

## OBSERVATIONS

## Status of Research Funding by the American Diabetes Association—5th and Final Year

In 1998, the American Diabetes Association (ADA) announced an ambitious 5-year plan for funding research, namely that by Fiscal Year 2003, one of 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 5th and final year, Fiscal Year 2003, are included in Table 1.

We obviously did not come close to realizing this ambitious goal. In my 1998 Presidential Address, I compared the ADA to a large ship in which a new course first required a change of direction (which would occur slowly) before proceeding toward and hopefully reaching a new port. It's obvious that we have not reached that port, and realistically speaking, we probably never will. However, I would be remiss if I didn't point out the following. In each of the previous years, the increase in funding for Research Awards and Grants was much less than 50% of the increase in Total Public Support. In the last fiscal year, in which there was a severe economic downturn, Total Public Support increased much less than in previous years. However, the increase in research funding actually exceeded the increase in

Total Public Support. To return to a perhaps tortured metaphor, although we probably will never reach the port promised 5 years ago, we seem to be headed in the right direction. That's certainly a positive sign and speaks well for the future of research funding by the ADA.

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## Difference in Presentation of Charcot Osteoarthropathy in Type 1 Compared With Type 2 Diabetes

The majority of patients developing Charcot osteoarthropathy (COA) are in their 6th and 7th decades, and 80% of them have had diabetes for over 10 years (1). However, no reports have assessed the differences in the demographic features of patients with type 1 and type 2 diabetes. The purpose of this study was to compare the age of presentation and duration of diabetes at the onset of COA in type 1 and type 2 diabetes.

We reviewed 85 patients presenting with acute COA to the Diabetic Foot Clinic. In agreement with previous studies, their mean age was  $51 \pm 12.4$  years (mean  $\pm$  SD) and mean duration of dia-

betes  $19 \pm 10$  years. The patients were divided into two groups according to the type of diabetes: group 1 included 44 patients with type 1 diabetes (17 men, 27 women), and group 2 included 41 patients with type 2 diabetes (22 men, 19 women). The diagnosis of acute COA was based on the recent development of red hot swollen foot, skin foot temperature difference ( $>2^\circ\text{C}$ ) compared with the opposite foot, and typical radiological findings of COA (2).

In patients with type 1 diabetes, the most frequent decade for presentation of COA was the 5th decade (40–49 years), while for patients with type 2 diabetes it was the 6th decade (50–59 years). In type 1 diabetes, the highest rate of presentation was among those with duration of diabetes for 20–24 years, while for type 2 diabetes, the highest rate of presentation was in patients with duration of diabetes of 5–9 years.

At the time of onset of COA, patients with type 1 diabetes had longer duration of diabetes than the patients with type 2 diabetes ( $24 \pm 8.4$  vs.  $13 \pm 8.1$  years,  $P < 0.001$ ) but developed Charcot osteoarthropathy at an earlier age ( $42 \pm 10.2$  vs.  $59 \pm 7.8$  years,  $P < 0.001$ ). There was a significant correlation between age and duration of diabetes in type 1 diabetic patients ( $r = 0.487$ ,  $P < 0.01$ ). However, no association was observed between age and duration of diabetes in type 2 diabetic patients ( $r = 0.28$ ,  $P > 0.05$ ).

This study has demonstrated that there are type differences in the demographic features of patients with type 1 and type 2 diabetes developing COA. In type 1 diabetes, the age of onset was lower when compared with that of type 2 diabetes. It is thus important to be aware that COA can present at a young age in patients with long-standing type 1 diabetes. There is a striking similarity in the distribution of peak age and duration and a similar reported peak prevalence of autonomic neuropathy in type 1 diabetes (3).

There was a relative preponderance of type 1 diabetes (51.7%) compared with type 2 diabetes in our series, which has not been reported previously, and this requires further study.

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Table 1—Total Public Support

Fiscal year	Total Public Support (millions of dollars)	Amount devoted to research (millions of dollars)	Percent
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	147.8	33.9	22.9 (not $\geq 33.0$ )



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## Strong Inverse Correlation Between Serum Adiponectin Level and Heart Rate–Corrected QT Interval in an Apparently Healthy Population

A suggestion for a direct antiatherogenic effect of adiponectin

Recently, hypoadiponectinemia was found to be associated with coronary artery disease in humans (1). Conversely, hyperadiponectinemia caused by a transgenic overexpression of the adiponectin gene prevented atherosclerosis in the mouse with genetic preponderance to it (2,3). The facts suggest adiponectin has a direct antiatherogenic effect in vivo, as suggested in in vitro studies (4). However, adiponectin is an insulin-sensitizing adipocytokine, and increased insulin re-

sistance (IR) is a well-established atherogenic factor. Therefore, it is possible that the observed correlations (1–3) with adiponectin and atherosclerosis occurred through its insulin-sensitizing effect (3,5). To know if adiponectin possesses a direct antiatherogenic effect beyond its insulin-sensitizing action in an apparently healthy population, we analyzed the relationship among serum adiponectin, heart rate–corrected QT interval (QTc), and the established risk factors of atherosclerosis in Japanese health examinees. Most importantly, measurement of serum-specific immunoreactive insulin (IRI) was included to quantify the degree of IR. QTc was used as a marker of subclinical atherosclerosis because it predicts future cardiac mortality (6) and correlates well with the carotid intima-media thickening (7), both in apparently healthy populations.

The data of 102 consecutive male health examinees (aged  $54 \pm 11$  years) from the Japanese general population were analyzed. Using fasting blood samples, we measured serum adiponectin ( $8.1 \pm 4.4 \mu\text{g/ml}$  [mean  $\pm$  SD]), IRI ( $47.2 \pm 27.1 \text{ pmol/l}$ ), triglycerides ( $1.62 \pm 0.85 \text{ mmol/l}$ ), total cholesterol ( $5.38 \pm 0.98 \text{ mmol/l}$ ), HDL cholesterol ( $1.37 \pm 0.31 \text{ mmol/l}$ ), and plasma glucose ( $5.7 \pm 1.0 \text{ mmol/l}$ ). Adiponectin was determined by radioimmunoassay using commercially available kits (Linco Research, St. Charles, MO) and IRI by human insulin-specific enzyme immunoassay (Abbott Laboratories, Abbott Park, IL). Anthropometric parameters and blood pressure ( $125 \pm 16/75 \pm 10 \text{ mmHg}$ ) were also obtained and the 12-lead electrocardiogram recorded. QTc ( $392 \pm 17 \text{ ms}$ ) was determined by computational analysis according to the Bazett's formulation. Adiposity was measured with impedance method. An index of insulin sensitivity (QUICKI) was  $0.36 \pm 0.03$  ( $1/[\log(\text{insulin in } \mu\text{U/ml}) + \log(\text{glucose in mg/dl})]$ ).

