the development of medical treatments for diabetes symptoms and complications and on the basic science groundwork to support a cure. While this work is necessary, it will fail to stem the tide of U.S. adults and children who become insulin resistant as a result of poor eating patterns and sedentary lifestyles. We need to elevate social and cultural factors to the fore and stress primary prevention as strongly as treatment. The role of our current U.S. economic model, business practices, and political institutions has not yet been featured in the debate on our obesity epidemic. Research should clarify the link between these factors and sedentary lifestyles and obesity. Lessons from the fight against smoking teach us that business and politics have a central influence on our health behaviors and healthcare costs.

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Leptin Is Reduced in Lean Subjects With Type 2 Diabetes in Bangladesh

Although leptin levels are increased in obesity (1), obese subjects with type 2 diabetes display reduced leptin (2–4), which may be due to altered fat distribution (5). This study examined whether leptin levels are also reduced in lean subjects with type 2 diabetes.

Fifty nonobese Bangladeshi women with type 2 diabetes (aged 37.2 ± 1.3 years) were selected randomly from the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) outpatient department (28 were on diet and exercise, and 22 were on oral hypoglycemic agents; HbA_{1c} 9.6 ± 0.8%). A total of 50 nondiabetic age- and BMI-matched health professional women (aged 33.4 ± 1.9 years) served as control subjects. Circulating leptin (RIA; Linco, St. Charles, MO), BMI, waist-to-hip ratio (WHR), and mid-arm circumference (MAC) were measured. A 75-g oral glucose tolerance test (OGTT) was undertaken with measurements of glucose and insulin (radioimmunoassay).

Diabetic subjects had lower leptin (11.1 ± 1.6 vs. 16.2 ± 1.9 ng/ml, $P < 0.001$), higher WHR (0.86 ± 0.02 vs. 0.84 ± 0.01; $P = 0.034$), and lower MAC (23.7 ± 0.4 vs. 25.4 ± 0.7 cm; $P < 0.001$) than nondiabetic subjects, without any difference in BMI (22.8 ± 0.4 vs. 23.0 ± 0.6 kg/m^2). Leptin correlated to MAC ($r = 0.46$, $P < 0.001$) but not to WHR ($r = 0.01$). Although fasting insulin did not differ between the groups (84.2 ± 16.6 vs. 92.7 ± 34.2 pmol/l), the 60-min insulin levels during the OGTT were lower in the diabetic subjects (209 ± 22 vs. 467 ± 38 pmol/l, $P < 0.001$) in spite of higher 60-min glucose levels in the diabetic subjects (14.2 ± 4.8 vs. 6.8 ± 2.1 mmol/l; $P < 0.001$). In the diabetic subjects, leptin correlated significantly to fasting insulin independent of BMI ($r = 0.65$, $P = 0.007$).

This shows that lean diabetic subjects also exhibit low leptin levels, as previously observed for moderately obese diabetic subjects (2–4). The lower leptin levels in diabetes might be explained by altered fat distribution, since we observed higher WHR and lower MAC in the diabetic subjects. This is consistent with a higher leptin secretion from subcutaneous fat tissue than from intraabdominal fat tissue (6). Other possibilities also exist, such as the low insulin or different caloric intake, or the degree of physical activity, which was not determined in this study. The lower leptin might be of importance for accumulation of cellular lipids that is associated with diabetes (7).

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MTHFR Gene Polymorphism as a Risk Factor for Diabetic Retinopathy in Type 2 Diabetic Patients Without Serum Creatinine Elevation

Diabetic retinopathy (DR), a serious microangiopathic complication of diabetes, is the leading cause of catastrophic loss of vision in Japan. Methylenetetrahydrofolate reductase (MTHFR) is an enzyme involved in remethylation of homocysteine to methionine. A point mutation (C677T) in the MTHFR gene leads to impaired activity and is the most common genetic determinant of moderate hy-

perhomocysteinemia in the general population (1). Neugebauer et al. (2) reported a significantly higher prevalence of the mutant allele in diabetic patients with retinopathy. However, in their study, patients with retinopathy showed severe renal failure with higher levels of serum creatinine compared with those without retinopathy. Considering that renal failure accelerates atherosclerosis, we investigated the relationship between the MTHFR genotype and DR in 156 type 2 diabetic patients with <133 μmol/l serum creatinine level. According to international standards, patients with retinopathy in each genotype were classified into three groups: no DR (NDR), nonproliferative DR (NPDR), and proliferative DR (PDR). Their genotypes were analyzed using the PCR-restriction fragment–length polymorphism method (3).

