OBSERVATIONS

Poor Correlation of Pulse-Wave Velocity and Intima-Media Thickness in Diabetic Subjects

Various noninvasive in vivo assessments have recently been applied to the estimation of atherosclerosis in subjects with diabetes. The measurement of pulse-wave velocity (PWV) has been popular with the advance of apparatus, especially in Japan (1–3). However, it remains unknown whether PWV may be valid and reproducible, especially in diabetic study populations (4). In a recent issue of *Diabetes Care*, Hope et al. (5) addressed the important question of whether it is valid to apply PWV in diabetic subjects. They found that the generalized transfer function, as derived in an index population, did not describe the relationship between peripheral and central arterial waveforms (4,5).

In the present study, we examined the relationship between PWV and another technique to evaluate the early atherosclerotic lesion, i.e., intima-media thickness (IMT) of the carotid artery in subjects with type 2 diabetes and those without it. IMT of the common carotid artery was measured with high-resolution B-mode ultrasonography (SSA-770A; Toshiba, Tokyo, Japan) with an electrical linear transducer (midfrequnecy 7.5 MHz), as previously reported (6,7). The localized thickness >2.0 mm was excluded as plaque lesion (6). Brachial-ankle PWV (baPWV) was measured with an automated device (ABI-form; Nippon Colin, Komaki, Japan) that can monitor bilateral brachial and ankle-pressure wave forms using the volume plethysmographic method (1–3). The study population included a total of 245 consecutive Japanese subjects with type 2 diabetes (128 men and 117 women, mean age 65.6 ± 9.2 years [means ± SD]) and a total of 91 subjects without diabetes (35 men and 56 women, mean age 62.3 ± 9.9 years). Although there was a significant positive correlation between baPWV and IMT in subjects with diabetes, the coefficient was very small ($r^2 = 0.033$, $P < 0.005$). In contrast, there was a significant correlation with high coefficient between baPWV and IMT in subjects without diabetes ($r^2 = 0.286$, $P < 0.0001$). Furthermore, baPWV was not significantly related to the presence of plaque in either group.

This preliminary result suggests that PWV is not a feasible index for the early atherosclerotic lesion. It is not, at least in diabetic subjects, considered to be an equivalent to IMT or plaque, which are established indexes for early and advanced atherosclerotic lesion, respectively. Our result was in contrast to another report (1) that indicated a significant positive correlation between PWV and IMT in both diabetic ($r = 0.482$) and control ($r = 0.424$) subjects. It remains to be elucidated whether PWV can be used as a reliable index to evaluate antiatherogenic action of some drug in diabetic subjects (3).

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The Human Insulin Analog Aspart Can Induce Insulin Allergy

The human insulin analog aspart is produced by recombinant technology that replaces the proline at position 28 on the β-chain of insulin with negatively charged aspartic acid. Insulin aspart exists as hexamers that rapidly dissociate into monomers and dimers after the subcutaneous injection (1); it appears that it has a reduced antigenicity. It has been confirmed to be less immunogenic for development of antibodies than human insulin (2). Several case reports indicated that the human insulin analog aspart does not cause insulin allergy and is a safe alternative in insulin allergy (3,4). But a case report showed that the patient developed cutaneous allergic reactions not only to human insulin but also to the analogs aspart and lispro (5). However, here we report two cases of cutaneous allergic reaction to insulin aspart (Novorapid; Novo Nordisk, Bagsvaerd, Denmark) and no allergic reactions to human insulin (Novolin R and Novolin N; Novo Nordisk).

A 48-year-old woman with type 2 diabetes diagnosed 5 years prior was re-

ferred to our hospital in September 2003 for treatment of uncontrolled diabetes. Because of difficult-to-control hyperglycemia, three daily injections of Novorapid were prescribed. After 4 days, she noticed local skin rash and flare at the injection sites 5–15 min after insulin injection. Although she had been treated with antiallergic drugs, her allergic reaction continued and the skin rash spread. She had no previous history of allergy. She had been treated with Novolin R for acute pyelonephritis 2 years before and no local or systemic allergic reactions had occurred. The skin prick test with Novolin R was negative. We changed Novorapid to Novolin R. Subsequently, her skin rash disappeared 3 days later. However, about half a month after the start of Novolin R, the patient injected herself with Novorapid once by mistake, resulting in a systemic allergic reaction appearing immediately thereafter (generalized urticaria). By treatment with antiallergic drugs, this symptom disappeared. The patient was treated with two daily injections of premixed human insulin (Novolin 30R; Novo Nordisk) after discharge from our hospital. During the 3 months after the start of treatment with Novolin 30R, no allergic reactions occurred.

A 52-year-old man with newly diagnosed type 2 diabetes was referred to our hospital in December 2003. Because of hyperglycemia (fasting plasma glucose >14 mmol/l), three daily injections of Novorapid and one injection of Novolin N at bedtime were prescribed. After a few days, he developed local skin rash and itching at the injection sites ~5 min after insulin injection. There was no known history of allergy. The percentage of eosinophils in his peripheral white blood cell count was 8.7% (normal <7%). He showed a high level of total IgE (1,380 IU/ml; normal <360 IU/ml) and human insulin–specific IgE (12.50 IU/ml; normal <0.34) measured by radioallergosorbent test. The skin prick test for Novorapid was positive, whereas the skin prick test with Novolin R, Novolin N, and Novolin 30R was negative. Thus, he was diagnosed with Novorapid allergy. His insulin was changed to Novolin R, and the skin wheal cleared up a few days later. No antiallergic drugs were used.

These two cases demonstrated skin allergic reaction to insulin aspart Novorapid without any evidence of allergic reactions to Novolin R and Novolin N. Our data suggest that the human insulin aspart, as a variety of exogenous insulin, can induce insulin allergy.