First, correlation between each clinical variable and QTc was evaluated by Spearman's rank correlation and linear regression analysis. Adiponectin, percentage adiposity, and age, but none of the other variables, were significantly correlated with QTc. Based on this finding the multiple regression analysis was performed by taking QTc as a dependent variable and adiponectin, percentage adiposity, and age as independent variables.

All of the three variables were significantly correlated with QTc, and the correlation was most strong and significant between adiponectin and QTc: adiponectin ( $\beta = -0.272$ ,  $P = 0.0048$ ), percentage adiposity ( $\beta = 0.228$ ,  $P = 0.0330$ ), and age ( $\beta = 0.216$ ,  $P = 0.047$ ). Adiponectin and QUICKI ( $P = 0.004$ ) were significantly correlated after adjustment for plasma glucose, triglycerides, and BMI. Thus, we confirmed a well-established insulin-sensitizing effect of adiponectin in this population.

Finally, we attempted to establish a relationship between hypoadiponectinemia and abnormal elongation of QTc by multiple logistic regression analysis. To this end, QTc  $\geq 420 \text{ ms}$  was adopted as a cutoff for the abnormal QTc (normal QTc  $< 420 \text{ ms}$ ,  $n = 95$ ; QTc elongation  $\geq 420 \text{ ms}$ ,  $n = 7$ ) because it was associated with a significantly higher cardiovascular mortality in a prospective study of an apparently healthy population (6). After consideration of all variables listed above as possible predictors, low level of adiponectin was the only variable significantly related to the abnormal elongation of QTc ( $P = 0.047$ , RR 0.730, 95% CI 0.535–0.995).

We found an unequivocal inverse correlation between adiponectin and QTc, and more importantly, hypoadiponectinemia was the only variable significantly related to abnormal elongation of QTc. In this apparently healthy population, a significant correlation between insulin sensitivity and QTc was absent. Our data strongly suggest that adiponectin possesses a direct antiatherogenic effect in humans during the evolution of atherosclerosis.

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## Seasonal Changes in Body Composition and Blood HbA<sub>1c</sub> Levels Without Weight Change in Male Patients With Type 2 Diabetes Treated With Insulin

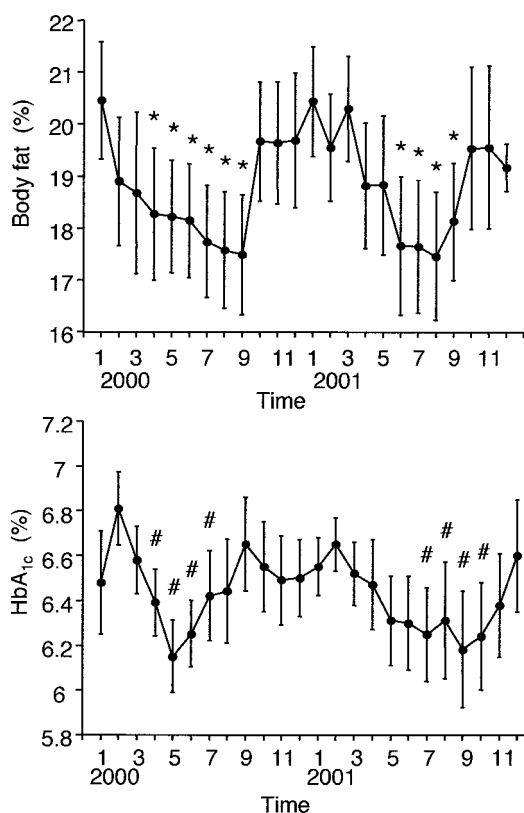
We have often observed increases in plasma glucose and HbA<sub>1c</sub> levels in patients with type 2 diabetes during the winter in Japan. This phenomenon has been explained in part by weight gain due to increases in food intake and decreases in exercise during the winter. However, HbA<sub>1c</sub> levels are also increased during the winter season in most patients with type 2 diabetes without weight gain. In this study, we examined the relationship between seasonal changes in body composition and blood HbA<sub>1c</sub> levels in patients with type 2 diabetes treated with insulin over a 2-year period.

Eleven male patients with type 2 diabetes treated with insulin were investigat-

ed. The mean (±SD) age was 60.4 ± 10.1 years, and BMI was 20.9 ± 1.9 kg/m<sup>2</sup>. The daily dosage of insulin was 17.5 ± 5.5 units (0.31 ± 0.07 units/kg). All patients had accomplished stable plasma glucose control for >4 years without any changes in insulin dosage. They had no diabetes complications and no other diseases aside from diabetes. The subjects were taking no other medication. The dosage of insulin was not changed during the experimental period.

The patients attended as outpatients every month. Body fat was determined by bioelectrical impedance analysis using a body composition analyzer (TBF-305; Tanita). Body composition was measured 3 h after breakfast every month for 2 years. The data obtained over the 2-year period were analyzed by ANOVA.

Body weight did not change during the period (56.4 ± 2.6 kg in January 2000, 57.4 ± 2.9 kg in December 2000, and 55.9 ± 3.0 kg in July 2001). As shown in Fig. 1, body fat began at 20.5 ± 1.1% in January 2000 (mean ambient temperature 4.5°C), decreased to 18.3 ± 1.3% in April 2000 and 17.5 ± 3.8% in September 2000 (24.0°C), increased to 20.4 ± 3.3% in January 2001 (4.5°C), and decreased



**Figure 1**—Seasonal changes in body fat (upper panel) and blood HbA<sub>1c</sub> levels (lower panel). \*P < 0.05 vs. January 2000; #P < 0.05 vs. February 2000.

again to  $17.6 \pm 1.3\%$  in June 2001 ( $26.2^\circ\text{C}$ ). Blood  $\text{HbA}_{1c}$  levels were  $6.81 \pm 0.16\%$  in February 2000, decreased to  $6.39 \pm 0.15\%$  in April 2000, increased to  $6.65 \pm 0.12\%$  in February 2001, decreased to  $6.25 \pm 0.21\%$  in July 2001, and increased to  $6.60 \pm 0.25\%$  in December 2001.

