OBSERVATIONS

Status of Research Funded by the American Diabetes Association—Year 4

In 1998, the American Diabetes Association (ADA) announced an ambitious Five Year Plan for funding for research, namely that by Fiscal Year 2003, one of every three Total Public Support dollars raised by the ADA would be allocated to Research Awards and Grants. Since 1998, I have kept the Professional Section apprised of progress toward that goal by yearly letters published in this journal. The results of the 4th year, Fiscal Year 2002, are included in Table 1.

The reason for keeping the Professional Section informed of progress (or lack thereof) toward the stated goal is past observations. I have been involved with the ADA since 1972, and in my experience, research funding goals are rarely reached. In the early 1980s, ~20% of funds were allocated to research. A goal of 100 million dollars for research was established, to be attained by the end of the decade. Throughout the decade, the proportion of monies given to research remained at ~20%, with absolute amounts increasing from 2.6 to 7.0 million dollars. Toward the end of the decade, the 100 million dollar goal by 1990 was revised, so that attaining it did not have to occur until 1993.

Apparently, the impossibility of reaching this goal was realized and the next research goal, stated in the early 1990s, was that "nearly 30%" of funds would be allocated to research. However, the commitment to research, which was 23% of Total Public Support in Fiscal Year 1988, declined to less than 11% in Fiscal Year 1992. The absolute amount in 1992 of 5.9 million dollars increased to 12.8 million dollars (or 14% of total public support) in 1997. The situation in 1998 when the "one in three" dollars goal was stated is noted in Table 1.

It is obvious that we are not going to come close to "one in three" dollars of Total Public Support going to Research Awards and Grants by the end of the 5th year. There are two ways to consider this; the "half-empty or half-full glass" scenarios. I view this as a "half-empty glass" in that we make commitments that we can't realistically meet. On the other hand, John Graham, the ADA's Chief Executive Officer, views this as a "half-full glass." He points out that without these very ambitious goals, we would not have come as far as we have.

That is the history and current situation regarding funding for Research Awards and Grants by the ADA. Professional Section members might want to weigh in concerning which approach they favor before the next Five Year Plan for research funding is decided.

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Table 1—*Total public support*

Fiscal year	Total public support (millions of dollars)	Amount devoted to research (millions of dollars)	%
1998	90.8	15.5	17.1
		Clock starts ticking	
1999	101.5	18.2	17.9
2000	117.8	22.4	19.0
2001	134.6	27.4	20.4
2002	146.3	31.7	21.7
2003	—	—	≥33.0?

Validation of Interstitial Fluid Continuous Glucose Monitoring in Cystic Fibrosis

Diabetes is a complication of cystic fibrosis (CF) that is of growing clinical importance. The recognition of diabetes complications in CF subjects (1) has emphasized the need for more accurate monitoring of glycemia. This is complicated by the many factors affecting glycemia in CF subjects, ranging from the consequences of malabsorption to the caloric burden of supplemental nutrition, as well as the metabolic effects of infection and drugs (2). The recent introduction of devices that provide a continuous glucose profile has revealed clinically relevant excursions in glycemia previously overlooked by conventional measures (3). They are able to provide the detailed glucose profile required in CF patients before and after an established diagnosis of cystic fibrosis–related diabetes (CFRD). Many of these new methods rely on sampling glucose levels in interstitial fluid and its correlation with plasma glucose. They have been shown in non-CF subjects to be strongly correlated with capillary and plasma glucose values (4–8). However, an individual continuous glucose monitoring system (CGMS) value may differ considerably from plasma glucose measured simultaneously (9). Altered subcutaneous tissue composition in CF might affect cellular and interstitial fluid kinetics and reduce the reliability of these devices. To date, the validity of these devices in CF patients has not, to our knowledge, been tested.

We recruited 21 (14 male, age 27 ± 12 years [mean ± SD]) nondiabetic CF subjects age-matched with 21 (8 male, age 29 ± 8 years) nondiabetic non-CF control subjects. After an overnight fast each subject underwent insertion of a CGMS (MiniMed, Sylmar, CA) followed by an Oral Glucose Tolerance Test (OGTT). The CGMS remained in place for another 48 h before it was removed, and the data were downloaded. During this time capillary blood glucose (CBG) samples were performed four times each day using a Precision Glucose Sensor (MediSense), and the values were entered into the CGMS. Any subjects with <24 h of data were excluded from analysis. There were no adverse events and tolerability of the device was excellent in both groups.