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Hypoadiponectinemia Is Closely Associated With Nonalcoholic Hepatic Steatosis in Obese Subjects

Nonalcoholic fatty liver disease is a clinicopathological syndrome that is closely associated with obesity and other metabolic syndrome features (1).

Recent research has shown that adiponectin is a novel adipocyte-derived hormone with antidiabetic and antiatherogenic properties (2). In humans, plasma adiponectin levels are significantly lower in insulin-resistant states (2), thus suggesting that this adipocytokine is an important marker of the metabolic syndrome. Administration of adiponectin to mice has been shown to produce beneficial effects on glucose metabolism (2). Furthermore, administration of this protein was also effective in ameliorating liver biopsy features and liver test results in *ob/ob* mice (3). Accordingly, after controlling for age, sex, and BMI, hypoadiponectinemia was significantly correlated with increased serum alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) levels in overweight (4) and obese (3) healthy individuals. Although it was hypothesized that such a relationship was probably due to concomitant hepatosteatosis, no morphologic liver examinations were performed in any of these studies. Therefore this hypothesis remains to be demonstrated.

In this pilot study, we enrolled 38 obese healthy individuals (28 men and 10 women, age 46 ± 2 years) with an alcohol consumption of <20 g/day. Subjects with ultrasonographically diagnosed hepatic steatosis (n = 26) had markedly lower plasma adiponectin (by enzyme-linked immunosorbent assay) concentrations than those (n = 12) without hepatic steatosis (5.3 ± 3 vs. 10.1 ± 4 μg/ml [mean ± SD], $P < 0.001$); the former also had significantly higher values for BMI (34 ± 2 vs. 32 ± 1 kg/m^2), waist-to-hip ratio (1.07 ± 0.02 vs. 0.99 ± 0.03), homeostasis model assessment of insulin resistance (6.42 ± 1 vs. 4.34 ± 1), plasma triglycerides (3.1 ± 1 vs. 2.2 ± 1 mmol/l), ALT (57 ± 6 vs. 38 ± 5 units/l), and GGT (70 ± 5 vs. 45 ± 4 units/l) and tended to have lower HDL cholesterol. Age, sex, blood pressure, and other liver function tests were comparable between the groups. Importantly, the significant differences in plasma adiponectin concentrations that were observed between the groups were only slightly weakened after adjustment for age, sex, BMI, waist-to-hip ratio, homeostasis model assessment of insulin resistance, and plasma lipids. In multivariate analyses, hypoadiponectinemia significantly predicted ($P < 0.001$) the presence of hepatic steatosis and the increased levels of GGT and ALT, independently of potential confounders, in-

cluding insulin resistance and measures of total and regional adiposity.

Thus, these results show that hypoadiponectinemia is closely associated with nonalcoholic hepatic steatosis in obese healthy individuals, thus suggesting that hypoadiponectinemia might be, at least partly, responsible for hepatic steatosis and liver test abnormalities found in these subjects. 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.

This clinical finding, however, is consistent with a recent study demonstrating that adiponectin administration was effective in alleviating obesity-induced hepatomegaly, steatosis, and serum ALT abnormality in mice (3). The potential hepatoprotective mechanisms include induction of hepatic fatty acid oxidation, inhibition of fatty acid synthesis, and suppression of tumor necrosis factor-α production in the liver. Therefore, in addition to its antidiabetic and antiatherogenic potentials, adiponectin or its agonists may represent a novel agent for the treatment of liver diseases.

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COMMENTS AND RESPONSES

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

Response to consensus statement

I commend the authors of the consensus statement in *Diabetes Care* for focusing our attention on the physical health of people with schizophrenia and serious mental illnesses and on the need for glucose monitoring (1). There is little consensus about the risk of diabetes in people with schizophrenia and the role of atypical antipsychotic drugs (2–4). Recently I was a member of a group of international psychiatrists and diabetologists who reviewed the evidence surrounding this issue (proceedings have been published in a supplement to the April 2004 issue of the *British Journal of Psychiatry*). I was, therefore, interested to see that the conclusions published in *Diabetes Care* differed in some respects from our deliberations and those of the U.S. Food and Drug Administration (FDA). In September 2003, the FDA wrote to the manufacturers of all atypical antipsychotic drugs to ask that their respective labels be changed to recommend regular glucose testing for all schizophrenia patients at risk of diabetes. The FDA went on to explain that "[p]recise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available."

The *Diabetes Care* consensus statement suggests that the risk of hyperglycemia for some "atypicals," such as clozapine and olanzapine, is greater than for others (1). It is unclear how this opinion was reached, because although a bibliography was given, the work was unreferenced. One may speculate that the weight given to the 35 retrospective studies was greater than that for the prospective trials (4); the placebo-controlled studies (5–7) and the longest prospective study (8), which assessed glucose over 1 year and compared clozapine and chlorpromazine, are not mentioned in the bibliography.

None of the retrospective studies can state how many patients given each drug received blood tests. This is a crucial confounder, as patients receiving typical antipsychotics have less blood monitoring than those receiving "atypicals" (9). Any study that introduces glucose screening will undoubtedly find new previously undiagnosed diabetes because of the high prevalence of undiagnosed type 2 diabetes.

I am unaware of any prospective trial showing any difference among "atypicals" in terms of emergent glucose abnormalities. The best trial data comparing aripiprazole with olanzapine over 6 months found that emergent glucose abnormalities were identical (4.7 vs. 4.5%) (5,7). The use of placebo cohorts is critical to understanding what part of the risk of glucose abnormalities is attributable to drugs. There are two such datasets, and the incidence of diabetes in the placebo cohorts does not differ from that in the active-drug group (5,6).