Body fat and  $\text{HbA}_{1c}$  levels were increased in winter and decreased in summer without any appreciable change in body weight. Previous reports have suggested that there is no seasonal variation in body fat in healthy subjects (1). Lower  $\text{HbA}_{1c}$  levels have been observed in the spring and summer and higher levels in the autumn and winter in patients with type 1 diabetes undergoing intensive insulin treatment (2). The most plausible explanations for the seasonal variations in  $\text{HbA}_{1c}$  could be the increases in insulin resistance in winter. Plasma cortisol and tissue sensitivity to glucocorticoids are higher in winter (3), which could contribute to increased body fat. However, there have been no studies to determine the precise relationship between  $\text{HbA}_{1c}$  and body fat in type 2 diabetes treated with fixed-dose insulin. In conclusion, seasonal changes in body fat rather than body weight might attribute to seasonal variations in plasma glucose control in patients with type 2 diabetes.

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## Reversible Quadriplegia and Nonketotic Hyperosmolar Coma

Is it an exceptional association or an overlooked complication?

**A** thrombotic stroke or cerebropontine myelinolysis associated with high serum osmolarity and cerebral edema are well-known complications of hyperosmolar nonketotic coma (1). Although critical illness polyneuropathy (CIP) is not included in the “textbook” differential diagnosis, there is one case report showing an association of CIP to hyperosmolar nonketotic coma (2).

We report on a case of a 56-year-old white woman with unknown diabetes who was admitted to the emergency department because of fever, chills, arthralgia, and fatigue. At presentation, she was confused, lethargic, and dehydrated. Initial laboratory studies revealed blood glucose 916 mg/dl, creatinine 1.7 mg/dl, sodium 146 mEq/l, and potassium 5.3 mEq/l. Plasma osmolarity was 342 mOsm/l. Urinalysis was negative for ketones.

The patient was diagnosed with hyperosmolar nonketotic coma and treated with normal saline, potassium, continuous insulin infusion, and antimicrobial therapy according to culture results. Strict blood glucose control was achieved in a few days and maintained thereafter with four daily insulin injections. Anti-GAD and  $\alpha$ -islet cell antibodies were negative, while fasting serum C-peptide was 6 ng/ml.

During days 1–4, the patient remained in the intensive care unit. The neurological examination revealed pupils that were round, equal, and light responsive. The tendon reflexes were present and normal, and there were no symptoms or signs of peripheral neuropathy. On day 5, neurological examination revealed all four limbs to be flaccid and areflexic. A brain computed tomography scan was normal, and lumbar puncture with analysis of cerebrospinal fluid showed normal concentration of protein and no nucleated cells. Since electromyogram was consistent with severe axonal sensorimotor peripheral neuropathy, other conditions such as Guillain-Barré syndrome were excluded and a diagnosis of CIP was made.

On day 30, the patient’s limbs were responsive to pain and she was able to voluntarily move her arms, while the lower limbs remained paretic. A further electrophysiological study showed improvement in the axonal damage; in particular, a marked increase in upper limb sensory nerve action potential amplitudes was observed, whereas compound motor action potentials remained compromised. On day 60, the recovery in motility was complete in her arms but only partial in her legs. Four months after the admission, the patient was able to walk with support.

Severe and acute hyperglycemia should be included in the list of other well-known conditions such as coma, severe lung disease, sepsis, multiple trauma, postsurgical complications, and shock, which may be complicated by CIP, by different mechanisms (3,4). Consistent with this view, in vivo and in vitro animal studies have shown that acute and severe hyperglycemia ( $>500$  mg/dl) can result in increased apoptosis of neurons and reduced neurite growth (5).

At variance with classical diabetic neuropathy, which is mainly related to poor blood glucose control and diabetes duration, in our patient, CIP was mainly caused by coma, sepsis, and, as we suggest, severe hyperglycemia. The apparent delayed onset is consistent with CIP; despite CIP affecting 80% of intensive care unit patients after 7 days, the occurrence of CIP on day 5 is not surprising (2). In fact, the woman was probably exposed to a high concentration of glucose ( $>500$  mg/dl) for a few days before admission. So, in this patient, the role of hyperglycemia in causing CIP is both direct (by means of its acute neurotoxicity) and indirect (by causing the sepsis).

In such an acute clinical picture, CIP could not be an exceptional event, but rather a relatively common complication that should be kept in mind. For all these reasons, we recommend that electromyogram be performed in patients with hyperosmolar nonketotic coma and sudden-onset quadriplegia. The aim is not only to differentiate CIP, which is reversible in 80% of cases (4), from more usual complications (mainly Guillain-Barré syndrome) with worse prognosis, but also to find out the prevalence of this condition in diabetic patients.

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## Relationship Between Moderate Alcohol Consumption and Adiponectin and Insulin Sensitivity in a Large Heterogeneous Population

In the January issue of *Diabetes Care*, Sierksma et al. (1) reported that moderate alcohol consumption increased adiponectin serum levels and improved insulin sensitivity in a small group of insulin-resistant middle-aged men using a longitudinal study. This finding prompted us to examine the effect of moderate alcohol consumption on these parameters in our large heterogeneous group of nondiabetic subjects with and without family history of type 2 diabetes

(2,3). Subjects with clinically suspected alcohol abuse were excluded from the study. Data on alcohol consumption (derived from a simple questionnaire) and insulin sensitivity (estimated from the oral glucose tolerance test using a validated index [4]) were available in 852 subjects (299 men and 586 women) and serum adiponectin concentrations in 752 subjects. Alcohol consumption categories were defined as follows: Alc 0 = no alcohol consumption ( $n = 145$ ), Alc 1 = alcohol consumed only occasionally ( $n = 363$ ), Alc 2 = alcohol consumed 2–3 days a week (including at weekends only) ( $n = 296$ ), Alc 3 = alcohol consumed on >5 days a week ( $n = 48$ ).