Comparison of paired CBG/CGMS values revealed a correlation coefficient of 0.77 ($P < 0.001$) for the CF group and 0.70 ($P < 0.001$) for the control group. The mean absolute difference (mean ± SD) between the CBG/CGMS values was 10.7 ± 8.7% for the CF group and 10.5 ± 8.7% for the control group.

Paired venous/CGMS values, ob-

tained in 14 CF subjects and 15 control subjects, revealed comparable yet weaker correlation coefficients of 0.57 ($P < 0.001$) and 0.36 ($P < 0.001$) for the CF and control groups, respectively. The mean absolute difference between the venous/CGMS samples was 24.9 ± 21.0% for the CF subjects and 28.8 ± 22.9% for the control subjects. Individual data revealed stronger correlation coefficients, with a median of 0.94 (range 0.42–0.99) in CF subjects and 0.86 in control subjects (0.44–0.98). Ten of 14 CF subjects and 11 of 15 control subjects had a correlation coefficient >0.8. The mean CGMS values were highly correlated with the mean plasma glucose values at each of the five points of the OGTT (correlation coefficient CF 0.94 [$P = 0.005$], control 0.93 [$P = 0.008$]). These results are consistent with previous studies in non-CF subjects, which have shown that CGMS in an individual reflects the trend but not the absolute value in plasma glucose (9). However, the the mean values obtained by CGMS for a group of subjects will closely reflect the mean of simultaneous plasma values.

We conclude that this CGMS method is well tolerated in CF and that the correlations seen between capillary and plasma glucose values are similar to those seen in the non-CF patients. The CGMS is therefore appropriate to use in CF. However, as in non-CF patients, the mean absolute difference between CGMS and plasma means caution is needed when interpreting solitary CGMS values.

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The Effect of Oral Glucosamine Sulfate on Insulin Sensitivity in Human Subjects

As glucosamine is presently in wide use due to its purported beneficial effects in patients with osteoarthritis, it seemed important to consider its possible adverse effects on glucose metabolism. Many subjects who take glucosamine for osteoarthritis are obese, insulin resistant, diabetic, or at risk for the development of diabetes, and it is established that glucosamine induces insulin resistance in rats and mice. Hypotheses suggest that glucosamine causes insulin resistance by directly entering the hexosamine biosynthetic pathway. It has been proposed that this provides a model for glucotoxicity-induced defects in insulin action and secretion (1), since, under hyperglycemic conditions, a larger amount of glucose flux is metabolized through the hexosamine pathway. Therefore, we undertook this study to determine if glucosamine, taken at recommended doses for the treatment of osteoarthritis, had any detrimental effect on glucose metabolism.

Seven obese (BMI ≥27 kg/m^2) and seven lean subjects (BMI ≤27) participated in the study. Three of the obese subjects and two of the lean subjects had impaired glucose tolerance (IGT). Each subject had a baseline 4-h meal tolerance test (MTT) and a frequently sampled intravenous glucose tolerance test, before and after 4 weeks of glucosamine sulfate (500 mg, three times/day).

At baseline, fasting plasma glucose and insulin levels were 5.4 ± 0.3 mmol/l and 14.4 ± 3.6 μU/ml in the obese subjects compared with 4.8 ± 0.3 and 10.8 ± 4.9 in the lean subjects, respectively. After 4 weeks of treatment with glucosamine sulfate, there were no changes in fasting plasma glucose, insulin, or lipoprotein levels.

After 4 weeks of treatment with glucosamine sulfate, there was no change in the area under the 4-h plasma glucose curve (AUC_{gluc}) (1,551 ± 55 vs. 1,539 ± 55 mmol · l^{-1} · min^{-1}) and the 4-h MTT plasma insulin curve (AUC_{ins}) (17,903 ± 8,745 vs. 17,861 ± 9,406 mU/l · min) in all subjects.