The allelic frequency of the C677T mutation was 0.40. Genotype frequencies were in accordance with the Hardy-Weinberg equation (677C/677C, 35.3%, $n = 55$; 677C/677T, 50.0%, $n = 78$; 677T/677T, 14.7%, $n = 23$; χ^2 test, $P = 0.9995$). Statistical analyses showed no association of genotypes with clinical parameters such as sex, age, known diabetes duration, BMI, HbA_{1c}, fasting blood glucose, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, and creatinine (data not shown). The frequency of 677T/677T homozygous patients with retinopathy was the highest among the three genotypes (677T/677T, 60.9%; 677C/677T, 25.6%; 677C/677C, 32.7%; χ^2 test, $P = 0.007$). The frequency of 677T/677T homozygous patients with NPDR was the highest among the three genotypes (677T/677T, 39.2%; 677C/677T, 17.9%; 677C/677C, 18.2%; χ^2 test, $P = 0.03$). This implies that the first signs of DR could appear earlier in 677T/677T homozygous patients than in those with the other two genotypes. These data indicate that the 677T/677T mutation in the MTHFR gene could be an independent risk factor for retinopathy. Based on the previous reports that hyperhomocysteinemia induces endothelial dysfunction, causing angiopathy (4), it is possible that the decrease in serum homocysteine level, such as with a high-folate diet, prevents the onset of DR, especially in diabetic patients with the C677T mutation. In summary, presence of the MTHFR genotype in diabetic patients can be a predictive marker of the progression of DR. Additionally, it is proposed that treatment for diabetes based on the MTHFR gene polymorphism could delay the progression of DR.

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A Low Glycemic Diet Significantly Improves the 24-h Blood Glucose Profile in People With Type 2 Diabetes, as Assessed Using the Continuous Glucose MiniMed Monitor

Low glycemic index (LGI) diets have been shown to improve glucose tolerance in clinical studies; however, this does not necessarily ensure similar effectiveness when given to free-living individuals making their own food choices. This concern was reflected in the current position of the American Diabetes Association (1) in that "although LGI foods may reduce postprandial hyperglycemia, there is insufficient evidence of long-term benefits to recommend general use of LGI diets in type 2 diabetic patients." Despite this, the glycemic index (GI) method for classifying carbohydrates has been endorsed by a number of influential bodies, including the Food and Agriculture Organization of the United Nations/World Health Organization joint committee. Commonly consumed LGI foods include pasta, noodles, and fruit; however, others such as lentils, beans, and peas have limited acceptance. In a previous study (2), we successfully used the substitution of a key carbohydrate food at each meal to reduce the overall GI of the diet.

The MiniMed continuous glucose monitoring system (CGMS) is based on the electrochemical detection of subcutaneous interstitial fluid and can be operated in situ for up to 3 days (3). It records values in a pager-sized monitor every 5 min, providing 288 glucose readings every 24 h.

The aim of this study was to examine the effects of an LGI diet consumed for 7 days by free-living patients with type 2 diabetes who were monitored for two 24-h periods using the CGMS.

A total of 18 people who were attend-

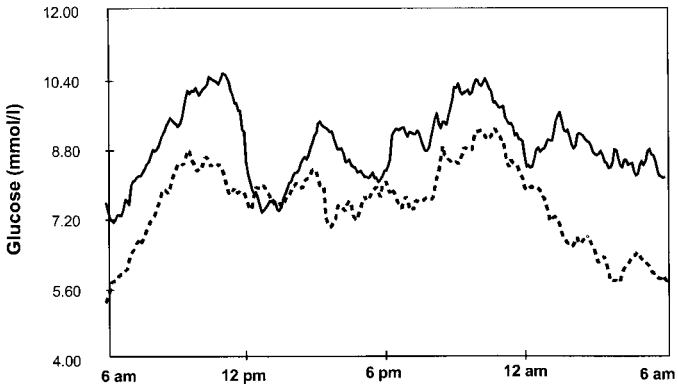

Figure 1—*Mean 24-h AUC for glucose at baseline (——) and in response to an LGI (----) after 7 days* (n = *11*).

ing Hammersmith Hospitals Trust diabetes clinic for treatment of type 2 diabetes agreed to participate. Four people dropped out. Of the final 14 participants (aged 54 ± 7 years, HbA_{1c} 8.1 ± 1.4%, and BMI 39.0 ± 13.5 kg/m^2), 6 patients were receiving insulin in addition to oral hypoglycemic agents. No change in medication occurred over the study period.

A reduction in the GI of the diet occurred during the 24-h monitoring period (57 ± 2 vs. 49 ± 1, $P < 0.001$) in 11 of 14 subjects, whereas energy and other macronutrients remained constant. In these 11 patients there was a significant reduction in fasting glucose at 6 A.M. (8.0 ± 1.0 vs. 5.3 ± 0.8 mmol/l, $P < 0.01$), mean glucose (8.9 ± 1.0 vs. 7.5 ± 0.1 mmol/l, $P < 0.02$), 24-h area under the curve (AUC) for glucose (12,844 ± 1,354 vs. 10,839 ± 832 mmol/l per min, $P < 0.04$), and overnight 8-h AUC glucose (4,315 ± 590 vs. 3,428 ± 261 mmol/l per min, $P < 0.05$) (Fig. 1).

Our study highlights the benefits of an LGI diet in free-living patients with type 2 diabetes and the potential for CGMS to provide valuable information on glycemic excursions that would be missed by more conventional monitoring. An LGI diet can dramatically improve a patient's glycemic control within a short period; if achievable over the longer term, this may contribute to a decrease in diabetic complications.