In Alc 0, insulin sensitivity was significantly lower ( $18.0 \pm 1.0$ ) compared with subjects in category 1 ( $18.6 \pm 0.6$ ), category 2 ( $21.1 \pm 0.6$ ), and category 3 ( $21.4 \pm 1.7$ ) ( $P = 0.04$  after adjusting for sex, age, and percentage body fat). Because of sex differences in alcohol metabolism (5) and adiponectin serum levels (3), the relationship between alcohol consumption on adiponectin was analyzed separately in men and women. Adiponectin serum levels were higher in men consuming alcohol on 2 or more days a week (Alc 2 + 3) ( $9.2 \pm 0.3 \mu\text{g/ml}$ ) compared with men consuming no or occasional alcohol (Alc 0 + 1) ( $8.4 \pm 0.3 \mu\text{g/ml}$ ,  $P = 0.05$  after adjusting for percentage body fat). Abstinent women (Alc 0) were found to have significantly lower adiponectin serum concentrations ( $11.7 \pm 0.5 \mu\text{g/ml}$ ) than women consuming alcohol (Alc 1 + 3) ( $13.3 \pm 0.3 \mu\text{g/ml}$ ,  $P = 0.03$  after adjusting for percentage body fat).

In summary, our findings support the notion that moderate alcohol consumption has positive effects on insulin sensitivity and adiponectin serum levels. These effects are not only present in the small homogenous group studied by Sierksma et al. (1), but can also be demonstrated in a large and more heterogeneous group of healthy subjects. In women, the alcohol effects seem to be demonstrable at lower doses than in men.

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## COMMENTS AND RESPONSES

### How Long Should Insulin Be Used Once a Vial Is Started?

Response to Grajower et al.

I wish to comment on the commentary by Grajower et al. (1) regarding how long insulin should be used once a vial is started. I agree with Dr. Grajower that





refrigerated storage. The tests include exposing cartridges of insulin to temperature cycling and resuspension tests (TCRTs) in addition to high temperature and extreme agitation tests (HTEATs). Although the article cited (3) reported specifically on testing of Humulin R (solution samples), Humulin NPH, and Humulin 70/30 (suspension samples), these tests are applied consistently to all of our insulin solutions and suspensions, including the analogs.

The conditions of the TCRT include temperature cycling (25–37°C) in an incubator, with resuspensions conducted twice daily on a mechanical device outside the incubator. Cartridges are placed on a resuspension machine that rolls and inverts the cartridges; tests include three sets of 10 rolls and 10 inversions twice daily. At least 50 cartridges per lot are tested. The sample size will vary depending on the test end points. Three end points are assessed throughout the TCRT. These end points include visual assessment by trained operators, total insulin potency as measured by reverse-phase high-performance liquid chromatography, and acid clarification of pooled samples. The last test detects insulin aggregation and confirms the finding of the visual assessment. Insulin potency is no longer measured by *in vivo* bioassay. Instead, we determine the label claim amount of insulin per unit of volume, defined as potency, using high-performance liquid chromatography.

The conditions of the HTEAT include continuous high temperature (37°C), exposure in an incubator, and periodic daily agitation (30 rpm for 4 h) by rotation inside the incubator. In addition, cartridges are placed in the resuspension device after incubation but before visual assessment is conducted. This resuspension test performs the same rolls and inversions as the TCRT. At least 38 cartridges per lot are tested. Sample size will vary depending on the test end points. Visual assessment by trained operators occurs on days 0, 2, 5, 7, 9, 11, 14, 17, 21, and 28 to detect change in color and clarity for clear solutions and large aggregates (clumps) and/or material adhesion to the cartridge wall (frosting) for suspensions. Acid clarification is performed to confirm the visual changes.

The results of the physical stress tests vary depending on the formulation. Insulins in solution, such as insulin lispro and

regular insulin, are not affected by the physical stress tests described above. For insulins in suspension, no visible changes are detected after exposure to the TCRT stress conditions. However, insulin suspensions exposed to the HTEAT stress conditions exhibit visible changes over the 28-day period. Four categories of visual change define the results of the test, including slightly grainy, grainy, clumpy, and severely clumpy. Any macroscopic visual changes detected are further evaluated by microscopic analysis. A micrograph by fluorescent backlighting is taken to detect clumping or frosting, which is then verified by optical microscopy. Insulins in suspension that show aggregated crystals before the end of the 28-day period are then acidified. A lack of dissolution after acidification confirms the presence of insoluble denatured insulin, which may indicate loss of potency.

It is important to note that changes in the visual appearance of insulins in suspension subjected to the HTEAT do not always correlate with reduced potency as measured by reversed-phase high-performance liquid chromatography. Based on the analytical criteria of the study, both the slightly grainy and grainy samples produce acceptable results. Samples designated as clumpy or severely clumped do not pass the criteria due to excessive variability in potency. In summary, the in-use dating recommendations for Lilly insulins are derived from the above analytic methods and results.

Eli Lilly must comply with product standards imposed by the U.S. FDA as well as with standards established by other regulatory agencies, e.g., The U.S. Pharmacopeia (USP), both in the U.S. and abroad. Regulatory agencies interpret the results of the TCRT and the HTEAT to guide nonrefrigerated storage dating considerations. As a result of different interpretations by various regulatory agencies, in-use dating periods for Lilly insulins range from 7 to 28 days, depending on the regulatory agency and formulation.

Like Dr. Molitch, many patients and other health care professionals have recommended that Lilly make a smaller insulin vial. Lilly must consider many factors when determining the size of insulin vials, such as average daily use. Another critical factor is maintaining compliance with existing standards. For

example, until 15 May 1995, the USP specifically stated that U-100 insulin products should be packaged in 10-ml size bottles and that U-500 insulin products should be packaged in 20-ml size bottles (2). Developing insulin vials smaller than those currently available would benefit only a small minority of patients who take insulin. Importantly, creating smaller vials would require developing entirely new manufacturing facilities, much testing, and extensive regulatory review, all of which would ultimately increase the cost of insulin.

Lilly understands that labeling recommendations for insulin use may affect how health care professionals prescribe insulin and may have a financial impact on patients. We strive to help patients manage their diabetes by producing products that are safe, potent, and in compliance with regulatory agency requirements. Lilly appreciates the opportunity to provide more information about in-use dating recommendations for insulins. We hope that this response gives health care professionals and patients a better understanding of the reasons for these recommendations.