Insulin sensitivity was significantly reduced at baseline in the obese compared with the lean subjects (lean: 3.58 ± 0.6; obese: 1.2 ± 0.4 × 10^{-4} min^{-1} · μU^{-1} · ml^{-1}; $P < 0.01$). After 4 weeks of treatment with glucosamine, there was no difference in insulin sensitivity in the combined group of subjects (2.37 ± 0.46 vs. 2.55 ± 0.58; $P = 0.67$), nor was there any difference when the subjects were analyzed according to BMI (obese or lean) or glucose tolerance (normal glucose tolerant or IGT).

Although there are many studies showing that acute or chronic administration of glucosamine and activation of the hexosamine pathway can cause insulin resistance, few studies on humans exist. Monauni et al. (2) reported that acute, short-term (6-h) intravenous glucosamine infusion had no detectable effects on glucose metabolism during a euglycemic clamp. Similarly, Pouwels et al. (3) reported that a 5-h infusion of glucosamine did not affect whole-body glu-

cose uptake in human subjects. To date, there have been no studies on the chronic effects of oral glucosamine on insulin sensitivity.

We did not measure plasma glucosamine levels or metabolites of the hexosamine pathway, and, as such, it is possible that the glucosamine load given to our subjects may have been insufficient to produce insulin resistance. However that was not the intent of this study. We wanted to determine whether the recommended dose of glucosamine for treatment of osteoarthritis was detrimental to glucose metabolism in humans, and our data indicate that it is not. Given the common usage of glucosamine supplementation in insulin-resistant and other susceptible populations, these negative findings have significant clinical interest. Based on our results, we think it is unlikely that long-term treatment regimens or the use of glucosamine in diabetic subjects would lead to adverse effects on glucose metabolism. However, since we did not study these specific conditions, definitive conclusions on these issues warrant further study.

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Multiple Tumors in Mitochondrial Diabetes Associated With tRNA$^{Leu(UUR)}$ Mutation at Position 3264

In 1997, we reported the first identified case of mitochondrial diabetes caused by a T-to-C transition at position 3264 (1). The proband was a 64-year-old man. His family tree revealed maternally inherited diabetes. He had diabetes, cerebellar ataxia, hearing loss, olfactory dysfunction, bilateral facial nerve palsy, oculomotor palsy, and cervical lipoma. Heteroplasmy of the 3264 mutation, maternal inheritance of diabetes, absence of 3264 mutation in control subjects, and symptoms related to mitochondrial dysfunction suggested that this 3264 mutation was pathogenic.

During a 6-year follow-up period, he developed left-sided hearing loss and had an acoustic neuroma at age 68 years (13 mm × 15 mm). He died at age 70 years of hepatic failure due to hepatocellular carcinoma. Hence, during his lifetime, this patient experienced multiple tumors (gastric cancer, hepatocellular carcinoma, benign lipoma, and acoustic neuroma). Furthermore, it is noteworthy that his five brothers and sisters, who died after age 30 years, all died of malignancies, i.e., gastric cancer, hepatocellular carcinoma, prostate cancer, and laryngeal cancer.

Evidence has recently accumulated indicating that mitochondrial abnormalities may play important roles in tumorigenesis. Amuthan et al. (2) suggested a new pathway by which mitochondrial DNA and membrane damage may contribute to tumor progression and metastasis. Fumarate hydratase and succinate dehydrogenase are mitochondrial enzymes functioning in the tricarboxylic acid cycle. Mutations of these enzymes reportedly cause leiomyomatosis and hereditary paragangliomas, respectively (3,4). Because mitochondria are key organelles in the induction of oxidative stress and control of apoptosis (5,6), and because the development of four types of tumors in an individual with a rare mitochondrial disorder is unlikely to be a coincidence, we speculate that mitochondrial dysfunction due to the 3264 mtDNA mutation might have induced oxidative stress associated with tumorigenesis, or render tumor cells susceptible to disordered caspase cascades, in our patient.

In conclusion, although a single case study is insufficient to determine pathogenesis, the present case does suggest associations among mitochondrial dysfunction, diabetes, and tumorigenesis.

