

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 ± 12.4 years (mean \pm SD) and mean duration of dia-

betes 19 ± 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 ± 8.4 vs. 13 ± 8.1 years, $P < 0.001$) but developed Charcot osteoarthropathy at an earlier age (42 ± 10.2 vs. 59 ± 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 ≥ 33.0)

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References

1. Sanders LJ, Frykberg RG: Charcot neuroarthropathy of the foot. In *Levin and O'Neal's The Diabetic Foot*. 6th ed. Bowker JH, Pfeifer MA, Eds. St. Louis, MO, Mosby, 2001, p. 439–465
2. Frykberg RG: Charcot foot: an update on pathogenesis and management. In *The Foot in Diabetes*. 3rd ed. Boulton AJM, Connor H, Cavanagh P, Eds. Chichester, U.K., John Wiley & Sons, 2000, p. 235–260
3. O'Brien IA, O'Hare JP, Lewin IG, Corral RJ: The prevalence of autonomic neuropathy in insulin-dependent diabetes mellitus: a controlled study based on heart rate variability. *QJM* 61:957–967, 1986

Soluble CD40L in Young Type 1 Diabetic Individuals Without Clinical Microvascular and Macrovascular Complications

The past decade has been characterized by growing interest in the idea that atherosclerosis is an inflammatory disease. Interaction of the multipotent immunomodulator CD40 ligand (CD40L) with its receptor CD40 has emerged as an important contributor to the inflammatory processes that lead to atherosclerosis and thrombosis. CD40 and CD40L are expressed on endothelial and smooth muscle cells, monocytes, and platelets, and CD40-CD40L interaction has been shown to promote a wide array of prothrombotic and inflammatory effects both in vitro and in vivo (1). In addition to the cell-associated form, CD40L also exists in a soluble form, which is fully active biologically, termed soluble CD40L

(sCD40L). Elevated sCD40L levels are found in patients with acute coronary syndromes (2) and are predictive of increased risk of future cardiovascular events in clinically healthy women (3).

At present, little is known regarding the impact of the diabetic state itself on sCD40L levels, particularly in type 1 diabetic patients. It has been reported in only one recent study (4), in which both type 1 and type 2 diabetic patients were enrolled, that type 1 diabetic subjects ($n = 49$) had significantly higher sCD40L levels than control subjects. Similar results were found in a type 2 diabetic group (4); however, in that report the study population also included type 1 diabetic patients with clinically manifest macro- and microvascular complications, or who were taking antihypertensive and hypolipidemic drugs, or who were smokers, which are all factors known to adversely affect plasma inflammatory markers. Therefore, we believe that the results of this study should be interpreted with some degree of caution to draw firm conclusions regarding the adverse effects of diabetes itself on sCD40L levels.

In this pilot study, we endeavored to evaluate a selected group of lean, normotensive, normolipidemic, nonsmoking, young type 1 diabetic patients without any clinical evidence of chronic complications. We compared serum sCD40L levels (ELISA kit; Bender MedSystems Diagnostics) in 27 young adults with type 1 diabetes regularly attending our diabetes clinic with those of 19 healthy volunteers who were matched for age (mean \pm SD) (31 ± 9 vs. 32 ± 6 years), sex (M/F 18/9 vs. 12/7), BMI (23.5 ± 2 vs. 23 ± 3 kg/m²), systolic (125 ± 12 vs. 123 ± 10 mmHg) and diastolic (80 ± 7 vs. 80 ± 5 mmHg) blood pressure, and lipids (total cholesterol 4.7 ± 0.8 vs. 4.9 ± 0.8 mmol/l, triglycerides 1.2 ± 1 vs. 1.1 ± 0.6 mmol/l). All of the participants were nonsmokers. The average glycemic control of patients was good (HbA_{1c} $6.5 \pm 1\%$), and their average duration of diabetes was of 10.6 ± 7 years. None of the patients had retinopathy (by ophthalmoscopy), sensorimotor neuropathy (by biothesiometer), or nephropathy (by urinary albumin excretion rate). To exclude the presence of clinical macroangiopathy, a resting electrocardiogram, measurement of ankle brachial pressure index, and carotid ultrasonography were performed in all of the diabetic patients.

Serum sCD40L concentrations of type 1 diabetic patients were substantially superimposable on those of healthy control subjects (2.35 ± 1.1 vs. 2.39 ± 0.9 ng/ml, comparison by Mann-Whitney *U* test). In the control group, sCD40L levels did not correlate significantly with other variables. In the diabetic group, sCD40L correlated positively with age (Spearman's coefficient = 0.53; $P < 0.01$), and sP-selectin concentration (Spearman's coefficient = 0.70; $P < 0.001$), whereas it did not correlate with sex, BMI, blood pressure, plasma lipids, HbA_{1c}, and fibrinogen concentrations.