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## The Metabolic Syndrome: The Emperor Needs Some Consistent Clothes

Response to Vinicor and Bowman

**D**rs. Vinicor and Bowman (1) point to a number of challenges associated with formalizing medical syndromes for clinical and public health purposes in this issue of *Diabetes Care*. I agree with the issues they raise; it is not yet clear whether the metabolic syndrome is a separate syndrome or simply a collection of commonly recognized cardiovascular risk factors. The current working definitions provide a useful means for clinicians to identify high-risk patients and manage them accordingly. Researchers can use the criteria to readily identify patients with the syndrome and enhance our understanding of the basic pathophysiology and management. Although the vigorous and systematic evaluation of proposed criteria for the metabolic syndrome is necessary and valuable, we need to keep the criteria simple and clinically relevant. An example of the use of an original set of criteria that was later elucidated by further research is the case of rheumatic fever. The original definition of rheumatic fever, the Jones criteria, was based on the occurrence of specific manifestations (2). We now know that evidence of recent group A streptococcal infection (positive throat culture or elevated antistreptolysin O or other streptococcal antibody titers) is much more important than whether any of the specific manifestations is present. There may also be a limit to what can be gained by perfecting the current working definition of metabolic syndrome. Rather, progress with regard to the metabolic syndrome will more likely come from an improved understanding of its pathophysiology. With regard to the metabolic syndrome and insulin resistance, important research (3–14) has recently appeared in the medical literature that may provide important clues to help substantially improve our understanding. While there is no doubt that this research will generate as many new questions as answers, available criteria to identify individuals with metabolic syndrome serve to appropriately focus

our attention and facilitate future progress to benefit our patients.

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## Aspirin Resistance in Diabetic Patients

Response to Sacco et al.

**T**he results in the small diabetic subgroup of the Primary Prevention Project (PPP) study (744 patients), implemented by 287 additional patients (enrolled in outpatient clinics) were recently published in *Diabetes Care* (1). The PPP trial (2) was originally designed to test the hypothesis that platelet thromboxane (TxA2) generation would act as an intermediate “common” mechanism of cardiovascular risk in addition to specific risk factors (namely old age, hypertension, hypercholesterolemia, diabetes, obesity, and family history of myocardial infarction). The results of the original PPP trial extended the indications for aspirin treatment beyond secondary prevention in men and women with major cardiovascular risk factors, as routinely seen in a unique scenario such as general practice. As there was no obvious excess risk for hemorrhagic cerebrovascular complications, the results of the PPP trial not only widened the categories of candidates to a low-cost prophylaxis but also offered clear support to a crucial pathogenic role of platelet TxA2 in the final steps of the atherosclerotic process (3). Sacco et al. (1) now suggest that diabetic patients are less responsive to aspirin therapy than other high-risk individuals enrolled in the PPP trial. It was not shown, however, whether aspirin would have in contrast been effective if other similarly small subgroups of people at risk would have been compared with the rest of the selected population. This is of importance, as it has been previously reported that aspirin may be less

effective in subjects with hypertension (4) or hypercholesterolemia (4–6). On one hand, a significantly higher percentage of subjects with hypertension and hypercholesterolemia were present in the diabetic group randomized to aspirin, compared with the no-aspirin group (1); this could have further contributed to the negative results. On the other hand, it appears somewhat contradictory to state that a clear benefit of aspirin could only be shown in the heterogeneous group of nondiabetic patients, which included 68.8% hypertensive and 39.9% hypercholesterolemic subjects (1). It therefore appears premature to raise the fashionable issue of “aspirin resistance” (7,8) in diabetic patients (1) until adequately sized, statistically powered clinical trials and/or large meta-analyses can match the efficacy and safety of aspirin in primary prevention in different subgroups of patients with different vascular risk profiles, rather than in small groups of diabetic patients.

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## Is Aspirin Resistance a Real Problem in People With Type 2 Diabetes?

Response to Sacco et al.

We read with great interest the article by Sacco et al. (1) on the problem of aspirin efficacy in primary prevention of cardiovascular events in type 2 diabetic patients. In our opinion, this is an important yet somewhat understudied area in the field of diabetes care. The Diabetes Prevention Project (DPP) trial has shown lower effects of primary prevention of cardiovascular disease with low-dose aspirin in diabetic subjects compared with nondiabetic subjects. The mechanism(s) of reduced sensitivity of platelets taken from diabetic subjects are not fully understood (2). We conducted a study aimed to evaluate a possible association between the parameters relevant to metabolic control of diabetes and platelet sensitivity to aspirin in blood taken from 31 aspirin-treated, poorly controlled type 2 diabetic patients and 48 healthy volunteers (150 mg/day for a week). Platelets' ability to adhere and aggregate was determined with a platelet function analyzer (PFA-100), as well as turbidimetric and whole-blood aggregometry, using collagen, ADP, and arachidonic acid as platelet agonists. We found that aspirin reduced platelet reactivity up to sixfold less effectively in diabetic than in control subjects. In the diabetic subjects, the response of platelets to aspirin was inversely associ-

ated with HbA<sub>1c</sub> and total cholesterol and positively associated with HDL cholesterol (3). These findings support our belief that metabolic control of diabetes contributes to reduced platelet sensitivity to aspirin. Extensive protein glycation may attenuate aspirin's ability to acetylate target platelet proteins in diabetic patients. Also, lipid disturbances in platelet membranes might substantially contribute to aspirin efficacy (4); notwithstanding, anti-inflammatory actions may also be important in aspirin-mediated reduction of the overall cardiovascular risk. Hence, monitoring of antiplatelet action of aspirin should be considered at least in high-risk patients. There is a need for simple, fast, reliable, and cheap diagnostic methods for this purpose.

To summarize, “aspirin resistance” is a real and clinically important problem, and some people with diabetes might require more intensive treatment to reduce glucose and lipid concentrations and thereby improve platelet response to aspirin. Patients with poorly controlled diabetes may need larger doses of aspirin or an additional antiplatelet agent to avoid thrombotic complications. However, the risk of bleeding must be always balanced against the beneficial cardiovascular effect.

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## Aspirin Resistance in Diabetic Patients

Response to de Gaetano

The limitations of the Primary Prevention Program (PPP) diabetes substudy have been previously discussed in the original article (1) and in the accompanying editorial (2). Nevertheless, the comments of Dr. de Gaetano (3) require some important additional considerations.

1) The results of the substudy are not the outcome of a post hoc analysis, since an oversampling of diabetic patients was planned before the study started to specifically explore the role of aspirin in these patients.

2) Dr. de Gaetano suggests that the lower-than-expected effect of aspirin could have also emerged if other subgroups, namely patients with hypertension or hypercholesterolemia, would have been examined. This is not the case— aspirin was effective in reducing the risk for total cardiovascular events in both subgroups (OR 0.66, 95% CI 0.50–0.86 and 0.75, 0.52–1.09 for patients with hypertension and hypercholesterolemia, respectively). The benefit of aspirin in these subgroups was even greater after the exclusion of patients with diabetes (0.57, 0.41–0.80 and 0.65, 0.43–1.00, respectively).