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Value of a Grocery Cart and Walker in Identification and Management of Symptomatic Spinal Stenosis in Diabetic Patients Presenting With Peripheral Neuropathy or Claudication

Lumbar spinal stenosis (SS) may produce symptoms similar to and frequently mistaken for diabetic peripheral neuropathy (DPN). Both axial loading (1), as seen with walking, and spinal extension (2), seen in an erect position, decrease the diameter of both the central spinal canal and lateral recesses. Common extremity symptoms include neurogenic-induced claudication (of the legs) and neurogenic positional pedal neuritis (of the feet) (3), and are frequently reduced by flexion of the spine, facilitated by leaning forward on a grocery cart (4) or wheeled walker.

A "Grocery Cart Test" (3) (the comparison of walking distance and time with and without wheeled support) is utilized in our private practice to investigate possible SS in patients presenting with DPN (including walking limitation) or claudication. Of patients later confirmed to have SS, most over 5′4″ reported good improvement (>75%) in uninterrupted walking duration and distance using a grocery cart. Patients with SS under 5′4″ do not consistently improve with a grocery cart (42″ handle), and those under 5′2″ do not consistently improve with a standard-size walker (34″ handle), as they do not necessarily flex the spine to hold the handle. A shorter walker (cut down to a 30″ handle) provided improvement for shorter patients (4′10″ to 5′2″). We noted that to maximize flexion, some patients rest their forearms on the transverse bar of a grocery cart handle, something not possible with a walker with two separate handles. Our patients with classic arterial claudication symptoms, including relief of claudication by standing and the ability to stand erect without extremity symptoms, did not improve significantly (>50%) with the cart.

This appears to be a useful screening method to identify symptomatic SS in patients presenting with DPN or claudication. It is also an effective guide to educate patients regarding the effect of spinal mechanics on their activity level, and can assist in convincing appropriate patients to accept the use of a walker as part of their lifestyle. Many patients subsequently reported a greatly increased activity level and freedom of movement after using a three- or four-wheeled walker of an appropriate height, and some reported reduced neuritic pain. Clinical use of this information and further investigation is indicated.

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Increasing Pneumococcal Immunizations Among People With Diabetes Using Patient Reminders

People with diabetes are at high risk for morbidity and mortality from influenza and pneumonia (1). Both the Centers for Disease Control and Prevention and the American Diabetes Association recommend that individuals with diabetes receive a pneumococcal and an annual influenza immunization regardless of age (2,3). Although the prevalence of pneumococcal immunizations among people with diabetes has increased, the level is still suboptimal, particularly among those aged <65 years (4). Efforts to increase the coverage level of immunizations in adults have largely been directed toward those ≥65 years of age who are Medicare beneficiaries (5,6). Thus clinicians and younger individuals with diabetes may be less likely to consider pneumococcal immunization. Several interventions have been shown to increase adult immunizations, including provider and patient reminder/recall, assessment and feedback to physicians, and standing orders for immunization (7). This report describes a quality improvement effort to increase pneumococcal immunizations in people with diabetes using a simple computerized diabetes monitoring system to facilitate patient reminders.

The Montana Department of Public Health and Human Services began to work in collaboration with three practices in Great Falls, MT, to monitor and improve diabetes care. The settings included a multispecialty practice, a community health center, and an Indian health center. Each of these practices used the Diabetes Care Monitoring System (DCMS), an electronic data system developed for primary care practices to track the delivery of care to patients with diabetes (8). Briefly, patients were identified in the electronic billing system at each practice at baseline. Patients who had one or more diabetes-related (ICD-9-CM 250.x–250.9) office visits in the 12-month period before installing the DCMS were included. Demographic information, the most recent dates and results for selected

tests and examinations, and the dates of the last influenza and pneumococcal immunizations were abstracted from each patient's medical record and entered. After installation, information about newly identified patients with diabetes was added to the system as they presented for care. A one-page patient summary was generated and placed in the medical record to highlight services due at the next office visit. This sheet became a template for updating the computer-based data, thus making current information available for each subsequent visit. The DCMS readily produced lists identifying all patients whose records did not reflect a specific service, such as pneumococcal immunization. As of December 2002, there were 1,857 patients with diabetes being monitored in these clinics, including 1,591 in the multispecialty practice, 186 patients in the community health center, and 80 in the Indian health center. The mean (±SD) age of patients was 60.7 ± 16.3 years, and 53% were women.

