OBSERVATIONS

Mutations in the Hereditary Hemochromatosis Gene Are Not Associated With the Increased Body Iron Stores Observed in Overweight and Obese Women With Polycystic Ovary Syndrome

We recently reported (1) that serum ferritin levels are increased in overweight and obese women with polycystic ovary syndrome (PCOS) independently of inflammation. This finding suggested increased body iron stores in these women, raising the possibility that genes related to iron metabolism are altered in PCOS.

Classic hereditary hemochromatosis is an autosomal recessive disorder caused by mutations in the *HFE* gene, resulting in increased intestinal iron absorption and iron accumulation in several organs. In the study by Sanchez et al. (2), >80% of the Spanish patients with hereditary hemochromatosis were homozygous for the *HFE* C282Y mutation or compound heterozygotes for the *HFE* C282Y and H63D mutations.

Although hereditary hemochromatosis has low penetrance in young women, we studied the *HFE* genotypes of 78 PCOS patients and 43 control subjects characterized in our previous report of increased body iron stores in PCOS (1). Genotyping was conducted by PCR/restriction fragment–length polymorphism methods using the *Pml*I and *Bcl*I restriction enzymes for the C282Y and H63D mutations, respectively. The ethics committee of the Hospital Ramón y Cajal approved the study, and informed consent was obtained from all participants.

We did not find homozygosity for the C282Y substitution in *HFE* in any PCOS patient or control subject. Three patients with PCOS but no control subjects were compound heterozygotes for the C282Y and H63D mutations ($\chi^2 = 1.696$, $P = 0.552$), but their serum ferritin levels were 14, 82, and 113 pmol/l (normal range 11–325), ruling out a condition of iron overload.

Forty-eight of the patients (61.5%) and 24 of the control subjects (55.8%) had one or more mutated alleles of the C282Y and H63D genotype alleles, whereas all other women were homozygous for wild-type alleles of both *HFE* mutations ($\chi^2 = 0.377$, $P = 0.539$). The *HFE* mutations studied here did not influence serum ferritin levels when considering PCOS patients and control subjects as a whole (C282C [$n = 110$] 109 ± 94 pmol/l vs. C282Y [$n = 11$]110 ± 115 pmol/l [$F = 0.122$, $P = 0.728$]; H63H [$n = 57$] 108 ± 98 pmol/l vs. H63D and D63D [$n = 64$] 110 ± 94 pmol/l [$F = 0.499$, $P = 0.481$]; and interaction between both genotypes [$F = 0.834$, $P = 0.363$]) or separately (data not shown).

Finally, a multivariate stepwise linear regression analysis model retained BMI ($\beta = 0.263$, $P = 0.003$) and PCOS status ($\beta = 0.238$, $P = 0.007$) as predictive variables of serum ferritin levels ($R^2 = 0.127$, $F = 8.557$, $P < 0.001$), whereas carrier status for C282Y and/or H63D mutations, as well as having oligo/amenorrhea compared with having regular cycles, were excluded as predictors.

In summary, PCOS is not associated with the C282Y and H63D mutations in *HFE*, and these mutations did not influence serum ferritin levels in our series. As discussed earlier (1), other mechanisms are possibly related to the increase in body iron stores observed in overweight and obese PCOS patients.

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On the Weighted-Average Relationship Between Plasma Glucose and HbA_{1c}

HbA_{1c} (A1C) is widely used to assess glycemic control in clinical and research settings, but the precise relationship between A1C and preceding self-monitored plasma glucose measurements is recognized to be complex. It has been reported that measuring plasma glucose levels in the 120 days before an A1C measurement has a nonuniform effect on the result depending on the time that has elapsed between the glucose level and subsequent A1C measurement (1). Tahara and Shima (2) attempted to model this weighted-average relationship between plasma glucose and A1C by measuring decreases in glucose and corresponding decreases in A1C in patients admitted to the hospital. Their model gives maximum weighting to glucose measurements immediately before the A1C measurement, with the weighting linearly decreasing for glucose measurements further back in time, reaching zero weighting for plasma glucose >120 days before the A1C.