3) The lower-than-expected effect of aspirin in individuals with diabetes was consistently found across the whole spectrum of cardiovascular end points considered, and it is highly unlikely that this coherence can be simply due to the play of chance.

4) The results of the PPP trial should not be considered in isolation but evaluated in the context of the existing evidence, which is surprisingly scant. A recent meta-analysis documented a significant effect of antiplatelet therapy in a broad range of high-risk subgroups but

failed to show a clear benefit in diabetic patients, with a nonsignificant 7% proportional reduction in serious vascular events (4). Within the meta-analysis, results relative to aspirin were mainly derived from the Early Treatment Diabetic Retinopathy Study (ETDRS), the only one specifically conducted in 3,711 diabetic patients (5). In this trial, treatment with aspirin for an average of 5 years was associated with a nonsignificant 9% reduction in serious vascular events (vascular death, nonfatal myocardial infarction, or nonfatal stroke). Our data are highly consistent with the existing evidence, showing a nonsignificant 10% reduction in the risk of the same end point, as compared with a 41% reduction in nondiabetic individuals.

5) There is a general consensus that primary prevention should be recommended on the basis of the overall cardiovascular risk of an individual patient, rather than on the presence of specific risk factors. To this respect, patients at high cardiovascular risk are by definition heterogeneous, since they often carry several risk factors at the same time, and we cannot see any contradiction in stating that aspirin is effective in a broad range of high-risk patients, with presumably the only exception of individuals with diabetes.

6) Aspirin resistance is only one of the possible explanations for the lower efficacy of aspirin in individuals with diabetes. To our knowledge, the problem of aspirin resistance in the presence of diabetes has never been adequately addressed. To this respect, it seems to us a serious hypothesis to explore, rather than a fashionable issue.

7) We have clearly stated that our data cannot be considered as a conclusive proof against the use of aspirin in patients with diabetes. We believe that the main merit of our study was simply to raise the problem—before the data were published, it seemed that a general consensus was present about the efficacy of aspirin for the primary prevention of cardiovascular events in diabetes. It is now clear, and also Dr. de Gaetano seems to agree, that additional, large-scale trials are needed. It should also be considered that the vast majority of diabetic patients are already treated with ACE inhibitors and/or statins. Whether aspirin adds any benefit in these individuals remains to be proved.

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## Autoimmune Hypoglycemia in a Type 2 Diabetic Patient With Anti-Insulin and Insulin Receptor Antibodies

Response to Kim et al.

Kim et al. (1) recently reported autoimmune hypoglycemia in a type 2 diabetic patient with anti-insulin and insulin receptor antibodies. The pa-

tient was a 72-year-old woman with suitable clinic and laboratory data for autoimmune hypoglycemia. Her plasma glucose was 40 mg/dl, insulin 103.7  $\mu$ U/ml, and C-peptide 4.1 ng/ml. The authors state, "Patients with this condition have low circulation insulin, C-peptide levels, and refractory hypoglycemia." We believe that this sentence is discordant with the rest of the letter and patients' given data.

Hypoglycemia owing to insulin antibodies is rare but should be considered in any patient with hypoglycemia in the setting of nonsuppressed insulin levels, i.e., insulin levels that are markedly elevated, usually >100  $\mu$ U/ml, as in the given patient (2). Free insulin levels may be normal or high, and C-peptide levels are not suppressed (3).

In hypoglycemia due to insulin receptor antibodies, insulin levels are usually higher than appropriate for the glucose concentration. This finding raises the possibility of a pancreatic tumor (4); however, C-peptide and proinsulin levels are usually appropriately low during hypoglycemia, which helps distinguish the condition from insulinoma.

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## Autoimmune Hypoglycemia in a Type 2 Diabetic Patient With Anti-Insulin and Insulin Receptor Antibodies

Response to Sahin, Tutuncu, and Guvener

We offer many thanks to Sahin, Tutuncu, and Guvener for reading our letter (1) with interest and for their comments (2). In response to the specific points raised, we provide the following reply.

1) In the last paragraph we stated that patients with this condition have low circulating insulin, C-peptide levels, and refractory hypoglycemia. In this sentence, we did not describe our patient, but rather autoimmune hypoglycemia with insulin receptor antibody. Patients with anti-insulin antibody have high total insulin, low or normal free insulin, and low C-peptide levels (3). But a few cases had high C-peptide levels (4,5). Large amount of serum C-peptide may express an overproduction of proinsulin synthesis in the pancreas (4). Our patient had high total insulin and C-peptide levels.

2) In hypoglycemia due to insulin receptor antibodies, insulin levels are usually high. High C-peptide levels raise the possibility of a pancreatic tumor, for example, insulinoma. We thought that the possibility of an insulinoma was very low. Imaging studies were done, including magnetic resonance imaging scan, octreotide scan, computed tomography, arterial portography, and mesenteric aortography. Imaging studies showed nonspecific findings. The most important laboratory test in the differential diagnosis is a direct assay for the presence of antibodies directed against the insulin and its receptor (6). Our patient had anti-insulin and insulin receptor antibodies.

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## Diagnosing Insulin Resistance by Simple Quantitative Methods in Subjects With Normal Glucose Metabolism

Response to Ascaso et al.

Ascaso et al. (1) evaluated insulin sensitivity in 65 healthy subjects using minimal model analysis of an insulin-modified frequently sampled intravenous glucose tolerance test (FSIVGTT) to estimate the insulin sensitivity parameter derived from minimal model ( $SI_{MM}$ ) (2), as well as simple surrogates including fasting insulin, homeostasis model assessment (3), QUICKI (4), and the McAuley index (5). A statistically significant correlation was observed between  $SI_{MM}$  and all of the other surrogate indexes examined. However, using  $SI_{MM}$

as the reference method, the authors claim that the McAuley index has the best correlation with  $SI_{MM}$  and the highest sensitivity and specificity (0.75 and 0.91, respectively). Therefore, the authors conclude that among several simple surrogate indexes, the McAuley index is the most sensitive and specific measure of insulin sensitivity.