Overall, therefore, our results indicate that young type 1 diabetic individuals with good glycemic control and without clinically manifest chronic complications have sCD40L levels substantially similar to those of a matched group of lean, normotensive, normolipidemic, and nonsmoking healthy control subjects. The apparent discordance of our results with those recently reported by Varo et al. (4) may be partly explained by significant differences in the study population, including chronic complication status, degree of glycemic control, and atherogenic risk profile of patients. Our data do not exclude, obviously, the possibility that sCD40L plays an important part in the pathophysiology of macro- and microvascular complications of diabetes through its multiple inflammatory and prothrombotic effects, including platelet activation (2), as confirmed by the strong association of sCD40L with sP-selectin concentration observed in our study. This hypothesis lends itself to testing using interventions to influence sCD40L secretion and actions (such as antiplatelet treatment with abciximab). Nevertheless, the evidence from this and other studies (4) supports the hypothesis that the increase of sCD40L levels in type 1 diabetic patients can, at least in part, be explained by the presence of clinical micro- and macrovascular complications, smoking, or other traditional coronary risk factors. Interpretation of our results, however, requires care because of the relatively small number of patients. Future studies using larger cohorts will be needed to validate this hypothesis.

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References

1. Schönbeck U, Libby P: CD40 signaling and plaque instability. *Circ Res* 89:1092–1103, 2001
2. Heeschen C, Dimmeler S, Hamm CW, van den Brand MJ, Boersma E, Zeiher AM, Simoons ML: Soluble CD40 ligand in acute coronary syndromes. *N Engl J Med* 348:1104–1111, 2003
3. Schönbeck U, Varo N, Libby P, Buring J, Ridker PM: Soluble CD40L and cardiovascular risk in women. *Circulation* 104:2266–2268, 2001
4. Varo N, Vicent D, Libby P, Nuzzo R, Calle-Pascual AL, Bernal MR, Fernandez-Cruz A, Veves A, Jarolim P, Varo JJ, Goldfine A, Horton E, Schönbeck U: Elevated plasma levels of the atherogenic mediator soluble CD40 ligand in diabetic patients: a novel target of thiazolidinediones. *Circulation* 107:2664–2669, 2003

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 ± 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 ± 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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References

1. Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, Arita Y, Okamoto Y, Shimomura I, Hiraoka H, Nakamura T, Funahashi T, Matsuzawa Y: Association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler Thrombo Vasc Biol* 23:85–89, 2003
2. Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M, Ohashi K, Sakai N, Shimomura I, Kobayashi H, Terasaka N, Inaba T, Funahashi T, Matsuzawa Y: Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation* 106:2767–2770, 2002
3. Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, Uchida S, Ito Y, Takakuwa K, Matsui J, Takata M, Eto K, Terauchi Y, Komeda K, Tsunoda M, Murakami K, Ohnishi Y, Naitoh T, Yamamura K, Ueyama Y, Froguel P, Kimura S, Nagai R, Kadowaki T: Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. *J Biol Chem* 278:2461–2468, 2003
4. Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, Ishigami M, Kuriyama H, Kishida K, Nishizawa H, Hotta K, Muraguchi M, Ohmoto Y, Yamashita S, Funahashi T, Matsuzawa Y: Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation* 103:1057–1063, 2001
5. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T: Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 8:1288–1295, 2002
6. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J: QTc interval prolongation predicts cardiovascular mortality in an apparently healthy population. *Circulation* 84:1516–1523, 1991
7. Festa A, D'Agostino R, Rautaharju P, O'Leary DH, Rewers M, Mykkanen L, Halfner S M: Is QT interval a maker of subclinical atherosclerosis in nondiabetic subjects? The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke* 30:1566–1571, 1999

Seasonal Changes in Body Composition and Blood HbA_{1c} Levels Without Weight Change in Male Patients With Type 2 Diabetes Treated With Insulin

We have often observed increases in plasma glucose and HbA_{1c} 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_{1c} 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_{1c} 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/m². 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