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COMMENTS AND RESPONSES

Diabetes and Cholesterol Metabolism

The succinate hypothesis

In the recent article by Simonen et al. (1) demonstrating increased cholesterol synthesis in obese patients with diabetes, the authors did not consider a possible mechanism suggested by the "succinate hypothesis," which is elegantly summarized by Fahien and MacDonald (2) in a separate article. Fahien and MacDonald showed that succinate esters are potent insulin secretagogues (almost as potent as glucose) through generation of succinyl-CoA (S-CoA). This seemed to be specific to S-CoA, since other citric acid cycle (CAC) molecules (malate, α-ketoglutarate, fumarate, and citrate) did not promote insulin release. S-CoA stimulates the enzyme succinyl-CoA-acetoacetate transferase (reaction 3, Fig. 1) to increase the production of aceto-acetyl-CoA, which can be utilized to form hydromethylglutaryl (HMG)-CoA, and mevalonate-biosynthetic precursors of cholesterol. In fact, the authors postulate that insulin release is triggered by production of mevalonate.

If this same pathway occurs in the liver, then the increased glucose of diabetes would be metabolized to pyruvate that can then enter the mitochondria. Conversion to acetyl-CoA and oxaloacetate by

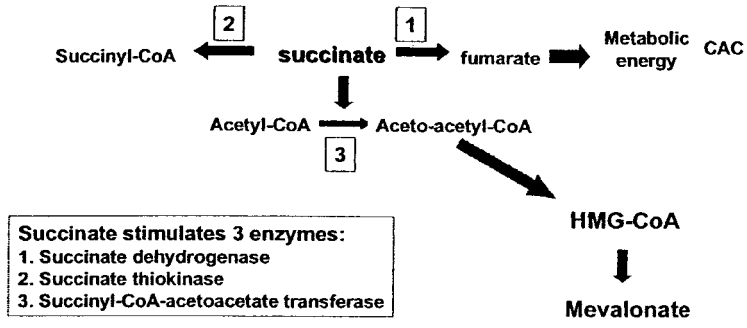

Figure 1—*A simplified scheme for the interaction between succinate and HMG-CoA metabolism (modified from Fig. 1, ref. 2).*

pyruvate dehydrogenase and pyruvate carboxylase would lead to increased production of acetyl-CoA and succinate that could result in increased production of HMG-CoA, mevalonate, and, presumably, cholesterol (Fig. 1).

Several authors have shown that cholesterol absorption is decreased and that cholesterol biosynthesis is increased in diabetes (3). The increased cholesterol synthesis is reduced by insulin (4). Since either metabolic alteration could be primary, and the other follow pari passu, it would be important to identify the initiating event in the hyperglycemic state. The succinate hypothesis would then suggest that the increased synthesis of cholesterol is primary. The data in the article by Simonen et al., which show a tighter correlation between glucose levels and increased cholesterol synthesis than with decreased cholesterol absorption, also support the primary role of synthesis.

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Diabetes and Cholesterol Metabolism

The succinate hypothesis

Markedly increased cholesterol synthesis and low absorption of cholesterol in our obese patients with type 2 diabetes (1) prompted Dr. Ertel (2) to question whether the "succinate hypothesis" could explain the changes in cholesterol metabolism.

According to the succinate mechanism, summarized by Fahien and MacDonald (3), a basic requirement for insulin release would be the generation of mevalonic acid. This would be regulated by insulinotropic action of succinate and other nutrient secretagogues through several intracellular metabolic (cytosolic and mitochondrial) reactions in islet and apparently also hepatic cells. Intact pancreatic islets synthesize and metabolize mevalonate, the production of which results in the release of insulin from islet cells. Lovastatin and simvastatin, inhibitors of mevalonate production, can inhibit glucose-induced release of insulin from islets, which can be prevented by mevalonate (3). Accordingly, statin treatment, especially the use of long-term ones, should be associated with decreased insulin secretion and perhaps reduced development of diabetes. No exact insulin measurements have been performed during statin treatments, but in one study, the development of diabetes appeared to be reduced by statin (4).

Ertel (2) assumed, according to the succinate mechanism, that the metabolism of pyruvate is enhanced in hepatic mitochondria of diabetes, resulting in increased production of hydroxymethylglutaryl (HMG)-CoA, mevalonate, and cholesterol, apparently in the presence of obesity and excess insulin. It should be emphasized that this also might occur during normal conditions without diabetes or obesity. Namely, nondiabetic men with blood glucose in the highest tertile have higher cholesterol synthesis, lower cholesterol absorption, and a lower insulin sensitivity index (despite having higher insulin) than those with blood glucose levels in the lowest tertile (5). This indicates that cholesterol metabolism is changed proportionately to insulin resistance, reaching higher levels in overweight and obesity. Additional change in altered cholesterol metabolism is probably seen proportionately to insulin resistance also by diabetes, as demonstrated in the article by Simonen et al. (1). Since overweight conditions without and with diabetes increase hepatic synthesis of not only cholesterol, but also of triglycerides, the succinate mechanism could cover lipid and also fatty acid metabolism in a larger scale. However, the mechanism of reduced cholesterol absorption efficiency still remains open.

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