While the data presented by Ascaso et al. may be sound, the conclusions drawn are not supported by the data. The main problem with the interpretation of the data comes from not including a true reference standard that is a direct measure of insulin sensitivity (e.g., euglycemic-hyperinsulinemic glucose clamp).  $SI_{MM}$  derived from an FSIVGTT is not a direct measure of insulin sensitivity. Moreover,  $SI_{MM}$  has well-documented systematic and random errors that are problematic even when insulin-modified FSIVGTTs are used (4,6–9). When compared with glucose clamp–derived measurements of insulin sensitivity ( $SI_{Clamp}$ ), QUICKI is a substantially and significantly better estimate of insulin sensitivity than  $SI_{MM}$  (4). Moreover, in hypertensive subjects, changes in QUICKI after therapeutic intervention are significantly correlated with changes in  $SI_{Clamp}$ , while changes in  $SI_{MM}$  are unrelated (9). Thus, discordance between QUICKI and  $SI_{MM}$  most likely reflects problems associated with the minimal model approach rather than inaccuracies manifested by QUICKI. Indeed, a number of independent groups have found excellent correlations between QUICKI and reference glucose clamp measurements in normal, obese, and diabetic populations (10–16), as well as in pregnant women and women with gestational diabetes (17). Because Ascaso et al. used  $SI_{MM}$  as their reference method and they do not include a direct measure of insulin sensitivity in their analysis, it is problematic to make sound conclusions regarding the relative merits of various surrogate indexes for insulin sensitivity. An additional problem with the analysis presented by Ascaso et al. is that they do not use statistical methods to compare the differences in sensitivity and specificity among the various indexes. For example, it is uncertain whether the sensitivity and specificity of the McAuley index (0.75 and 0.91, respectively) are significantly better than that reported for QUICKI (0.65 and 0.87, respectively). In summary, when evaluating the relative merits

of simple surrogate measures for insulin sensitivity, it is important to include a direct measurement of insulin sensitivity as a reference standard and to use appropriate statistical analysis so that valid conclusions may be made.

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## Diagnosing Insulin Resistance by Simple Quantitative Methods in Subjects With Normal Glucose Metabolism

Response to Karne, Chen, and Quon

We thank Karne et al. for their comments (1) on our article (2). The ideal method to evaluate insulin resistance and insulin sensitivity, outside of the euglycemic-hyperinsulinemic clamp, has not yet been fully established. However, the minimal model, extensively used during the past decades, is considered a valuable surrogate of the clamp (3–5). The genetic factors involved in insulin sensitivity are better determined with the minimal model approach than with indirect methods based on fasting glucose and insulin values (6). Thus, the minimal model, as used in our study, provides more complete information on both, insulin resistance and insulin sensitivity than that given by indirect indexes (7–9). Although, as stated by Karne et al., the minimal model is not a direct measure of insulin sensitivity, the evidence in the literature supports its use as a valid surrogate of the clamp.

Minimal model results have been compared with those obtained by indirect indexes, establishing a good correlation. However, indexes based solely on fasting blood glucose and insulin could not always reliably estimate insulin resistance, since it is possible to have insulin resistance without hyperinsulinemia and conversely hyperinsulinemia without insulin resistance (10). A modified version of QUICKI recently published (11) provides a significantly better correlation with minimal model results than that obtained with QUICKI and homeostasis model assessment for insulin resistance. Interestingly, as observed by us, the values obtained with these latter two indexes were similar.

Karne's comments on hypertensive subjects and estimation of insulin resistance with minimal model are not substantiated by the results published by other authors (11).

We consider that the minimal model provides reliable data on insulin sensitivity and insulin resistance. Indirect methods, such as those included in our study, are useful in the study of large number of subjects. It is possible that the predictive value of indirect indexes bears relationship with the evolutionary moment of the insulin resistance syndrome and the onset of metabolic abnormalities. In our study, all indexes correlated significantly with the minimal model results. The McAuley index and the clinical parameters of the metabolic syndrome were the best indicators of insulin resistance. The best indirect method is still to be defined. It is possible that the new modified version of QUICKI will provide some advantage.

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## Benefits and Risks of Solitary Islet Transplantation for Type 1 Diabetes Using Steroid-Sparing Immunosuppression

Response to Hirshberg et al.

The report by Hirshberg et al. (1) describes the National Institutes of Health (NIH) experience in islet-

only transplantation using the medical indication of severe hypoglycemia. Although the report details islet transplantation, there was little hypoglycemic information. Because of the potential side effects comparing the medical indication and the treatment, we have scientific, educational, and ethical concerns.

The first concern is the relative morbidity and mortality between severe hypoglycemia and islet transplantation. The mortality associated with severe hypoglycemia is unclear, but estimates show that 0–4% of type 1 diabetic patients die of hypoglycemia (2–4). Is there a mortality estimate with the immunosuppression regimen plus transplantation? Regarding morbidity, hypoglycemic rates appear significant in the Diabetes Control and Complications Trial (DCCT), but these events generated a hospitalization rate of only 1.1 per 100 patient years (4). At least 2 of 6 patients in the transplant group had life-threatening side effects and a hospitalization rate of over 22 per 100 patient-years.

It would be appropriate to define and quantitate hypoglycemic events before and after transplantation. Hypoglycemic complications, e.g., accidents, emergency room visits, and all-cause hospitalizations before and after transplantation should be compared. It was unclear whether islet transplantation or changes in exogenous insulin regimens reduced the rates of severe hypoglycemic events.

There was no description of the methods and personnel involved in the management of severe hypoglycemia before transplantation. Successful educational methods are reported; were educational methods used? Were patients treated with the most effective regimens currently available, e.g., ultralente twice a day, glargine insulin, and rapid-acting insulin analogs? It should be clear that NPH and regular insulins were not being used before transplantation. Was continuous subcutaneous insulin infusion (CSII) used, and were CSII basal rate–only methods used? For future studies, the use of glucose sensor devices may also appear useful. Since continuous intraperitoneal insulin infusion (CIPII) has been described to markedly reduce severe hypoglycemic events, were the patients offered com-

passionate use of CIPII? All of the above treatments, when used by experienced clinicians, appear considerably safer than the procedures described for islet transplantation.

Regarding ethics, did consent forms advise patients of the above successful severe hypoglycemia treatments?

Since additional U.S. sites will use islet transplantation for treatment of severe hypoglycemia, such teams must include collaborators with expertise regarding severe hypoglycemia. In future islet transplantation studies, the transplantation teams may wish to standardize not only a definition of severe hypoglycemia, but also diagnostic and treatment protocol algorithms before islet transplantation. The NIH would seem the obvious site to initiate such protocols.