Treviño (3) reported that this weighted-average relationship leads to an anomalous relationship between the exponential decay rates of glucose (G_t) and A1C. We have reviewed this result and believe that no such anomaly exists. Treviño subtracted A1C calculated from the Tahara model (H_t) from "the mean of patient-admission A1C values" (H_{start}), obtaining the counterintuitive result that a faster decay in blood glucose results in a slower

decay in ($H_{start} - H_t$). However, this "inverted" decay is likely to be due to subtracting H_t from a constant value. His expression for H_t is an absolute A1C value, not a change in A1C. An initial value, G_s, has been specified for G_t, and hence an initial value is implicit in his calculations. Subtracting H_t from a constant would not be expected to give a valid A1C estimate.

To verify this conclusion, we simulated a patient with a constant glucose level followed by an exponential decay upon admission to the hospital. During the preadmission time period, the simulated A1C reached a steady state under the constant glucose conditions, which avoided any ambiguity over the initial value (H_{start}) of A1C. In this simulation, the decay rates of H_t then varied in the same way as those for the glucose data, as would be intuitively expected. The use of two initial values by Treviño, one for *H* and one for *G*, appears to have led to the anomalous result previously reported, rather than any inherent defect in the weighted-average relationship proposed by Tahara and Shima.

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Is Pregnancy Outcome Worse in Type 2 Than in Type 1 Diabetic Women?

Most research on pregestational diabetes has focused on type 1 diabetes, and surprisingly little knowledge exists concerning outcomes of pregnancies of women with type 2 diabetes. A dearth of published data suggest outcomes similar to those of type 1 diabetic women (1,2), although recent studies report poorer outcomes in women with type 2 diabetes (3–7).

We retrospectively compared maternal and perinatal outcomes of 93 consecutive singleton pregnancies in women with type 2 diabetes and 532 consecutive singleton pregnancies in women with type 1 diabetes referred to the Diabetes and Pregnancy Unit at University Hospital La Paz from 1984 to 2004.

Women with type 2 diabetes were significantly older ([means ± SD] 31.8 ± 5.5 vs. 29.4 ± 4.7 years, $P < 0.001$), were more frequently obese (45.2 vs. 9%, $P < 0.001$), and had a shorter duration of diabetes (5.7 ± 6 vs. 11.8 ± 7.1 years, $P < 0.001$). The rate of preconceptional care (16.1 vs. 22.6%, $P = 0.175$) and gestational age at first visit (12.1 ± 6.8 vs. 11.5 ± 6.9 weeks' gestation, $P = 0.529$) did not differ between type 2 and type 1 diabetic women. Maternal and perinatal outcomes are shown in Table 1. Insulin requirements and HbA_{1c} (A1C) were lower during all three trimesters of preg-