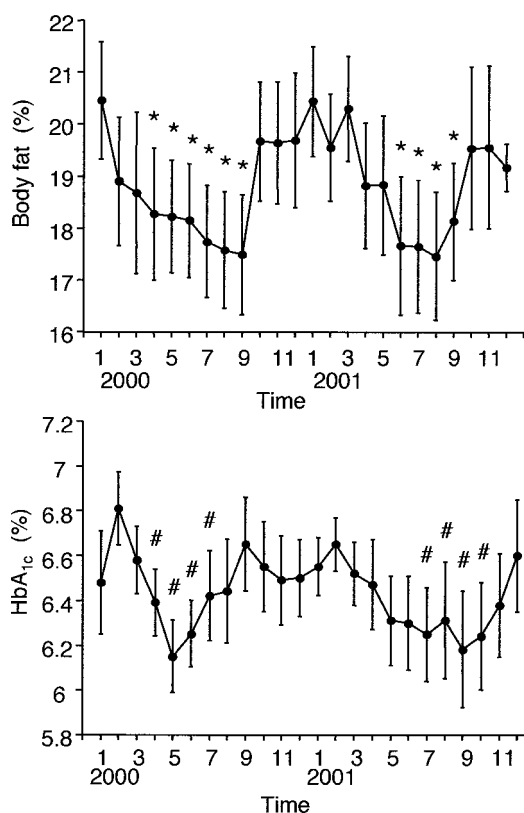


Figure 1—Seasonal changes in body fat (upper panel) and blood HbA_{1c} levels (lower panel). *P < 0.05 vs. January 2000; #P < 0.05 vs. February 2000.

again to $17.6 \pm 1.3\%$ in June 2001 (26.2°C). Blood 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 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 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 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 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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References

1. Plasqui G, Kester AD, Westerterp KR: Seasonal variation in sleeping metabolic rate, thyroid activity, and leptin. *Am J Physiol Endocrinol Metab* 285:E338–E343, 2003
2. Nordfeldt S, Ludvigsson J: Seasonal variation of HbA_{1c} in intensive treatment of children with type 1 diabetes. *J Pediatr Endocrinol Metab* 13:529–535, 2000
3. Walker BR, Best R, Noon JP, Watt GC, Webb DJ: Seasonal variation in glucocorticoid activity in healthy men. *J Clin Endocrinol Metab* 82:4015–4019, 1997

Reversible Quadriplegia and Nonketotic Hyperosmolar Coma

Is it an exceptional association or an overlooked complication?

A thrombotic stroke or cerebro-pontine 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, arthromyalgia, 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 α -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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References

1. Chiasson JL, Aris-Jilwan N, Bélanger R, Bertrand S, Beuregard H, Ekoé JM, Fournier H, Havrankova J: Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *CMAJ* 168:859–866, 2003
2. Kennedy DD, Fletcher SN, Ghosh IR, Coakley JH, Monson JP, Hinds CJ: Reversible tetraplegia due to polyneuropathy in a diabetic patient with hyperosmolar non-ketotic coma. *Intensive Care Med* 25:1437–1439, 1999
3. Hund E: Neurological complications of sepsis: critical illness polyneuropathy and myopathy. *J Neurol* 248:929–934, 2001
4. Bolton CF: Sepsis and the systemic inflammatory response syndrome: neuromuscular manifestations. *Crit Care Med* 24:1408–1416, 1996
5. Honma H, Podratz JL, Windebank AJ: Acute glucose deprivation leads to apoptosis in a cell model of acute diabetic neuropathy. *J Peripher Nerv Syst* 8:65–74, 2003

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 ± 1.0) compared with subjects in category 1 (18.6 ± 0.6), category 2 (21.1 ± 0.6), and category 3 (21.4 ± 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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References

1. Sierksma A, Patel H, Ouchi N, Kihara S, Funahashi T, Heine RJ, Grobbee DE, Kluff C, Hendriks HF: Effect of moderate alcohol consumption on adiponectin, tumor necrosis factor- α , and insulin sensitivity. *Diabetes Care* 27:184–189, 2004
2. Thamer C, Stumvoll M, Niess A, Tschritter O, Haap M, Becker R, Shirkavand F, Bachmann O, Rett K, Volk A, Haring H, Fritsche A: Reduced skeletal muscle oxygen uptake and reduced β -cell function: two early abnormalities in normal glucose-tolerant offspring of patients with type 2 diabetes. *Diabetes Care* 26:2126–2132, 2003
3. Tschritter O, Fritsche A, Thamer C, Haap M, Shirkavand F, Rahe S, Staiger H, Maerker E, Haring H, Stumvoll M: Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. *Diabetes* 52:239–243, 2003
4. Matsuda M, DeFronzo RA: Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 22:1462–1470, 1999
5. Chrostek L, Jelski W, Szmikowski M, Puchalski Z: Gender-related differences in hepatic activity of alcohol dehydrogenase isoenzymes and aldehyde dehydrogenase in humans. *J Clin Lab Anal* 17:93–96, 2003

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

this is an important issue, and I am glad that Dr. Mayer Davidson and *Diabetes Care* have chosen to obtain responses from the American Diabetes Association and the pertinent pharmaceutical manufacturers of insulin. However, I found the responses from Aventis, Eli Lilly, and Novo Nordisk to be totally unsatisfactory and self-serving.