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M.A.C. has received honoraria for speaking engagements from Aventis Pharmaceuticals, and Aventis provides funds to the research center in order to conduct studies on glargine insulin.

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## Benefits and Risks of Solitary Islet Transplantation for Type 1 Diabetes Using Steroid-Sparing Immunosuppression

Response to Charles and Selam

We thank Drs. Charles and Selam for their thoughtful comments (1) regarding our study describing the National Institutes of Health (NIH) islet transplantation experience (2). We agree that the question remains open whether islet transplantation and subsequent antirejection therapy decrease the morbidity and mortality associated with diabetes. In fact, one of our article's main messages is the need to develop criteria for identifying patients with "end-stage" diabetes for whom a therapy's known and unknown risks are most likely to favor an appropriate risk/benefit ratio. We have recently published similar concerns regarding the more mature pancreas transplantation therapy (3). Our islet transplant study, formally approved by our institutional review board, was designed to test only whether the NIH team could reproduce the exciting successes then recently reported from Edmonton, using a steroid-free immunosuppressive strategy with defined islet isolation, graft characterization, transplantation, and posttransplant patient monitoring (4), not to formally address the risk/benefit ratio of this still experimental technique or to compare the therapy with other treatment approaches. As an inclusion criterion (borrowed largely from criteria to determine eligibility for a pancreas transplant), all of our patients had severe hypoglycemia (defined as requiring the assistance of others more than once in the preceding 20 months and not explained by a clear precipitating event) or hypoglycemia unawareness (defined as an inability to sense hypoglycemia with blood glucose levels <54 mg/dl). During the fairly detailed evaluation to determine protocol eligibility, we advised all potential enrollees on the use of modern insulin regimens designed to more closely mimic the normal physiologic insulin pattern,

i.e., basal insulin levels with meal-associated boluses. In fact, several candidates achieved improved glycemia control sufficient to withdraw from further protocol participation. Three of our transplanted patients were treated (before transplant) with continuous insulin infusion systems, and the other three were treated with multiple daily insulin injections.

Our patients were well informed that islet transplantation remained an experimental procedure and were made aware of the multiple known and hypothetical risks of the procedure as well as the risks associated with long-term immunosuppression. We did not offer our patients the option of intraperitoneal insulin infusion through an implantable pump (IPII). Although promising, this procedure also remains experimental. Of note, one study (5) recently reported that in a head-to-head comparison of IPII and islet transplantation, the transplant recipients had less hypoglycemia. That being said, which treatment approach is the superior one with regard to more global end points (e.g., quality of life, prognosis for survival, etc.) has yet to be critically addressed.

Finally, we agree that part of the selection process for all future islet transplant trials should include attention to all the latest in accepted diagnostic and treatment approaches for diabetes. We hope to soon initiate a clinical research protocol that will incorporate these principles.

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## Type 2 Diabetes Prevalence in Asian Subjects

Response to McNeely and Boyko

McNeely and Boyko (1) recently demonstrated that the BMI-adjusted odds ratio for type 2 diabetes in Asian Americans was 1.6 times that of white Americans. Interestingly, there was no significant difference between the preadjusted values of these two ethnic groups. As the BMI adjustment only affected Asians, it is possible that the influence of BMI on the development of type 2 diabetes is more potent in Asians than in other ethnic groups (1).

It is well known that the average BMI of Asians is lower than that of other ethnic groups, principally because of the significantly lower proportion of obese subjects (BMI  $\geq 30$  kg/m<sup>2</sup>), an observation that was also noted in the recent U.S. study (1). We have reported previously that lower BMI is of particular relevance in patients with type 2 diabetes (2). The BMI of Japanese diabetic patients is similar to that of the Japanese population as a whole (~23 kg/m<sup>2</sup> for both), indicating that Japanese diabetic patients on average are not obese. This contrasts with white diabetic

patients who have a much higher BMI (29 kg/m<sup>2</sup>) than that of the white population as a whole (24 kg/m<sup>2</sup>). The similarity in BMI between diabetic and nondiabetic subjects is an important characteristic of type 2 diabetes in Asians and has been shown in both Japanese and Thai cohorts (3).

It can be speculated that these results suggest that Asians are more susceptible than other ethnic groups to type 2 diabetes in response to a relatively small increase in BMI, despite having a lower baseline BMI (4). The mechanism underlying this phenomenon is unclear, but we have recently found in Japanese subjects that overeating is not necessarily correlated with obesity (5) and that being overweight (maximum BMI  $\geq 25$  kg/m<sup>2</sup>) is not significantly associated with the risk of type 2 diabetes (6). Therefore, the development of type 2 diabetes linked to obesity caused by overeating, which is regarded as a common feature in the white population, may not be typical in Asians. This suggests that it may be necessary to develop modified diabetes care and prevention strategies for different ethnic groups.

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## Type 2 Diabetes Prevalence in Asian Subjects

Response to Sone et al.

**W**e thank Sone et al. (1) for their letter in response to our article (2) on the prevalence of type 2

diabetes in Asian Americans. Dr. Sone raises some interesting points that highlight the need for more studies of type 2 diabetes in Asian populations.

We did not include an analysis of the association between BMI and diabetes prevalence for Asian Americans in our report. However, after considering Dr. Sone's comments, we thought these results might be of interest to others.

We performed additional analyses using the methods described in our article (2). The odds ratio (OR) for type 2 diabetes, adjusted for age and sex, was 1.15 (95% CI 1.03–1.26) for every 1-kg/m<sup>2</sup> increase in BMI among Asian Americans over age 30. Results were very similar for Americans of all ethnicities (adjusted OR 1.14, 95% CI 1.13–1.14). Compared with those with BMI <25 kg/m<sup>2</sup>, overweight (BMI 25–29 kg/m<sup>2</sup>) and obese (BMI ≥30 kg/m<sup>2</sup>) Asian Americans had progressively increased odds of type 2 diabetes (ORs adjusted for age and sex were 1.89, 95% CI 0.87–3.98, and 7.24, 2.47–21.24, for overweight and obese groups, respectively). The OR was not statistically significant for the overweight Asian-American group. However, when considering these results overall, the 2001 Be-

havioral Risk Factor Surveillance System data provide clear evidence of an association between increased BMI and increased odds of type 2 diabetes in Asian Americans.

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