Table 1—*Maternal and perinatal outcomes*

	Type 2 diabetes	Type 1 diabetes	*P*
*n**	93	532	
Prepregnancy BMI (kg/m^2)	28.9 ± 6.5	23.3 ± 3.1	<0.001
Maternal weight gain during pregnancy (kg)	11.7 ± 5.0	13.7 ± 4.2	<0.001
Glycemic control during pregnancy			
A1C at admission (%)	6.4 ± 1.19	7.2 ± 1.19	<0.001†
A1C second trimester (%)	5.8 ± 0.84	6.3 ± 0.9	<0.001†
A1C third trimester (%)	5.8 ± 0.76	6.2 ± 0.8	0.001†
Insulin requirements			
First trimester (units/kg)	0.38 ± 0.19	0.68 ± 0.18	<0.001†
Second trimester (units/kg)	0.48 ± 0.23	0.76 ± 0.21	<0.001†
Third trimester (units/kg)	0.62 ± 0.31	0.93 ± 0.26	<0.001†
Pregnancy-induced hypertension	18 (19.4)	82 (15.4)	0.358
Preeclampsia	6 (6.5)	17 (3.2)	0.134
Caesarean delivery	41 (44.1)	298 (56)	0.032
Gestational age (weeks of gestation)	37.1 ± 1.6	36.7 ± 1.7	0.018
Preterm delivery	28 (30.4)	186 (35.4)	0.406
Birth weight (g)	3,182 ± 623	3,243 ± 606	0.375
Birth weight ratio	1.09 ± 0.2	1.13 ± 0.18	0.019
Large for gestational age	22 (23.9)	187 (35.6)	0.032
Small for gestational age	3 (3.3)	5 (1)	0.100
Perinatal mortality	1 (1.1)	9 (1.7)	1.000
Major congenital malformations	6 (6.5)	25 (4.7)	0.442
Neonatal hypoglycemia	24 (26.1)	172 (32.8)	0.226
Neonatal hyperbilirrubinemia	34 (37)	223 (42.5)	0.359
Neonatal hypocalcemia	4 (4.3)	30 (5.7)	0.805
Birth trauma	7 (7.6)	29 (5.5)	0.467
Neonatal sepsis	9 (9.8)	55 (10.5)	1.000
Neonatal polycythemia	14 (15.2)	71 (13.5)	0.626
Neonatal respiratory distress syndrome	7 (7.6)	95 (18.1)	0.010

Data are means ± SD or *n* (%) unless otherwise indicated. *In the case of stillbirths (one in type 2 and seven in type 1 diabetes), no perinatal data other than the presence of major congenital malformations was analyzed; †adjusted for multiplicity.

nancy in type 2 diabetic women. Maternal weight gain and the rate of caesarean deliveries were lower in type 2 diabetes. Gestational age at birth was significantly higher and the rate of large infants for gestational age lower in infants of women with type 2 diabetes. The rates of perinatal mortality and major congenital malformations were comparable in both groups. First-trimester A1C in type 2 and type 1 diabetic mothers with perinatal mortality was 9.9 and 8.1 ± 1.2%, respectively. Among pregnancies complicated by major congenital malformations, first-trimester A1C was >7% in 84% of women with type 1 diabetes and only in one woman (16.7%) with type 2 diabetes ($P = 0.006$). Neonatal distress respiratory syndrome was more frequent in infants of mothers with type 1 diabetes.

In our study, pregnancy outcomes in type 2 diabetic women were, if anything, similar to those with type 1 diabetes. In fact, women with type 2 diabetes had lower rates of large infants for gestational age, neonatal respiratory distress syndrome, and caesarean delivery.

As in some of the studies available, we found no significant differences in perinatal mortality or major congenital malformations between women with type 2 and type 1 diabetes (1–2). However, the results of five recent publications (3–7) suggest that type 2 diabetes could even represent a higher risk of perinatal mortality or congenital malformations than that conferred by type 1 diabetes. Similar rates of preconceptional care in women with type 1 and type 2 diabetes in our study could explain this discrepancy, as could the fact that gestational age at first visit to the clinic was comparable in both type 1 and type 2 diabetic women who did not undergo preconceptional care.

In our study, congenital malformations in type 2 diabetes were not related to poor first-trimester metabolic control in most cases. The concurrence in women with type 2 diabetes of factors other than glycemic control, such as obesity and older age, may account for this finding (8).

In conclusion, our study shows that pregnancy outcomes in type 2 diabetes are better than in type 1 diabetes when type 2 diabetic women receive as much intensified medical treatment during preconception and pregnancy as that given to type 1 diabetic women.

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COMMENTS AND RESPONSES

Glucose Abnormalities in Patients With Hepatitis C Virus Infection: Epidemiology and Pathogenesis

Response to Lecube et al.