Interestingly, during the randomized control trials, weight gain was not associated with the development of diabetes and the incidence of diabetes did not differ among the various "atypicals," despite differing propensity for weight gain. Linking short-term weight gain to the risk of diabetes ignores the many other genetic and environmental reasons why people with schizophrenia develop diabetes (10,11).

Antipsychotic medication is essential for people with schizophrenia, and effectiveness should be the most important consideration when selecting treatment. The FDA was nearer to the mark in its judgement, and choosing an antipsychotic drug on the basis of its potential to worsen glycemia is failing to understand the available data.

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Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

Response to consensus statement

The report from the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes Consensus Panel (1) contains valuable advice for the appropriate and prudent monitoring of patients who are at risk for type 2 diabetes. The recommendations made are similar to a prior consensus conference (2) and, if they are followed, will benefit our vulnerable patients by the early identification and treatment of metabolic disorders.

However, the report probably overreaches available evidence when suggesting that clinicians should consider prescribing one antipsychotic over another with the aim of avoiding diabetes. Although clear differences exist in liability for weight gain (and consequently dyslipidemias), quantifiable risk differences among the second-generation antipsychotics regarding an association with diabetes have been inconsistent in large published pharmacoepidemiological studies (3). For this reason, the U.S. Food and Drug Administration has notified the manufacturers of the second-generation antipsychotics that product labeling for all drugs in that class will require a new warning about hyperglycemia and diabetes (4). Furthermore, the risk attributable to antipsychotics appears small compared with established risk factors such as family history and advancing age. From the evidence, choosing a second-generation antipsychotic medication does not, in and of itself, have significant predictive value for treatment-emergent diabetes.

Moreover, the report did not adequately address the complex issues regarding antipsychotic efficacy. Although clinical trials may not show big differences in efficacy among antipsychotic groups, modest differences do exist, favoring not only clozapine but also risperidone and olanzapine (5). Although the consensus panel report acknowledged the primacy of appropriate treatment, for example with clozapine having unique benefits for treatment-refractory patients and those at significant risk for suicidal behavior, other antipsychotics may also have a favorable efficacy profile among treatment-refractory patients in specific treatment domains such as cognitive dysfunction (favoring risperidone and olanzapine) (6). Efficacy considerations are particularly important among patients with persistent aggressive behavior (again, favoring clozapine). Further complicating the risk-benefit equation is the observation that weight gain may be associated with response in about half of the responders to clozapine or olanzapine (7). In addition, interindividual differences in response may be huge, leading to patients receiving several sequential medication trials over the years to find the optimal regimen for that individual.

As clinicians and researchers in a state-operated psychiatric center, where the average patient has failed a number of medication trials, we find obtaining an adequate antipsychotic medication response to be a major challenge. When such a response is achieved, a major focus is to manage somatic problems should they emerge. Efficacy is the prime mover for treatment decisions (8). A switch from a beneficial antipsychotic regimen is usually the last resort after other management approaches have not been successful. Taken out of context, the consensus conference report might lead the inexperienced practitioner to switch medications prematurely and thus expose the patient to the risk of a deterioration in their symptoms and, ultimately, relapse.

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Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

Response to consensus statement

We of course welcome the fact that the issue of obesity and diabetes in the management of psychosis is taken seriously by the disciplines represented in this conference (1). However, as clinical psychiatrists we are concerned that some of the matters raised may give an unintentionally misleading message.

We are far from sure, for example, that the evidence supports the view that there is so much disparity in the incidence of obesity and diabetes among first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). Furthermore, there is no evidence, for that matter, of disparity between the experience in schizophrenia now and during the preantipsychotic period, especially from the 1920s onwards following the discovery of insulin. It seems likely that schizophrenia itself represents a significant risk factor for obesity and diabetes.

Moreover, concurrent substance abuse (especially of tobacco and cannabis) is frequent among this patient population (2), and this, along with well-established factors such as low activity, sedentary lifestyle, smoking, and, above all, poor diet (with reliance on processed and "junk" food), makes arguably the most significant contribution to the development of obesity, dyslipidemia, and diabetes. Relative risk due to family history or ethnicity is also highly relevant.

A failure to take these major confounding factors into account vitiates many of the conclusions concerning the metabolic effects of SGAs in recent literature. We do not think that there is currently any sufficient evidence to distinguish among antipsychotics (FGAs or SGAs), and we would not feel comfortable telling patients that a particular drug would not add to the risk of developing diabetes.

We are most anxious about the recommendation that "[i]f a patient gains >5% of his or her initial weight at any time during therapy, one should consider switching the SGA" (1). Weight fluctuation is common, can have many causes, is usually diet related (patients may be eating more regularly in the hospital than when in the community or they may have more appetite during the recovery phase of their illness), and may occur after treatment initiation but before the full therapeutic effect. For example, the preliminary data of the large-scale SOHO study (3) of over 10,000 European patients indicate that ~48% of patients put on >3 kg in weight over 1 year of treatment.

To follow literally the consensus advice could be potentially highly detrimental to the patient's treatment. We recognize that the cost-benefit balance is duly recognized and that the recommendation that switching should be considered does not command that switching must be done. But even the recommendations of a prestigious consensus panel have the force of law in the wider professional community, not to mention the pressure from consumers and their advocates who similarly take the recommendation as a command, considerably increasing the exposure of prescribers to litigation.

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Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

Response to consensus statement

In the February 2004 issue of *Diabetes Care*, the American Diabetes Association (ADA) published a summary of their conclusions drawn from the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (1). Although the ADA ranked the diabetes risk for second-generation antipsychotics (SGAs), the U.S. Food and Drug Administration's Division of Neuropharmacological Drug Products (DNDP) does not believe that the evidence currently available allows such a ranking.