In 2001, each of these three primary care practices used DCMS to monitor care, but none conducted any special outreach for immunizations. In fall 2002, each practice generated provider-to-patient letters for patients not known to have received a pneumococcal immunization. Both of the health centers used personalized letters signed by the clinical team. The multispecialty practice sent personalized reminder letters to their patients aged <65 years, and sent a generic reminder letter to all patients (with and without diabetes) aged ≥65 years.

To assess the effectiveness of this intervention, we conducted a time series evaluation over three time periods: September to December 2001, January to August 2002, and the intervention time period, September to December 2002. χ^2 tests were used to compare the proportion of patients with a pneumococcal immunization between the three time periods. We also compared the proportion of patients with a pneumococcal immunization by age to assess the effect in both older (aged ≥65 years) and younger patients (aged <65 years). Data analyses were performed using SPSS version 8.0 software (Chicago, IL).

Overall, the proportion of patients with a pneumococcal immunization increased by six percentage points between September and December 2001 (34–40%) and by one percentage point from January to August 2002 (40–41%). However, between September and December 2002, when patient reminders were sent, the overall proportion of patients with a pneumococcal immunization increased by 12 percentage points (41–53%), which was a significantly greater increase compared to the previous time periods ($P < 0.001$). Between September and December 2001, when no reminder intervention was used, the proportion of pneumococcal immunizations in patients aged ≥65 years increased six percentage points, and in those aged <65 years, the proportion increased five percentage points. In the following months (January to August 2002), there was a three– and less than one–percentage point increase in the proportion of older and younger patients with a pneumococcal immunization, respectively. During the intervention period, there was a 10–percentage point increase for patients aged ≥65 years and a 13–percentage point increase among patients aged <65 years. Both increases were significantly greater than those from the prior time periods ($P < 0.001$). Between September and December 2002, the percentage point increase in pneumococcal immunization increased in each of these practices (4, 14, and 21 percentage points) and two of the three practices (the largest and smallest) made statistically significant improvement in the overall proportion of patients immunized ($P < 0.05$).

Of the 1,857 patients with diabetes receiving care in these clinics during the intervention period, 778 had a pneumococcal immunization documented before September 2002. Of the 1,079 remaining patients not known to have a pneumococcal immunization, 525 (49%) had one or more clinic visits from September through December 2002 and 203 (39%) of these patients received a pneumococcal immunization during this period.

The use of a simple office-based electronic monitoring system to produce patient reminders was effective in increasing pneumococcal immunizations among both younger and older patients with diabetes in different practice settings. Patient reminders for immunization clinics generated in managed care settings have also been shown to increase pneumococcal immunization among individuals with diabetes (9). Continued effort will be needed to reach the Year 2010 National Health Objectives of a 90% pneumococcal immunization level among patients with diabetes aged ≥65 years, and 60% among patients with diabetes aged <65 years (10). The objectives are ambitious but attainable through using simple strategies to alert patients with diabetes of the need for immunization and to help practices provide the immunizations in a systematic way.

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Physical Signs of the Intrinsic Minus Foot

A recent article in *Diabetes Care* (1) reminded me that I have never seen in publication a full list of the clinical signs of the so-called "diabetic" or "intrinsic minus foot" that can be discerned on physical examination. It is the purpose of this letter to describe these signs, most of which are present in severe cases.

The term "intrinsic minus foot" was first coined by my long-term teacher and colleague, Heinz I. Lippman, MD, in 1976 (2). The longest motor nerves are those that activate the intrinsic muscles of the foot (lumbricals). Since diabetic neuropathies progress from distal to proximal, the lumbricals are the first muscles to be affected by neuropathy. The characteristics of the intrinsic minus foot that can be discerned on simple physical examination are described below.

1. Hammer toes: the lumbricals wrap around the toes in such a fashion that they extend the interphalangeal (i-p) joints and flex the metacarpal-phalangeal (m-p) joints. When they are denervated, the opposing muscles will cause flexion of the i-p joints and extension of the m-p joints with the resultant hammer toes.

2. Prominent plantar metatarsal heads: extension of the m-p joints causes the appearance of visible and palpable bony prominences on the bottom of the foot, at the base of each toe. At first, these prominences are found only at the bases of the first and fifth toes, but as neuropathy progresses, all of the toes are affected and calluses can be palpated under each metatarsal head.