We read with great interest the review article by Lecube et al. (1) on the pathogenic factors specifically linking hepatitis C virus (HCV) infection and glucose abnormalities. After analyzing the different mechanisms by which HCV is thought to contribute to the development of type 2 diabetes, Lecube et al. focus their attention on the role of proinflammatory cytokines, in particular tumor necrosis factor (TNF)-α and interleukin-6. They suggest that the activation of the TNF-α system in HCV-infected patients, which has been directly related to insulin resistance in their recent study (2), could be related to the T-helper (Th)1 immune response observed in the course of HCV infection. Accordingly, as shown in Fig. 1 of their review article, the activation of the TNF-α system following the Th1 immune-mediated response is central to the pathogenesis of both liver fibrosis and insulin resistance associated with HCV infection.

However, an apparent paradox is raised by an attempt to fit such interpretation with well-acquired data and the most recent evidence from literature. Indeed, a vigorous Th1 cytokine response has been classically observed in patients who clear their HCV infection, either spontaneously (3) or in response to antiviral treatment (4,5). By contrast, recent studies have demonstrated that insulin resistance is independently associated with a poor response to antiviral therapy in HCV patients (6,7), consistent with previous observations on the lower success rate of interferon alone or interferon plus ribavirin in obese and diabetic patients. Therefore, it is difficult to understand how an increased Th1 immune response, which is protective in relation to viral clearance, can be, at the same time, the major determinant of insulin resistance and responsible for a poor response to antiviral treatment.

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Glucose Abnormalities in Patients With Hepatitis C Virus Infection: Epidemiology and Pathogenesis

Response to Gentilucci et al.

We thank Gentilucci et al. (1) for their comments on our articles (2,3) regarding the pathogenic mechanisms of diabetes in patients with hepatitis C virus (HCV) infection. The authors question why an increased T-helper (Th)1 immune response can be simultaneously the major determinant of insulin resistance and responsible for a poor response to antiviral treatment. This question is based on the statement that Th1 immunoresponse favors HCV clearance. However, although a vigorous Th1 response could play an essential role in spontaneous viral clearance, this is not so evident after interferon treatment. It should be noted that in sustained responders, pretreatment intrahepatic mRNA levels of γ-interferon and tumor necrosis factor-α were lower than in nonsustained responders (4). In addition, a lower Th2 response during antiviral treatment (specifically a decrease in interleukin [IL]-10 rather than an increase of Th1) has been associated with a long-term virological response (5,6). Tsai et al. (7) and Eckels et al. (8) demonstrated that in vitro cytokine responses to recombinant HCV antigens were confined to IL-4 and IL-10 and proposed that such Th2 predominance might be conductive to viral persistence. Furthermore, Masaki et al. (9) reported that a lower Th1/Th2 ratio before interferon therapy may favor long-term virological response in patients with chronic hepatitis C. In addition, activation of naïve B-cells via CD81 has been involved in the immunological response triggered by HCV (10). Therefore, the immune mechanisms involved in the clearance of HCV after interferon therapy are complex and are far from being elucidated.

Low-grade inflammation mediated by activated innate immunity is an underlying pathogenic mechanism of insulin resistance and type 2 diabetes. Apart from the impairment of immune response, there is a cluster of alterations associated with insulin resistance such as obesity, ageing, hypertriglyceridemia, liver esteatosis, and fibrosis; these alterations are also risk factors for nonresponse to antiviral treatment. It has recently been demonstrated (11) that hyperinsulinemia blocks the inhibition of HCV virus replication by interferon. Therefore, it seems that there is a vicious circle in which insulin resistance facilitates the persistence of HCV and, alternatively, HCV favors insulin resistance.

Altogether, one can depict a complex scenario in which Th1 response is only one more of the actors. Future studies are needed to not only confirm that insulin resistance and type 2 diabetes are poor response predictors of antiviral treatment but also to unravel the mechanisms involved.

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A Clinical Screening Tool Identifies Autoimmune Diabetes in Adults

Response to Fourlanos et al.

Fourlanos et al. (1) report on a screening instrument designed to facilitate management of latent autoimmune diabetes of adults (LADA). They assert that in poorly controlled type 2 patients exhibiting two or more of five features (age <50 years, hyperglycemic symptoms, BMI <25.0 kg/m^2, and personal and family history of autoimmunity), the "logical " next step is confirmatory islet antibody testing (1).