Although Aventis provides data showing stability for 4 weeks, it does not provide data showing that Lantus becomes unstable after that time. Lilly provides data to suggest that the amount of potency lost with an unknown type of insulin (probably regular) is negligible at 30 days even when stored at room temperature. However, they use the Committee for Proprietary Medicinal Products standard to say that a bottle can be open for only 28 days from a sterility perspective. So why does Lilly recommend discarding Humulin NPH, Humalog Mix 75/25, and Humulin 70/30 after shorter times? Where are the data to support these recommendations? Novo Nordisk provides no information regarding their vial regular, NPH, 70/30, lente, or buffered regular preparations and only quotes the U.S. Pharmacopoeia, which itself provides no data. They then provide no data on NovoLog either, except to say that it should be discarded after 28 days. They also state that NovoLog used in pumps should be discarded after 48 h. Then follows a bewildering set of varying recommendations for different times for Novolog, Novolog 75/25 FlexPens, and Novolin N, R, and 70/30 InnoLet pens that ranges from 10 to 28 days. Where are the data?

Without data showing that these insulins become unstable after specified periods of time or showing high contamination rates, the recommendations to discard the bottles and cartridges seem to be more based on a desire to sell more insulin rather than on facts related to safety and efficacy. Many of our patients use insulin doses <15 units/day and therefore would have to throw away bottles containing >50% of the original amount of insulin. At the current prices being charged by these manufacturers, this is a considerable loss of money on the patient's part and a considerable excess profit for the manufacturers. The insulin-manufacturing community would do well to supply insulin vials in 5-ml amounts as well as 10-ml amounts.

Health care providers and patients deserve better information from these manufacturers. If there are data showing specified times for safety and efficacy, they should provide such data. The rambling responses provided here are unhelpful and seem to obfuscate rather than clarify a complex issue.

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M.E.M. is currently receiving research support from Eli Lilly and Aventis and has received honoraria from Lilly, Aventis, and Novo Nordisk.

Novo Nordisk and Aventis had no further comments on this issue.

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References

1. Grajower MM, Harris WC, Fraser CG, DeFelippis MR, Holcome JH, Santiago OM, Daugherty ML, Clark NG: How long should insulin be used once a vial is started? (Commentary). *Diabetes Care* 26: 2665-2669, 2003

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

Response to Molitch

We thank Dr. Molitch (1) for his comments in this issue of *Diabetes Care* regarding our previous response (2) concerning the issue of insulin stability. Dr. Molitch points out apparent differences among manufacturers in our original letter with respect to in-use recommendations, and he requests actual data on insulin potency and that insulin be provided in smaller containers. We appreciate the opportunity to comment further on these important questions.

First, we will provide storage recommendations for the Lilly insulin formulations and containers available in the U.S. Second, we will explain further why the storage guidelines vary by formulation and type of container. Third, we will provide supporting data and explanations for our recommendations.

In-use recommendations for insulins in vials differ from those for insulin in cartridges or prefilled insulin pens. Recommendations for insulin products in vials are the same regardless of the formulation. However, the in-use recommendations may differ for that formulation when the same insulin is available in a cartridge. The primary reason for the different in-use dating recommendation between vials and cartridges is based on differences in the expected use of these products. For example, insulin in cartridges is expected to undergo more rigorous agitation and exposure to more widely varying temperatures by patients than insulin in vials. The in-use dating guidelines established by the Food and Drug Administration (FDA) for cartridges take into account the smaller volume and fewer total units of insulin compared with vials, as well as the potential exposure of insulin to greater heat and mechanical agitation.

The recommended in-use dating once an insulin vial has been punctured is 28 days for Humalog, Humalog Mix 75/25, Humulin R, Humulin L, Humulin N, Humulin U, Humulin 70/30, and Humulin 50/50. Humalog in cartridges and prefilled pens may also be used for up to 28 days. In contrast, the recommended in-use dating for all other insulins available in the U.S. in prefilled pens varies among formulations, based on a variety of end points in stability studies. For example, Humalog Mix 75/25 and Humulin 70/30 in prefilled pens can be used for up to 10 days, whereas Humulin N is recommended to be used within 14 days.