3. Wasting of lumbricals: the lumbricals originate on the distal metatarsal bones on one side of each toe, wrap around the toe, and insert in the opposite side of each metatarsal. When sufficiently wasted by denervation, visible channels appear on the dorsum of the foot between the metatarsals. Contrary to the results of the referenced study (1), observations in our clinic of hundreds of patients with wasted interossei have shown that hammer toes are inevitably apparent when visible atrophy is present.

4. Upward rotation of the forefoot: extension of the m-p joints eventually leads to upward rotation of the entire forefoot. This can be quantified and tracked over time by placing a rigid ruler against the forefoot under the second toe so that it extends below the heel. The distance from the heel to the ruler can then be measured with a second ruler, perpendicular to the first.

5. Distal migration of the plantar metatarsal fat pads: normally these fat pads are thick enough under the metatarsal heads that they can be pinched by the examiner. Over time, weight bearing at these prominent sites will cause distal migration of fat so that it can no longer be pinched over the metatarsal heads but instead can be pinched more distally.

6. Weak extension of the hallux longus (great toe): normally the strengths upon extension and flexion of the toe are approximately equal (balanced). When the lumbricals are weakened, extension from the rest position may weaken because the toe is already fully extended. Weak flexion is also possible. This can be readily discerned by offering passive resistance to both directions of motion and estimating the force of each.

7. Cock-up deformity of the hallux longus with prominent extensor tendon: the impaired flexion at rest can cause the distal end of this toe to be visibly higher than the other toes. When this occurs, the extensor tendon of this toe is usually visibly prominent.

8. High arch: this feature is common in patients with intrinsic minus feet but cannot be attributed directly to atrophy of interossei. It clearly relates to tightening of the plantar fascia. The fascia then acts like a bowstring to flex the bones of the longitudinal arch. The fascia may be stretched by the upward rotation of the forefoot. It may also be shortened by glycation, as found in the palmer tendons of Duputreyn's Contracture.

9. Xerotic skin: inevitably seen in individuals with the intrinsic minus deformity. Dry skin is secondary to another condition, sympathetic neuropathy.

The above complex of visible and palpable signs is based on the observation of many patients over >20 years at a university-affiliated clinic devoted to foot pathology in a major New York City hospital.

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The Ability of Foot Compensation to Added Weight Is Reduced in Patients with Diabetic Neuropathy

The foot, via its structure, has the ability to adapt to various conditions, such as increased body weight and walking on uneven terrain. It is also well known that diabetic foot ulcers occur at sites of high plantar pressures that result from an alternate foot structure due to diabetic neuropathy. The most common sites of ulceration occur under the metatarsal heads and the plantar aspect of the big toe.

The aim of this study was to observe the peak plantar pressures and contact times at the above anatomical sites under the effect of increased weight in patients with diabetic neuropathy.

We recruited two groups of type 2 diabetic patients. Group A ($n = 10$) was composed of patients with diabetic neuropathy (vibration perception threshold [VPT] >25 V, insensitivity 5.07 SW monofilament 10 g), and group B ($n = 10$) was composed of patients without neuropathy, comparable in age, sex, BMI, and duration of diabetes. Using the FootScan RS International barefoot pressure measurement system, peak plantar foot pressures were compared under three conditions. Baseline (C1) involved measurements without any additional weight. The second and third test conditions involved pressure measurements with an additional 5 kg (C2) and 8.5 kg (C3), respectively, evenly distributed in the pockets of a workout vest. Data recorded from under the metatarsal heads and big toe were used for analysis, and the mean peak pressures (MPP) in N/cm^2 and mean contact times (MCT) in milliseconds were obtained.

Differences among groups regarding continuous variables were analyzed with Student's *t* test or Mann-Whitney *U* test and Fisher's exact test for categorical variables, as appropriate. Differences in MPP and MCT during the three test conditions were estimated by Friedman's and Wilcoxon's tests. $P < 0.05$ (two tailed) was considered significant. In group A there was a significant increase in mean peak plantar foot pressures for each incremental increase of weight (MPP: $P < 0.001$, C1 vs. C2: $P = 0.017$, C1 vs. C3: $P = 0.005$, C2 vs. C3: $P = 0.005$). The mean contact times were also significantly increased in patients with diabetic neuropathy (MCT: $P = 0.007$, C1 vs. C3: $P = 0.037$, C2 vs. C3: $P = 0.022$). In group B, there were no statistically significant differences between the three conditions (MPP: $P = 0.74$, MCT: $P = 0.57$).