Although the effect of routine use of the instrument on outcomes such as HbA_{1c} is unknown, the article raises important questions relating to the management of clinically diagnosed type 2 diabetes. The authors state that LADA patients can require rapid escalation of oral therapy or early commencement of insulin (1). However, patients with severely deficient β-cell function but insufficient LADA features still need insulin therapy. In addition, some LADA patients achieve reasonable initial glycemic control with oral agents (2), with insulin available should this strategy fail.

We have concerns that the LADA instrument fails to meet the necessary criteria for a valid screening tool (3). In their small study, Fourlanos et al. report a sensitivity of 90% and specificity of 71%. However, the positive predictive value is 21%, indicating that the probability of correctly diagnosing LADA is low. This, and the high false-positive rate (28%), suggest a limited ability to identify patients most in need of early insulin therapy.

The authors' apparent intention is to promote the instrument as part of usual care. Because of this, and since the American Diabetes Association does not recommend islet antibody testing in type 2 diabetes (4), why do the authors recommend serological confirmation (1)? Even in the case of children, in whom education, dietary counsel, and treatment differ markedly by diabetes type, autoantigens may be present in a substantial number with otherwise straightforward type 2 diabetes (4). One reason for antibody testing may be to characterize LADA patients fully for intervention studies (1), but this would only be appropriate in specialist centers.

We contend that the management of poorly controlled type 2 diabetes in adults should be based on detailed clinical assessment (including the LADA instrument components), review of glycemic control, implementation of strategies (including educator and dietitian input) that might improve adherence to self-management, a discussion of available therapies (including insulin), and adequate monitoring and support. The use of the LADA instrument and/or autoantibody testing appears redundant in this setting.

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A Clinical Screening Tool Identifies Autoimmune Diabetes in Adults

Response to Davis et al.

We thank Davis et al. (1) for their comments regarding the recent publication of a clinical screening tool for latent autoimmune diabetes in adults (LADA) (2). It is appreciated that the authors' routine management of "poorly controlled adult type 2 diabetes" incorporates the "LADA instrument components." However, our observations of the management of such patients by internists and diabetes nurse practitioners in the community are often contrary to the practice of the authors. Adults with suboptimal glycemic control due to declining β-cell function (often secondary to autoimmune disease) are underrecognized, leading to delays in commencing insulin therapy. The clinical screening tool was developed to aid primary care physicians and diabetes nurse practitioners to consider the pathophysiological process of autoimmune β-cell destruction. The authors cite that the positive predictive value of the clinical screening tool is low

at 21% but do not mention that the negative predictive value of the tool is 99%; hence, the tool is highly reliable at excluding LADA and has a sensitivity of 90%, meaning that most LADA patients can be identified with the assistance of this noninvasive and cost-free clinical screening tool.

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Efficacy and Safety of Atorvastatin in the Prevention of Cardiovascular End Points in Subjects With Type 2 Diabetes: The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN)

Response to Knopp

We read with interest the results of the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) (1). The composite primary end point rate (10 mg/day atorvastatin versus placebo) showed a hazard ratio of 0.90 (95% CI 0.73–1.12, $P = 0.34$) after 4 years. Knopp et al. (1) highlight some of the differences between ASPEN and previous atorvastatin trials (Collaborative Atorvastatin Diabetes Study and Anglo-Scandinavian Cardiac Outcomes Trial) also involving diabetic individuals without established coronary heart disease (2,3).

Other differences may also be relevant. In ASPEN, 78.3% of those on atorvastatin and 76.4% of those in the placebo group were included in the analysis. This represents a substantial "drop-out" rate. Furthermore, by the end of the study, medication was taken by 67.5% of those in the atorvastatin group and 57.6% of those in the placebo group. The "drop-in" rate in ASPEN was also high; 26.9% of those on placebo and 15.4% of those in the atorvastatin group took concomitant hypolipidemic agents. Nevertheless, LDL cholesterol was reduced by 29% with atorvastatin relative to placebo. Is it possible that among the patients on atorvastatin, some took a second statin? If so, how many of the placebo-treated patients were taking a statin and for how long?