The ADA concluded that aripiprazole and ziprasidone have no effect on the risk of diabetes. The ADA notes that because

these two drugs have not been included in epidemiological studies, this conclusion is solely based on data from clinical trials that did not reveal the risk of treatment-emergent hyperglycemia and diabetes. We must point out that the clinical trial data have not provided strong evidence of a diabetes risk for any of the SGAs. It is not clear whether this is due to the timing of glucose measurements (random in most cases), the low absolute frequency for diabetes events, the short duration of many of the trials, or other factors. Therefore, the DNDP does not consider the absence of a signal in clinical trial data to rule out the risk of diabetes with SGAs.

Based on a review of epidemiological studies, the ADA concluded that there is an increased risk of diabetes with olanzapine and clozapine and discrepant results with quetiapine and risperidone. The ADA correctly identifies many of the limitations of these epidemiological studies, including "their retrospective nature, heterogeneity of methodology, selection or ascertainment bias, and absence of appropriate or well-characterized control subjects, . . . relatively short periods of study, . . . failure to control for a possible treatment sequence bias in 'switchover' studies, and . . . not always using clinically equivalent dosages of the medications." The DNDP believes that although these studies support an increased risk of treatment-emergent hyperglycemia or diabetes, compared with patients treated with older antipsychotic drugs, the limitations of these studies preclude firm conclusions about the relative risk for diabetes among the studied SGAs.

The ADA asserts that "weight gain and changes in body composition may account for many of the purported metabolic complications associated with SGA therapy, e.g., . . . diabetes. . . " The ADA correctly points out that SGAs have different weight gain liabilities. Although weight gain may be a factor in explaining the increased diabetes risk for SGAs, DNDP is not aware of evidence proving that the treatment-emergent diabetes risk for these drugs is wholly or in part due to treatment-emergent weight gain. Although weight gain is widely recognized as a risk factor for diabetes in the general population, the clinical trial and epidemiological evidence has not shown a direct link between these treatment-emergent side effects. A substantial proportion (~25%) of adverse event reports submitted to the U.S. Food and Drug Administration do not mention weight gain as part of the presentation of SGA-associated hyperglycemia or diabetes.

Although the DNDP agrees with the ADA's recommendation to monitor patients treated with SGAs for evidence of diabetes, we do not believe that the available evidence allows the ranking of diabetes risk for these drugs at this time. We agree with the ADA that additional studies are needed to clarify many of the issues surrounding the diabetes-SGA risk relationship. In the meantime, DNDP recommends that clinicians remain vigilant in monitoring all patients treated with SGAs to assure their safe use.

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Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

Response to Holt, Citrome and Volevka, Isaac and Isaac, and Boehm et al.

We appreciate the opportunity to comment on the letters that have been received in response to our recent consensus statement on antipsychotic drugs and obesity and diabetes.

Before addressing the specific issues raised in each of these letters, I think it is important to note why the American Diabetes Association (ADA) and other organizations produce consensus statements (1). As stated in our clinical practice recommendations, "the need for a consensus statement arises when clinicians or scientists desire guidance on a subject for which there is a relative deficiency of comprehensive evidence that might otherwise allow for a more definitive statement to be made." Therefore, it should be noted that such statements represent the expert opinion of the panel based on the presentations they heard, the literature they reviewed, and the considerable discussion among panel members while writing the statement. If there was a reasonable number of randomized control trials on the subject, there would be no need for a consensus statement, but rather the associations would issue an official "Position Statement" or clinical guideline. Thus, a consensus statement can be viewed as an expert recommendation that often precedes more definitive recommendations issued when sufficient additional data become available. These may or may not be different from those in the initial consensus statement.

The letter from Holt (2) comments that he was a member of another group that reviewed the evidence surrounding this issue and reached conclusions "that differed in some respects" from those of the ADA consensus panel. Their recommendations are due to be published soon. We are, of course, delighted that another group has deliberated seriously on this important clinical question and look forward to seeing their conclusions and recommendations. We hope that much new data come to bear on this issue in the near term. We also support Holt and each of the other correspondents in pointing out that antipsychotic medications are essential for people with schizophrenia and that their differential effectiveness is very important. We purposefully used the word "consider" throughout our statement to suggest that the advice we gave with regard to avoiding undesirable side effects should be one of many factors in deciding which medication to use. Such risk-benefit considerations are essential.

Citrome and Volevka (3) comment that "the report probably overreaches available evidence when suggesting that clinicians should consider prescribing one antipsychotic over another with the aim of avoiding diabetes." We disagree with this statement and believe that the

risk of developing diabetes must also be considered given the devastating effects of this disease and its complications. The efficacy of antipsychotic therapy is an extremely important factor but not the only one. They also express concern that our report might lead the inexperienced practitioner to inappropriately make changes in medications, exposing the patient to increased risk from an inadequately treated psychiatric illness. We would hope that practitioners think carefully about all the consequences of changing medications. We believe it would also be most unfortunate if they ignored the possibility that a patient could develop one or more of the serious side effects associated with these drugs. For that reason we strongly advocate and carefully described a monitoring regimen.

Isaac and Isaac (4) point out that the evidence may not support the view that there is a difference in the incidence of obesity in diabetes between those given first-generation antipsychotics and patients treated with second-generation antipsychotics (SGAs). Our panel did not address this issue since SGAs are far more widely used and preferred (with specific exceptions noted). They also point out that weight gain is common and can have many causes. We acknowledged that point, but it does not obviate the concern that many patients on SGAs gained substantial weight within weeks of drug initiation. There appears to be a differential propensity for weight gain depending on the drug selected.