Dr. Molitch requests specific stability information over time for each insulin formulation manufactured by Eli Lilly, especially those insulins available in cartridges and thus having shorter in-use dating than the same insulin available in vials. Lilly's in-use recommendations are based on the results of extensive laboratory testing. Because it is difficult to quantify how patients treat insulin, Lilly takes a conservative approach to in-use recommendations. We developed two automated physical stress tests to study the insulin formulations at conditions more extreme than the expected, typical patient usage. The details and results of this extensive testing have been published (3). These tests, developed with input from regulatory agencies, also help to determine adequate product dating during nonre-

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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References

1. Molitch ME: How long should insulin be used once a vial is started? Response to Grajower et al. (Letter). *Diabetes Care* 27: 1240–1241, 2004
2. Grajower M, Fraser CG, Holcombe JH, Daugherty ML, Harris WC, De Felippis MR, Santiago OM, Clark NG: How long should insulin be used once a vial is started? (Commentary). *Diabetes Care* 26: 2665–2669, 2003
3. Shnek D, Hostettler DL, Bell MA, Olinger JM, Frank BH: Physical stress testing of insulin suspensions and solutions. *J Pharm Sci* 87:1459–1465, 1998

The Metabolic Syndrome: The Emperor Needs Some Consistent Clothes

Response to Vinicor and Bowman

Drs. 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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References

1. Vinicor F, Bowman B: The metabolic syndrome: the emperor needs some consistent clothes (Letter). *Diabetes Care* 27:1243, 2004
2. Jones TD: The diagnosis of rheumatic fever. *JAMA* 126:481–484, 1944
3. Unger RH: Lipid overload and overflow: metabolic trauma and the metabolic syndrome. *Trends Endocrinol Metab* 14:398–403, 2003
4. Unger RH: The physiology of cellular lipoporegulation. *Annu Rev Physiol* 65:333–347, 2003
5. Schaffer JE: Lipotoxicity: when tissues overeat. *Curr Opin Lipidol* 14:281–287, 2003
6. Andrews RC, Herlihy O, Livingstone DE, Andrew R, Walker BR: Abnormal cortisol metabolism and tissue sensitivity to cortisol in patients with glucose intolerance. *J Clin Endocrinol Metab* 87:5587–5593, 2002
7. Masuzaki H, Paterson J, Shinyama H, Morton NM, Mullins JJ, Seckl JR, Flier JS: A transgenic model of visceral obesity and the metabolic syndrome. *Science* 294:2166–2170, 2001
8. Morton NM, Holmes MC, Fievet C, Staels B, Tailleux A, Mullins JJ, Seckl JR: Improved lipid and lipoprotein profile, hepatic insulin sensitivity, and glucose tolerance in 11beta-hydroxysteroid dehydrogenase type 1 null mice. *J Biol Chem* 276:41293–41300, 2001
9. Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW, Shulman GI: Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science* 300:1140–1142, 2003
10. Kelley DE, He J, Menshikova EV, Ritov VB: Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes* 51:2944–2950, 2002
11. Enns GM: The contribution of mitochondria to common disorders. *Mol Genet Metab* 80:11–26, 2003
12. Short KR, Vittone JL, Bigelow ML, Proctor DN, Rizza RA, Coenen-Schimke JM, Nair KS: Impact of aerobic exercise training on

age-related changes in insulin sensitivity and muscle oxidative capacity. *Diabetes* 52:1888–1896, 2003

13. Leverve XM, Guigas B, Demaille D, Bantandier C, Koceir EA, Chauvin C, Fontaine E, Wiernsperger NF: Mitochondrial metabolism and type-2 diabetes: a specific target of metformin. *Diabetes Metab* 29:6S88–6S94, 2003
14. Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI: Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med* 350:664–671, 2004

Aspirin Resistance in Diabetic Patients

Response to Sacco et al.

The 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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References

1. Sacco M, Pellegrini F, Roncaglioni MC, Avanzini F, Tognoni G, Nicolucci A, PPP Collaborative Group: Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care* 26: 3264–3272, 2003
2. Collaborative Group of the Primary Prevention Project (PPP): Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice: Collaborative Group of the Primary Prevention Project. *Lancet* 357:89–95, 2001 [Erratum appears in *Lancet* 357: 1134, 2001]
3. de Gaetano G: Aspirin and the prevention of ischemic heart disease: a Socratic dialogue between a cardiologist, a clinical pharmacologist and an expert of blood platelets. *Ital Heart J* 2:582–588, 2001
4. Meade TW, Brennan PJ: Determination of who may derive most benefit from aspirin in primary prevention: subgroup results

from a randomised controlled trial. *BMJ* 321:13–17, 2000

5. Steering Committee of the Physicians’ Health Study Research Group: Final report on the aspirin component of the ongoing Physicians’ Health Study. *N Engl J Med* 321:129–135, 1989
6. Friend M, Vucenik I, Miller M: Platelet responsiveness to aspirin in patients with hyperlipidaemia. *BMJ* 326:82–83, 2003
7. Patrono C: Aspirin resistance: definition, mechanisms and clinical read-outs. *J Thromb Haemost* 1:1710–1713, 2003
8. de Gaetano G, Cerletti C: Aspirin resistance: a revival of platelet aggregation tests? *J Thromb Haemost* 1:2048–2050, 2003

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_{1c} 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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References