In the ASPEN study (1), blood pressure was well controlled (mean 133/77 mmHg). The blood pressure in the Collaborative Atorvastatin Diabetes Study and the Anglo-Scandinavian Cardiac Outcomes Trial was ~138/78 and 143/80 mmHg, respectively (2,3). This difference may influence any benefit accruing from lipid lowering in ASPEN. There was also a change in protocol during the ASPEN study. Did this lead to a difference in the duration of follow-up in the primary and secondary prevention groups?

The differences outlined above, together with those mentioned by the ASPEN authors (1), may have contributed to the nonsignificant reduction in events reported in this trial.

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Efficacy and Safety of Atorvastatin in the Prevention of Cardiovascular End Points in Subjects With Type 2 Diabetes: The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN)

Response to Gazi and Mikhailidis

We appreciate the interest of Gazi and Mikhailidis (1) in the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) and their proposed reasons for the nonsignificant results (2).

We mention in our article the high rates of treatment "drop in" and "drop

out" and the potential impact on the primary end point (mostly due to changing guidelines and study design changes). While Gazi and Mikhailidis correctly state that there was a high incidence of dropouts, we should clarify that all subjects (including those who withdrew) were included in the final analysis. The authors ask if the substantial differential LDL cholesterol decrease of 29% between active and placebo groups could reflect active subjects taking a second statin. Of the 15% of atorvastatin-treated subjects taking concomitant lipid-lowering medications, the vast majority took an additional statin. However, considered on its own, this would not explain the 29% reduction in LDL cholesterol compared with placebo. Of the 26.9% of subjects in the placebo group who were taking concomitant lipid-lowering medications (mostly statins), 19.7% took them for ≥30 days. It is likely more important that 42% of subjects with cardiovascular events in the atorvastatin group had stopped their randomized medication >1 year before their event.

We agree that lower blood pressure, as well as lower baseline LDL cholesterol, younger age, lower smoking rates, and a smaller proportion of men combined to place primary prevention subjects in the ASPEN at lower CVD risk than those in the Collaborative Atorvastatin Diabetes Study (3). Despite this apparent lower risk, a greater incidence of cardiovascular events was observed in placebo-treated primary prevention subjects in ASPEN (10.8%) than in CARDS (9.0%), indicating inclusion of "softer" end points, such as hospitalization for angina pectoris and interventions. Nonetheless, trends in CVD event reduction with atorvastatin were at the expected rates for the fatal and nonfatal myocardial infarction end point and in the secondary prevention cohort (2).

The subjects in the secondary prevention group entered the study before the primary prevention group. Secondary prevention subjects would have remained in the study longer were it not for the Safety and Data Monitoring Board recommendation late in the study to stop the study drug in the secondary prevention cohort and begin active treatment. As a result, the durations of follow-up were similar: 4.50 and 4.38 years for secondary versus primary prevention subjects taking atorvastatin and 4.38 and 4.46 years, respectively, for those taking placebo.

The nonsignificance of the ASPEN results has many possible explanations. Nonetheless, the ASPEN study reminds us that the many risk factors for heart disease in diabetes require individualized management for a complete treatment approach.

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Prediction of Diabetic Foot Ulcer Occurrence Using Commonly Available Clinical Information

Response to Boyko et al.