The amount of increased weight must play a key role in the peak plantar pressures. With a relatively low amount of increased weight, in contrast to previous reports (1,2), our study suggests that there must be a factor or mechanism that makes the foot able to compensate for this added weight in non-neuropathic subjects. There must be an individual cutoff point for this "compensation," but this requires further investigation. In addition, our study suggests that the ability of foot compensation to added weight must be lost or reduced in neuropathic patients.

Patients with long-term diabetes and neuropathy have been noted to have fine structural changes in their Achilles tendons when observed under electron microscopy (3). This suggests that structural reorganization could be the result of nonenzymatic glycosylation (NEG). Increased rates of NEG reduce the shock-absorbing capacity of plantar tissues. Limited joint motion (LJM) is often associated with neuropathy (4,5), and when this mobility is impaired by NEG of collagen, the foot can no longer function as a mobile adapter. As the joints cannot move adequately to accommodate for increased weight, shearing forces increase.

Collectively, dysfunction of foot compensation in added weight results in elevated mean peak plantar pressures and mean contact times in patients with diabetic neuropathy.

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Vietnamese Type 2 Diabetic Subjects With Normal BMI but High Body Fat

Subjects with type 2 diabetes often have high percentages of BMI, abdominal fat, and body fat (BF%). The accumulation of fat in the body is a continuous process and has a strong effect on insulin resistance and type 2 diabetes (1,2). However, knowledge about diabetes in Vietnamese is still scarce. The aim of this study was to determine the anthropometric features of diabetes in Vietnamese.

Forty-eight newly diagnosed type 2 diabetic subjects and 96 nondiabetic control subjects, matched for age, sex, and locality, participated in the study. Weight, height, waist, and hip measurements were taken to calculate BMI and waist-to-hip ratio (WHR). BF% was also recorded. All statistical analyses were done with SPSS version 9.0.

In comparison with the control subjects, the diabetic subjects had a similar BMI (22.5 ± 3.4 vs. 22.9 ± 3.7 kg/m^2)

but a significantly higher WHR (0.91 ± 0.07 vs. 0.86 ± 0.08; $P < 0.01$) and BF% (31.1 ± 5.8 vs. 27.7 ± 6.2; $P < 0.001$). After using multiple regression analysis, the diabetic group showed positive associations with WHR (odds ratio 2.7, 95% CI 1.3–5.5) and BF% (2.6, 1.2–5.4).

Our study showed that for the Vietnamese, abdominal fat accumulation and BF% were risk factors for diabetic subjects even though their BMI level was normal. According to previous studies, there is a close relationship between BMI and diabetes (2) as well as a correlation between BMI and BF% (3). However, some diabetic patients who are not obese may have an increased BF% distributed predominantly in the abdominal regions (1). It is suggested that our findings may be characteristic of Vietnamese diabetic subjects. Further investigation is required to determine why Vietnamese subjects have normal BMI levels but exhibit a high accumulation of abdominal fat and possess a high BF%.

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COMMENTS AND RESPONSES

No Association Between the MTHFR Gene Polymorphism and Diabetic Retinopathy in Type 2 Diabetic Patients Without Overt Nephropathy