1. Sacco M, Pellegrini F, Roncaglioni MC, Avanzini G, Tognoni A, Nicolucci A, PPP Collaborative Group: Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care* 26: 3264–3272, 2003
2. Colwell JA, Nesto RW: The platelet in diabetes: focus on prevention of ischemic events. *Diabetes Care* 26:2181–2188, 2003
3. Watala C, Golanski J, Pluta J, Boncler M, Rozalski M, Wieclawska B, Kropiwnicka

A, Drzewoski J: Reduced sensitivity of platelets from type 2 diabetic patients to acetylsalicylic acid (aspirin): its relation to metabolic control. *Thromb Res*. In press

- Friend M, Vucenik I, Miller M: Platelet responsiveness to aspirin in patients with hyperlipidaemia. *BMJ* 326:82–83, 2003

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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References

- Sacco M, Pellegrini F, Roncaglioni MC, Avanzini F, Tognoni G, Nicolucci A, PPP Collaborative Group: Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care* 26: 3264–3272, 2003
- Colwell JA: Aspirin for primary prevention of cardiovascular events in diabetes (Editorial). *Diabetes Care* 26:3349–3350, 2003
- de Gaetano G: Aspirin resistance in diabetic patients (Letter). *Diabetes Care* 27: 1244–1245, 2004
- Antithrombotic Trialists' Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 324: 71–86, 2002
- ETDRS Investigators: Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study report 14. *JAMA* 268:1292–1300, 1992

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 μ 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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References

- Kim CH, Park JH, Park TS, Baek HS: Autoimmune hypoglycemia in a type 2 diabetic patient with anti-insulin and insulin receptor antibodies (Letter). *Diabetes Care* 27:288–289, 2004
- Redmon JB, Nuttall FQ: Hypoglycemic disorders. *Autoimmune Hypoglycemia* 8: 603–618, 1999
- Burch HB, Clement S, Sokol MS, Landry F: Reactive hypoglycemic coma due to insulin autoimmune syndrome: case report and literature review. *Am J Med* 92:681–685, 1992
- Taylor SI, Barbetti F, Accili D, Roth J, Gordon P: Syndromes of autoimmunity and hypoglycemia. *Endocrinol Metab Clin North Am* 18:123–143, 1989

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 Gunvener 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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References

- Kim CH, Park JH, Park TS, Baek HS: Autoimmune hypoglycemia in a type 2 diabetic patient with anti-insulin and insulin receptor antibodies (Letter). *Diabetes Care* 27:288–289, 2004
- Sahin M, Tutuncu N, Guvener ND: Autoimmune hypoglycemia in a type 2 diabetic patient with anti-insulin and insulin receptor antibodies (Letter). *Diabetes Care* 27:1246–1247, 2004
- Di Cerbo A, Tassi V, Scillitani A, Zoppetti G, De Filippis V: Characterization of insulin autoantibodies in a patient with autoimmune hypoglycemia. *J Endocrinol Invest* 18:299–304, 1995
- Uchigata Y, Hirata Y, Omori Y: Hypoglycemia due to insulin antibody (Letter). *Am J Med* 94:556–557, 1993
- Burch HB, Clement S, Sokol MS, Landry F: Reactive hypoglycemic coma due to insulin autoimmune syndrome: case report and literature review. *Am J Med* 92:681–685, 1992
- Taylor SI, Barbetti F, Accili D, Roth J, Gordon P: Syndromes of autoimmunity and hypoglycemia. *Endocrinol Metab Clin North Am* 18:123–143, 1989

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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References

1. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R: Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. *Diabetes Care* 26:3320–3325, 2003
2. Finegood DT, Hramiak IM, Dupre J: A modified protocol for estimation of insulin sensitivity with the minimal model of glucose kinetics in patients with insulin-dependent diabetes. *J Clin Endocrinol Metab* 70:1538–1549, 1990
3. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
4. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ: Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 85:2402–2410, 2000
5. McAuley KA, Williams SM, Mann JJ, Walker RJ, Lewis-Barned NJ, Temple LA, Duncan AW: Diagnosing insulin resistance in the general population. *Diabetes Care* 24:460–464, 2001
6. Quon MJ, Cochran C, Taylor SI, Eastman RC: Non-insulin-mediated glucose disappearance in subjects with IDDM: discordance between experimental results and minimal model analysis. *Diabetes* 43:890–896, 1994
7. Finegood DT, Tzur D: Reduced glucose effectiveness associated with reduced insulin release: an artifact of the minimal-model method. *Am J Physiol* 271:E485–E495, 1996
8. Cobelli C, Bettini F, Caumo A, Quon MJ: Overestimation of minimal model glucose effectiveness in presence of insulin response is due to undermodeling. *Am J Physiol* 275:E1031–E1036, 1998
9. Chen H, Sullivan G, Yue LQ, Katz A, Quon MJ: QUICKI is a useful index of insulin sensitivity in subjects with hypertension. *Am J Physiol Endocrinol Metab* 284:E804–E812, 2003
10. Mather KJ, Hunt AE, Steinberg HO, Paradisi G, Hook G, Katz A, Quon MJ, Baron AD: Repeatability characteristics of simple indices of insulin resistance: implications for research applications. *J Clin Endocrinol Metab* 86:5457–5464, 2001
11. Bastard JP, Robert JJ, Jardel C, Bruckert E, Grimaldi A, Hainque B: Is quantitative insulin sensitivity check index a fair insulin sensitivity index in humans? *Diabetes Metab* 27:69–70, 2001
12. Rabasa-Lhoret R, Bastard JP, Jan V, Ducruzeau PH, Andreelli F, Guebre F, Bruzeau J, Louche-Pellissier C, Maltrepierre C, Peyrat J, Chagne J, Vidal H, Laville M: Modified quantitative insulin sensitivity check index is better correlated to hyperinsulinemic glucose clamp than other fasting-based index of insulin sensitivity in different insulin-resistant states. *J Clin Endocrinol Metab* 88:4917–4923, 2003
13. Yokoyama H, Emoto M, Fujiwara S, Motoyama K, Morioka T, Komatsu M, Tahara H, Shoji T, Okuno Y, Nishizawa Y: Quantitative insulin sensitivity check index and the reciprocal index of homeostasis model assessment in normal range weight and moderately obese type 2 diabetic patients. *Diabetes Care* 26:2426–2432, 2003
14. Katsuki A, Sumida Y, Gabazza EC, Murashima S, Urakawa H, Morioka K, Kitagawa N, Tanaka T, Araki-Sasaki R, Hori Y, Nakatani K, Yano Y, Adachi Y: QUICKI is useful for following improvements in insulin sensitivity after therapy in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 87:2906–2908, 2002
15. Uwaifo GI, Fallon EM, Chin J, Elberg J, Parikh SJ, Yanovski JA: Indices of insulin action, disposal, and secretion derived from fasting samples and clamps in normal glucose-tolerant black and white children. *Diabetes Care* 25:2081–2087, 2002
16. Perseghin G, Caumo A, Mazzaferro V, Pulvirtani A, Piceni Sereni L, Romito R, Lattuada G, Coppa J, Costantino F, Regalia E, Luzi L: Assessment of insulin sensitivity based on a fasting blood sample in men with liver cirrhosis before and after liver transplantation. *Transplantation* 76:697–702, 2003
17. Kirwan JP, Huston-Presley L, Kalhan SC, Catalano PM: Clinically useful estimates of insulin sensitivity during pregnancy: validation studies in women with normal glucose tolerance and gestational diabetes mellitus. *Diabetes Care* 24:1602–1607, 2001

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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References

1. Karne RJ, Chen H, Quon MJ: Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism (Letter). *Diabetes Care* 27:1247–1248, 2004
2. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R: Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. *Diabetes Care* 26:3320–3325, 2003
3. Finegood DT, Hramiac IM, Dupre J: Modified protocol for estimation of insulin sensitivity with the minimal model of glucose kinetics in patients with insulin dependent diabetes mellitus. *J Clin Endocrinol Metab* 70:1538–1549, 1990
4. Saad MF, Anderson RL, Laws A, Watanabe RM, Kades WW, Chen YD, Sands RE, Pei D, Savage PJ, Bergman RN: A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance: Insulin Resistance Atherosclerosis Study. *Diabetes* 43:1114–1121, 1994
5. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MA, Monauni T, Muggeo M: Homeostasis model assessment closely mirrors the glucose clamp

technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 23:57–63, 2000

6. Bergman RN, Zaccaro DJ, Watanabe RM, Haffner SM, Saad MF, Norris JM, Wagenknecht LE, Hokanson JE, Rotter JI, Rich SS: Minimal model-based insulin sensitivity has greater heritability and a different genetic basis than homeostasis model assessment or fasting insulin. *Diabetes* 52:2168–2174, 2003
7. Garcia-Estevez DA, Araujo-Vilar D, Fiestras-Janeiro G, Saavedra-Gonzalez A, Cabezas-Cerrato J: Comparison of several insulin sensitivity indices derived from basal plasma insulin and glucose levels with minimal model indices. *Horm Metab Res* 35:13–17, 2003
8. Goddard IF: The minimal model: an evolving methodology. *Clin Sci (Lond)* 105:531–532, 2003
9. Agbaje OF, Luzio SD, Albarrak AI, Lunn DJ, Owens DR, Hovorka R: Bayesian hierarchical approach to estimate insulin sensitivity by minimal model. *Clin Sci (Lond)* 105:551–560, 2003
10. Ferrannini E, Balkau B: Insulin: in search of a syndrome. *Diabet Med* 19:724–729, 2000
11. Rabasa-Lhoret R, Bastard JP, Jan V, Ducruzeau PH, Andreelli F, Guebre F, Bruzeau J, Louche-Pellissier C, Maltrepierre C, Peyrat J, Chagne J, Vidal H, Laville M: Modified quantitative insulin sensitivity check index is better correlated to hyperinsulinemic glucose clamp than other fasting-based index of insulin sensitivity in different insulin-resistant states. *J Clin Endocrinol Metab* 88:4917–4923, 2003
12. Goff DC Jr, Zaccaro DJ, Haffner SM, Saad MF: Insulin sensitivity and the risk of incident hypertension: insights from the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 26:805–809, 2003