The letter from Boehm et al. (5) supports the preceding sentence, and we agree that proof is lacking, despite weight gain being widely recognized as a risk factor for diabetes and our conclusion that the weight gain from SGAs correlates with the new-onset cases of diabetes. We appreciate that more data may be required before the U.S. Food and Drug Administration's (FDA) Division of Neuropharmacological Drug Products itself adopts a ranking of diabetes risk for the various SGAs. However, the panel's review of the available information, which also included data presented by the FDA supporting a differential risk of diabetes among the SGAs, was sufficient to unanimously reach the judgment we made. Again, a consensus statement denotes expert judgement and opinion and provides clinical guidance. It is understandable that in order for drug labeling to change, a higher level of evidence is required. We point out that based on our analysis, the FDA correctly judged that there was sufficient evidence available on the first SGAs to become clinically available to merit a warning label. However, we believe that there is currently insufficient epidemiologic data to either implicate or exculpate the newer SGAs in this regard. We anticipate that the monitoring recommended in the consensus conference report will, if implemented, accelerate the accumulation of this valuable data and improve our ability to care for these complex patients.

In closing, our statement attempted to bring attention to important factors related to the care of patients with psychiatric disorders. In reaching consensus, the panel provided expert opinion on the available data, including which patients might be at increased risk of developing adverse metabolic sequelae and specifying the baseline and follow-up monitoring that would be appropriate. We do not believe our statement provides the final word on the subject. Indeed we look forward to all future publications on the issue, which will undoubtedly enhance our knowledge and provide even better clinical guidance.

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Randomized Trial Evaluating a Predominately Fetal Growth–Based Strategy to Guide Management of Gestational Diabetes in Caucasian Women

Response to Schaefer-Graf et al.

The randomized trial of Schaefer-Graf et al. (1) evaluating a fetal growth–based strategy to guide the management of gestational diabetes mellitus (GDM) in Berlin requires comment. The authors used measurement of fetal abdominal circumference (AC) at 20–35 weeks' gestation taken by only three ultrasonographers (physician investigators) to determine the need for insulin therapy (36 of 90 subjects) compared with self-monitored fasting blood glucose (>90 mg/dl) and 2-h postprandial blood glucose (>120 mg/dl) values obtained 2 days per week, which indicated the need for insulin treatment (27 of 97 subjects). The authors found that the ultrasound-based strategy provided outcomes (12% large for gestational age, 17% neonatal hypoglycemia, 14% transfer to the neonatal intensive care unit [NICU]) that were no different from the glycemic criteria strategy. However, the study design set up the glycemic control group for only partially intensified management by not requiring daily self-monitoring of fasting blood glucose (SMBG), which many other investigators have found to produce lower perinatal morbidity rates than in this study (2–6), treating GDM subjects with higher glucose diagnostic criteria than in Germany. The German authors also used tighter blood glucose treatment targets in the ultrasound-based than in the SMBG-based strategy.

The authors claimed that any physician certified for obstetrical ultrasound may be expected to produce reliable fetal AC measurements with standard equipment, since their interobserver coefficient of variance for the AC measurements was <7%. However, in most clinical settings in North America, technicians make the AC measurements and physicians trained in imaging read the films. As a result,

there is greater variance in the accuracy and repeatability of fetal AC measurements than in this study. This reduces the utility of this measurement in standard clinical practice as a criterion for insulin treatment.

The concept that some marker of fetal hyperinsulinemia should be the indicator for aggressive therapy in GDM is an old idea (7,8). The authors stated that fetal AC <75th percentile for gestational age as a marker of minimal adiposity reliably excludes elevated amniotic fluid insulin levels on the day of amniocentesis. However, Kainer et al. (9) found that the sensitivity of excess AC to predict pathological amniotic fluid insulin was only 67% and the specificity was 53%, and Schaefer-Graf et al. (10) originally found that 11 of 74 fetuses with AC <75th percentile had amniotic fluid insulin >97th percentile for 822 nondiabetic control subjects in the landmark study of Weiss (11). Schaefer-Graf et al. also originally showed that the majority of fetuses with AC >75th percentile had normal amniotic fluid insulin. The variance between fetal AC and amniotic fluid insulin is not surprising, since amniotic fluid insulin can vary with time of day and maternal-fetal glycemia in metabolically unstable women.

One wonders why 75 infants of GDM mothers in the German study (1), with normal fetal AC and no hyperglycemia on 2 days/week, had a 19% rate of neonatal hypoglycemia and 17% transfer to NICU. Perhaps it was related to the inclusion of subjects who smoked up to five cigarettes per day, or perhaps it was related to hyperglycemia on the nonmonitored days. The concept that all we have to worry about in GDM is fetal adiposity ignores the long-established fact that nonmacrosomic infants of diabetic mothers can have neonatal morbidity. Furthermore, recent data show that maternal-fetal hyperglycemia can affect fetal/placental gene expression, which might be important in short- and long-term outcomes. Finally, measurement of glycemic responses to daily food intake in GDM is attractive for its educational value in women at high risk of developing type 2 diabetes.

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Randomized Trial Evaluating a Predominately Fetal Growth–Based Strategy to Guide Management of Gestational Diabetes in Caucasian Women

Response to Kitzmiller

We truly understand the concerns raised by our study (1) investigating a mainly fetal growth–based management strategy of gestational diabetes mellitus (GDM), since our data questioned the maternal glycemia-based management that we have used for decades. We are grateful for the opportunity of discussion.

Kitzmiller (2) is right that two profiles per week may not be considered as intensified management and that we might have missed occasional events of hyperglycemia. The large-for-gestational-age (LGA) rate in the standard group might have been slightly lower with more insulin therapy. But then we would have ended up with a rate of LGA newborns lower than the normal 10%. The tight blood glucose treatment in the ultrasound group is part of the concept of ultrasound-based management that concentrates intensive intervention on fetuses at risk (3,4).