Maeda et al. (1) have recently demonstrated that the presence of the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene in diabetic patients can be a predictive for diabetic retinopathy (DR), especially nonproliferative DR (NPDR). We also genotyped the MTHFR polymorphism (C677T) in 366 type 2 diabetic patients without overt nephropathy, and no such association was found. The subjects had a mean age of 60.0 years, duration of diabetes of 11.7 years, HbA_{1c} of 7.3%, and serum creatinine of 0.71 mg/dl. The patients with urinary albumin excretion >300 mg/g creatinine were excluded. The allelic frequency of the C677T mutation was 0.39, and the genotypes were in Hardy-Weinberg equilibrium (677C/677C, 36.3%, $n = 133$; 677C/677T, 49.7%, $n = 182$; and 677T/677T, 14.0%, $n = 51$), similar to those in their study. Of our 366 diabetic patients, 14.2% ($n = 52$) had NPDR and 12.6% ($n = 46$) had proliferative DR (PDR). The remaining 73.2% ($n = 268$) had no DR. There was no association between the genotypes and clinical parameters such as age, duration of diabetes, HbA_{1c}, serum lipids, and serum creatinine. The frequency of the MTHFR (C677T) polymorphism in the patients with DR did not significantly differ from that in patients without DR (DR: 677C/677C, 33.7%; 677C/677T, 51.0%; and 677T/677T, 15.3% vs. without DR: 677C/677C, 37.3%; 677C/677T, 49.3%; and 677T/677T, 13.4%; χ^2 test, $P = 0.78$). In addition, there was no difference in the allele frequency between the NPDR and no DR group (χ^2 test, $P = 0.33$). After adjustment for duration of diabetes, HbA_{1c} level, and blood pressure, multiple regression analysis also showed no significant correlation between the MTHFR gene polymorphism and diabetic retinopathy ($P = 0.98$).

The discrepancy between our results and those reported by Maeda et al. is unclear, but fewer subjects and those without DR in their study may explain their conclusions. Other risk factors for DR such as overt nephropathy might be included in their study because the authors did not determine the presence of overt proteinuria; instead, they selected subjects according to their serum creatinine level, although they excluded renal failure. We selected our subjects not only by serum creatinine levels but also for the presence of overt proteinuria, and therefore excluded overt nephropathy. Although associations between hyperhomocysteininemia (2) or defective homocysteine metabolism (3) and risk of diabetic retinopathy have been reported, we conclude that the MTHFR gene polymorphism cannot be a predictive marker for diabetic retinopathy.

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Diabetic Retinopathy Possibly Results From Poor Blood Sugar Control Associated With MTHFR Gene Polymorphism in Type 2 Diabetic Patients

Response to Yoshioka et al.

We appreciate the comments of Dr. Yoshioka et al. (1). As described previously (2), we excluded the patients with >133 μmol/l serum creatinine level. In addition, the patients with >300 mg/dl urinary protein levels did not participate in our study. We considered that these exclusions must elucidate the effects of the methylenetetrahydrofolate reductase (MTHFR) gene polymorphism, not the effects of nephropathy, on the progression of diabetic retinopathy (DR) in type 2 diabetic patients. We agree with their comment that we analyzed the correlation with a smaller number of subjects. However, we cannot help referring to the difference in the backgrounds of the subjects between the two studies. In our study, the subjects had a mean age of 59.4 years, a mean diabetes duration of 10.8 years, a mean HbA_{1c} of 8.1%, and a mean serum creatinine of 0.76 mg/dl. The noteworthy difference between the two studies is the mean HbA_{1c} level (8.1 vs. 7.3%). The discrepancy may be attributable to this difference.

To support this hypothesis, the subjects with >9.8% HbA_{1c} level were excluded from the previous analysis (2) to get the mean HbA_{1c} level down to 7.3%, and then the data were analyzed again. As a result, there was no significant difference in the relationship between the MTHFR gene polymorphism and DR ($n = 124$, χ^2 test, $P = 0.08$). Fong et al. (3) described that epidemiological analysis of the U.K. Prospective Diabetes Study data showed a continuous relationship between the risk of microvascular complications and glycemia, such that for every percentage point decrease in HbA_{1c} (e.g., from 8 to 7%), there was a 35% reduction in the risk of microvascular complications. Based on this description, improved control of blood glucose may mask the retinopathic background derived from the MTHFR gene polymorphism. Thus, in this letter, we propose that the MTHFR gene polymorphism contributes to the progression of DR synergistically with impaired blood glucose control. In other words, blood glucose control could override the effects of the MTHFR gene polymorphism in type 2 diabetic patients.

Prospective cohort studies are required to understand the influence of the MTHFR gene polymorphism on the progression of DR. We thank Yoshioka et al. again for their comment, which has illuminated that blood glucose control may be associated with the effect of the MTHFR gene polymorphism on DR.

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