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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References

1. Hirshberg B, Rother KI, Digon BJ 3rd, Lee J, Gaglia JL, Hines K, Read EJ, Chang R, Wood BJ, Harlan DM: Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression. *Diabetes Care* 24:3288–3295, 2003
2. Portuese F, Orchard T: Mortality in insulin-dependent diabetes. In *Diabetes in America*. Washington, DC, U.S. Govt. Printing Office, 1995, p. 221–232 (NIH publ. no. 95-1468:221-232)
3. Cryer PE: Hypoglycemia in Diabetes. *Diabetes Care* 52:2083–2089, 2003
4. The DCCT Research Group: Adverse events and their association with treatment regimens in the DCCT. *Diabetes Care* 18:1415–1427, 1995

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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References

1. Charles MA, Selam J-L: Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression (Letter). *Diabetes Care* 27: 1249-1250, 2004
2. Hirshberg B, Rother KI, Digon BJ 3rd, Lee J, Gaglia JL, Hines K, Read EJ, Chang R, Wood

- BJ, Harlan DM: Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression: the National Institutes of Health experience. *Diabetes Care* 26:3288-3295, 2003
3. Venstrom JM, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM: Pancreas transplantation decreases survival for patients with diabetes and preserved kidney function. *JAMA* 290:2817-2823, 2003
4. Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV: Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 343:230-238, 2000
5. Kessler L, Passemard R, Oberholzer J, Benhamou PY, Bucher P, Toso C, Meyer P, Penfornis A, Badet L, Wolf P, Colin C, Morel P, Pinget M: Reduction of blood glucose variability in type 1 diabetic patients treated by pancreatic islet transplantation: interest of continuous glucose monitoring. *Diabetes Care* 25:2256-2262, 2002

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 ≥ 30 kg/m²), 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/m² 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/m²) than that of the white population as a whole (24 kg/m²). 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 ≥ 25 kg/m²) 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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References

1. McNeely MJ, Boyko EJ: Type 2 diabetes prevalence in Asian Americans: results of a national health survey. *Diabetes Care* 27: 66-69, 2004
2. Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N, Japan Diabetes Complication Study Group: Obesity and type 2 diabetes in Japanese patients (Letter). *Lancet* 361: 85, 2003 (Letter).
3. Aekplakorn W, Stolk RP, Neal B, Suriyawongpaisal P, Chongsuvivatwong V, Cheepudomwit S, Woodward M: The prevalence and management of diabetes

in Thai adults: the international collaborative study of cardiovascular disease in Asia. *Diabetes Care* 26:2758–2763, 2003

4. McNeely MJ, Boyko EJ, Shofer JB, Newell-Morris L, Leonetti DL, Fujimoto WY: Standard definitions of overweight and central adiposity for determining diabetes risk in Japanese Americans. *Am J Clin Nutr* 74:101–107, 2001
5. Sone H, Yoshimura Y, Ito H, Ohashi Y, Yamada N, Japan Diabetes Complications Study Group: Energy intake and obesity in Japanese patients with type 2 diabetes. *Lancet* 363:248–249, 2004
6. Wang L, Yamaguchi T, Yoshimine T, Katagiri A, Shirogane K, Ohashi Y: A case-control study of risk factors for development of type 2 diabetes: emphasis on physical activity. *J Epidemiol* 12:424–430, 2002

Type 2 Diabetes Prevalence in Asian Subjects

Response to Sone et al.

We 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/m² 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/m², overweight (BMI 25–29 kg/m²) and obese (BMI ≥30 kg/m²) 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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References

1. Sone H, Mizuno S, Ohashi Y, Yamada N: Type 2 diabetes prevalence in Asian subjects (Letter). *Diabetes Care* 27:1251–1252, 2004
2. McNeely MJ, Boyko EJ: Type 2 diabetes prevalence in Asian Americans: results of a national health survey. *Diabetes Care* 27:66–69, 2004