In contrast to most areas of medicine, a major dilemma in obstetrics is that there is no direct approach to the fetus. We have to rely on methods of surveillance that give us only indirect information about the well-being of the fetus. This implicates, per se, a lack of reliability. We all know about the high false-positive rate of fetal heart tracing. We are faced with the same problem in the management of GDM. From the Pedersen hypothesis, we know that severe maternal hyperglycemia is harmful for the fetus. Fasting glucose values >95 mg/dl and 2-h postprandial glucose >120 mg/dl are considered as an indication for insulin therapy. But where is the evidence for these values to be accepted as normal? When we look at the glucose values from pregnant women with normal glucose tolerance from Parretti's data (5), our thresholds seem to be too high. Where is the evidence that the

degree of placental glucose to the fetus is equal in each woman? What about the studies of twins demonstrating that each fetus reacts individually to an increased glucose supply?

Other than these uncertainties in assessing the consequences of maternal hyperglycemia on the fetus, we are faced with the problems of home glucose monitoring. A variability of ±10% from the reference value is accepted, per se. Additionally, we have to consider the skills and compliance of our patients because the predominate source of variability is the user. In our population in Berlin, and I know that it is also true for California and many other areas of the world, many women have a low degree of education, do not speak our language, or do not perform glucose profiles competently.

No doubt, we also have to be concerned about the reliability of fetal ultrasound. But I do not agree with Kitzmiller that the reliability is dependent on the medical degree of the ultrasonographer rather than on experience. I was impressed with the skills of the well-trained technicians at the University of Southern California at Los Angeles.

It is true that we (6) and Kainer et al. (7) reported that the fetal abdominal circumference (AC) measurement has a low sensitivity to detect a moderate fetal hyperinsulinism (cutoff >7 μU/ml). But according to our data, we seem to be able to exclude an amniotic fluid insulin level >16 μU/ml with 100% accuracy. In accordance to the long-term follow-up data from Metzger and Freinkel (8), even Weiss (9) reported that the morbidity of the children affected is limited to high amniotic fluid insulin (~>17 μU/ml). And to answer Kitzmiller's concern that we might miss a fetus with morbidity despite normal growth, at least from our data, there was no case of relevant hyperinsulinism with AC <75th percentile. This might be different in women with preexisting diabetes and vascular complications causing growth retardation.

We share Kitzmiller's concern that we may overtreat fetuses with an AC >75th percentile that is not due to hyperinsulinism. We definitely have to develop more specific ultrasound parameters to distinguish between diabetes and genetic-related macrosomia. But we face the same problem with our glycemia-based strategy: Weiss (9) reported that 50% of the fetuses had normal amniotic fluid insulin in women with a mean glucose value of 100 mg/dl, which is more or less equivalent to the above-mentioned cutoffs for insulin therapy. Thus, we already seem to overtreat 50% of the women when applying the present practice using solely glycemic criteria.

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A Standardized Triglyceride and Carbohydrate Challenge

Response to Mohanlal and Holman

We read with interest the article by Mohanlal and Holman (1) on the oral triglyceride tolerance test, showing that the test meal they propose is palatable, acceptable to subjects, and provides reproducible evaluation of postchallenge triglyceride profiles.

Although there is a tendency to consider postprandial hypertriglyceridemia as an independent risk factor for cardiovascular disease, no test meal for its evaluation has been universally accepted or normal ranges for postprandial triglycerides have been identified. Moreover, a clear distinction should be made between postprandial, which is the daily situation, and postchallenge hypertriglyceridemia.

The test meal proposed in the above study is not a regular meal and, as a test meal, has the disadvantage of a high carbohydrate content (almost to the level of an oral glucose tolerance test) eliciting insulin secretion, which modulates triglyceride removal from the circulation. However, insulin secretion varies greatly not only among diabetic subjects, but also among nondiabetic subjects, and it is very different between diabetic and nondiabetic subjects.

The total area under the curve (AUC) of triglycerides and postprandial triglyceride levels are not the best index of postprandial triglyceride responses because they are strongly influenced by fasting triglyceride concentrations. A much better index uses incremental AUC (IAUC) and incremental triglyceride levels because they reflect only the postchallenge triglyceride changes (2). Therefore, the difference in postprandial triglycerides between di-

abetic and nondiabetic subjects in the study of Mohanlal and Holman (1) is significant by the criterion of AUC because diabetic subjects have much higher fasting triglyceride levels (1.35 vs. 0.77 mmol/l), but when the criterion of IAUC is used, diabetic subjects do not have a significantly higher postprandial triglyceride response. Thus the greater "exposure" of diabetic subjects suggested in this study is mainly due to higher fasting triglycerides than excessive postprandial increase.

The extremely high ($r = 0.909$) correlation found between postchallenge and fasting triglyceride levels is misleading because fasting levels contribute >70% to the postprandial levels.

We have recently shown (3), using a test meal containing 40 g fat, 19 g protein, and only 10 g carbohydrates in nondiabetic subjects, that the triglyceride increment over the fasting value and the IAUC were not correlated with the fasting triglyceride concentration. Thus postprandial hypertriglyceridemia can occur irrespective of the fasting triglyceride concentrations and is better described by incremental values.

We think that each test meal has its advantages and disadvantages and that until a universally accepted oral triglyceride tolerance test (in analogy to the oral glucose tolerance test) is developed, test meals should be in each study and, moreover, incremental rather than absolute triglyceride values should be used for the evaluation of postchallenge hypertriglyceridemia.

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A Standardized Triglyceride and Carbohydrate Challenge

Response to Thanopoulou, Karamanos, and Roussi

We welcome the comments by Thanopoulou, Karamanos, and Roussi (1), who emphasize the unmet need for a standardized method to assess triglyceride tolerance. In the absence of an acceptable test meal that could readily be made available worldwide, our oral triglyceride tolerance test (OTTT) (2) provides a practical solution for the reproducible evaluation of postchallenge triglyceride tolerance in diabetic and nondiabetic subjects. The incorporation of 50 g of carbohydrate in the OTTT makes it more akin to everyday meals in that fat is usually ingested with carbohydrate and thus more likely to reflect the daily postprandial situation than an isolated fat load. We agree that careful interpretation and reporting of the lipid profiles observed is essential, particularly given the well-recognized close association between fasting and postchallenge triglyceride levels. The routine use of a standardized challenge such as the OTTT would permit more comparable data to be obtained for both clinical and trial-related evaluations of triglyceride tolerance. This in turn would allow for more precise determination of the relative importance of postchallenge triglyceride levels on clinical outcomes and the potential impact of therapies that might differentially affect them.

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Role of Simvastatin as an Immunomodulator in Type 2 Diabetes

Response to Lopes-Virella et al.

In reading the article by Lopes-Virella et al. (1), we were rather concerned that the authors referred to "creatinine kinase" as a marker of cardiac injury. We are certain that the authors wanted to refer to creatine kinase, which is usually abbreviated as CK, and not "creatinine kinase," as such an enzyme does not exist. Creatine kinase catalyzes the reversible phosphorylation of creatine to phosphorylcreatine, whereas the conversion of creatine to creatinine requires no enzymatic input.

A Medline search performed on 24 April 2004 for the incorrect term "creatinine kinase" revealed a total of 356 entries. Organizing these entries according to which decade they were published, we could see that from 1964 to 1974 there were 2 entries, from 1974 to 1984 there were 20 entries, from 1984 to 1994 there were 128 entries, and finally (rather worryingly) from 1994 to 2004 there were 206 entries. It evident that the number of entries for the incorrect term "creatinine kinase" has been steadily increasing. We are deeply concerned about this unjustified increase and wish to make more authors aware of the correct terminology.

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Improper Insulin Compliance May Lead to Hepatomegaly and Elevated Hepatic Enzymes in Type 1 Diabetic Patients

Response to Yu and Howard

We read with interest the recent letter by Yu and Howard (1) describing recurrent episodes of hepatomegaly and pronounced elevation of liver enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) in type 1 diabetic patients with poor metabolic control and treated with high daily doses of insulin (1.3–2.2 units · kg^{-1} · day^{-1}), considering the extra doses are to correct frequent hyperglycemia and/or diabetic ketoacidosis.

Here we describe similar experiences in our patients affected by autoimmune and nonautoimmune diabetes in the pediatric age range. In particular, we have observed a child with diabetes onset at the age of 66 days that was probably not of autoimmune origin (2) because he did not present with type 1 diabetes–susceptible non–Asp/Arg HLA DQ heterodimers (3) and showed the absence of islet cell antibodies, GAD, insulin autoantibodies, and insulinoma-associated protein 2. These last dosages were carried out on frozen serum because they were not all available at the time of diagnosis.

At age 3 years, he presented with the first episode of hepatomegaly and elevated liver enzymes. Other liver function tests, such as alkaline phosphatase, protrombin/partial prothombin time, and total bilirubin, were normal. Two other episodes were reported in the following 2 years. Although his metabolic control was acceptable on all three occasions, the insulin dose was maintained at a high level for the best possible HbA_{1c} (Table 1). This dose was almost twice the usual dose used at this age and is comparable to the 2.2 units · kg^{-1} · day^{-1} described by Yu and Howard.

Hepatic biopsy during the second episode showed abundant glycogen deposits in the hepatocytes and normal mitochondria. On all three occasions, continuous low-dose intravenous insulin normalized the liver enzymes in just a few days.

Now at age 15 years, aside from diabetes, he is in good health. During adolescence the maximum dosage of insulin was 1 unit · kg^{-1} · day^{-1}, which was lower than the dose described by Yu and Howard, yet we found no other episodes of liver damage.

In three other patients with type 1 autoimmune diabetes, we observed a pattern of liver dysfunction during puberty similar to Yu and Howard. In all patients, diabetes was very poorly controlled despite high insulin dosage (Table 1). Liver size and enzymes in these three patients also returned to normal after intravenous insulin. No liver biopsy was performed in any of these cases.

On the basis of our experience, we agree with Yu and Howard when they indicate the pathogenesis of this liver disease in chronic overtreatment with insulin and self-induced hyperinsulinism rather than low metabolic control or diabetes etiology.

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Table 1

Patient initials, sex, diabetes onset	First episode age, insulin dose, HbA_{1c} (%), AST, ALT (units/ml)	Second episode age, insulin dose, HbA_{1c} (%), AST, ALT (units/ml)	Third episode age, insulin dose, HbA_{1c} (%), AST, ALT (units/ml)
G.V., male, age 66 days	3.1 years, 1.3 units · kg^{-1} · day^{-1}, 5.5, 8,210, 5,880	3.8 years, 1.2 units · kg^{-1} · day^{-1}, 7.0, 2,000, 1,000	5.4 years, 1.1 units · kg^{-1} · day^{-1}, 8.0, 1,824, 1,604
B.A., female, age 13 years	17 years 1.5 units · kg^{-1} · day^{-1}, 12, 1,420, 1,290		
O.S., female, age 11 years	12 years 1.5 units · kg^{-1} · day^{-1}, 9.8, 1,370, 1,120		
P.V., female, age 7 years	11 years 1.1 units · kg^{-1} · day^{-1}, 13.8, 840, 720	13 years 1.4 units · kg^{-1} · day^{-1}, 12.0, 299, 260 amylase 362	

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Peripheral Arterial Disease in People With Diabetes

Response to consensus statement

As a general internist, I read the newest American Diabetes Association consensus statement (1) on peripheral arterial disease (PAD) in diabetic patients with great interest. In the statement, it is recommended that "a screening ABI (ankle-brachial index) should be performed in patients >50 years of age who have diabetes." The justification for this recommendation seems to be that PAD in diabetic patients is common, underdiagnosed, and results in increased morbidity.

I had assumed that the consensus statement was based on solid evidence, such as a systematic review. What seems to be lacking in this recommendation, as pointed out in the consensus statement, is proof that treating risk factors other than smoking halts the progression of or decreases morbidity in PAD.

As a pragmatist, I wonder what percentage of primary care providers currently own a Doppler machine and have been trained to use it and how many will purchase a $500 machine based on the recommendations of this consensus statement? How many minutes will it add to the day to screen all diabetic patients, and will insurance companies reimburse for screening asymptomatic patients? How often should screening be repeated? Will asymptomatic patients under optimal management benefit from knowing they have moderate PAD?

Would it not be better to make such a recommendation for screening after the evidence suggests benefit from tighter control of hyperglycemia, hypertension, and dyslipidemia?

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Peripheral Arterial Disease in People With Diabetes

Response to Hoyt

The American Diabetes Association develops evidence-based clinical practice recommendations, or position statements, on medical issues related to diabetes. These statements are typically based on a thorough, balanced review of the literature.

Consensus statements are developed when there are clinical issues and insufficient evidence to produce a definitive position statement, as is the case for peripheral arterial disease (PAD) in diabetes. Before the development of a consensus statement, a panel of experts listens to presentations on the particular subject. A consensus statement represents the panel's collective analysis, evaluation, and opinion, based in part on the presentations.

Based on the available evidence and the prevalence and burden of PAD in diabetes, the consensus panel believes that reasonable recommendations were made regarding screening and treatment.

A primary reason to diagnose PAD is to identify a person who has a high likelihood of having a cardiovascular event and begin intensive risk-reduction interventions. Although diabetes alone is considered a cardiovascular disease risk equivalent, most diabetic patients are not under optimal management. In fact, a recent study (1) found that just 7.3% of patients with diabetes meet the recommended goals for HbA_{1c}, blood pressure, and cholesterol. A diagnosis of PAD confers additional cardiovascular risk to the patient with diabetes and gives further impetus to aggressively manage risk factors that may be overlooked.

A diagnosis of PAD may also prevent a limb-threatening event. This applies especially to the asymptomatic patients who may suddenly develop critical limb ischemia. Thus, patients with diabetes and PAD should be placed in preventative care by foot care specialists. This includes skin care, nail care, and shoe prescriptions as recommended by the American Diabetes Association (2).

When medical societies and other organizations agree that particular screening tests are important and impact outcomes, reimbursement may likely be influenced. The panel believes that publishing these screening recommendations is the first step to ensuring that government and other health insurers reimburse for the ankle brachial index, the preferred screening test for PAD, in the future to help defray the costs of extra time and equipment that the busy practitioner must incur.

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Thiazolidinedione Use, Fluid Retention, and Congestive Heart Failure: a consensus statement from the American Heart Association and American Diabetes Association

Response to Nesto

The introduction of thiazolidinediones (TZDs) has been greeted with enthusiasm in part because of their ability to lower glucose by addressing an underlying pathological feature of diabetes and because TZDs have the potential to ameliorate several cardiovascular markers. This enthusiasm has been tempered by safety concerns. We, therefore, read with interest the American Diabetes Association/American Heart Association consensus statement (1) regarding TZD use, fluid retention, and congestive heart failure (CHF) .

We disagree with portions of this statement. In individuals without symptomatic heart disease, we would not start TZDs if the patient had preexisting edema or a history of heart failure, especially since no lower range for a depressed ejection fraction is stated. While this may have a salutary effect on glucose control, it introduces unnecessary complexity and confusion when considering future symptoms and signs. Likewise, we would wait to use TZDs in patients with symptomatic heart failure until ongoing clinical trials establish the safety of these medications in this patient population. We disagree strongly with components of the monitoring section. When someone who is free of CHF develops CHF after the start of a medication known to worsen CHF, a recommendation to "reconsider" or a "dosage change" is unduly restrained, especially given the uncertain time period that is required for the effect of TZDs to dissipate. Additionally, if edema develops after the start of TZDs, the statement invites consideration of alternate causes of edema. While this recommendation is intellectually defensible, it belies the reality that physicians will, with rare exception, stop a medication when a side effect develops that is clearly known to be caused by the medication. In both circumstances, we would stop the medication.

Until ongoing prospective clinical trials ascertain the safety of TZDs in the patients that we cite above, we believe that there should be a strong preference for alternate therapies.

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Thiazolidinedione Use, Fluid Retention, and Congestive Heart Failure: a consensus statement from the American Heart Association and American Diabetes Association

Response to Elasy and Griffin

We appreciate the letter from Elasy and Griffin (1) containing their approach to the use of thiazolidinediones (TZDs). The goal of our report (2) was to increase awareness of this potentially serious side effect of TZD use. Our recommendations were based on the evidence we reviewed and discussed. We do not disagree with the opinions expressed by Elasy and Griffin and believe that these decisions are always best made by the provider, carefully weighing all of the potential benefits and risks of these medications in their particular patient. We should state that there are many scenarios with individual patients in whom cardiac disease may have been clinically evident or is present at the time TZDs are being considered. The consensus document could not consider all of these and instead aimed to provide the practitioner with general guidelines. The authors of this letter have appropriately come to their own conclusions about the use of TZDs in selected patients with diabetes.

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R.W.N. has received honoraria from GlaxoSmithKline and Takeda.

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