In their article, Boyko et al. (1) describe a foot ulcer prediction tool that will be useful in practice, as it is based on simple clinical criteria. The tool is well validated but limited by the patients examined, who were predominantly male (98%), mainly with type 2 diabetes, and were recruited from a hospital diabetes clinic. We have already addressed these problems in a previous publication (2) using a similar, clinically focused foot ulcer prediction tool (3) that included many of the criteria recommended by the International Working Group on the Diabetic Foot (4). Our grading scheme categorized 3,526 patients into low, moderate, or high risk of ulceration. High-risk patients "were 83 times more likely to ulcerate than low risk" patients, and the chance of "low-risk" patients remaining ulcer-free after 2.4 years was 99.7% (2). This tool was valid for type 1 and type 2 diabetic male and female subjects in a population-based cohort. Such foot ulcer prediction tools are thus useful for "all-comers" in a general community setting, as well as in specialized hospital clinics.

Boyko et al. also raised the issue that patients at high risk of ulceration may be at increased risk of death. We demonstrated that the crude mortality rate for high-risk patients was 19.1% compared with 3.4% for low-risk patients (2). Thus, high risk of ulceration is associated with increased death rate as suspected by Boyko et al., which may result in an underestimation of the predictive value of these clinical tools, as patients may die before they develop foot ulcers.

These two studies complement each other by demonstrating that the overall foot ulcer risk assessment is greater than any individual criteria (1) and that the tool is valid in routine clinical practice for all patients in the community (2) and specialized centers (1,2). Foot ulcer prediction tools may be useful in directing educational initiatives and scarce health care resources to those at greatest need.

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Prediction of Diabetic Foot Ulcer Occurrence Using Commonly Available Clinical Information

Response to Leese and Morris

We appreciate the interest of Leese and Morris (1) in our article and enjoyed reading their publication (2), which was published 1 month before our own and hence was not cited by us (3). We wish to point out that their characterization of our population as having been "recruited from a hospital diabetes clinic" is not correct, as we clearly describe that our subjects were recruited from a general internal medicine clinic (3). With regard to the generalizability of our findings, they should be applicable to the ~25 million U.S. veterans and other males with similar clinical and demographic characteristics enrolled in a primary care setting. Although Leese and Morris write that they have "already addressed" foot ulcer prediction in their publication, they do not cite our publication from 1999, which presented a prediction model for diabetic foot ulcer and anticipated several of the findings of our recent article (4).

Leese and Morris describe their findings as useful for "all-comers" in a general community setting and in specialized clinics; they also suggest that their findings are valid for male and female subjects and for both types of diabetes (1). However, their data and analysis do not provide strong support for these statements for several reasons. First, although they used a population-sampling strategy that targeted 8,923 subjects with diabetes, only 3,526 (40%) underwent a clinical foot risk assessment. Thus, most subjects in the sampling frame were not included in the analysis, which certainly raises concerns regarding the validity of findings and limits the degree of confidence with which one can recommend these results for "all-comers." Second, although both sexes and diabetes types were included in their study, the appropriate analysis of interaction to determine whether the results apply similarly in these subgroups of interest was not performed.

Leese and Morris bring up the issue of competing risks, in that individuals at higher risk for diabetic foot ulcer are also at higher risk for death. They refer to our "suspicion" that the death rate in people at high risk for ulcer is increased, but this would not be our preferred wording, as we feel certain about this association, having published data reporting this finding in 1996 (5). Comparison of cumulative risks, as in their report, may thus lead to biased results due to differential follow-up times by degree of risk. Fortunately, analytic methods that compare failure times and employ censoring, which we used in our recent publication, can address this problem.

Hopefully these recent efforts to develop foot ulcer prediction models and others will lead to more accurate identification of individuals at higher risk of foot ulcer and stimulate the development of better preventive strategies to reduce morbidity and mortality from these complications.

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Standards of Medical Care in Diabetes–2006

Response to the American Diabetes Association

I recently encountered a discrepancy in the American Diabetes Association's (ADA's) recommendations regarding conventional versus SI units for HDL cholesterol (1). The article states "raise HDL cholesterol to >40 mg/dl (1.15 mmol/l)." Simple calculation shows that 40 mg/dl = 40 × 0.02586 mmol/l = 1.03 mmol/l, rather than 1.15 mmol/l. The same error is also noted in the 2005 version.

Furthermore, in regard to the ADA's recommendation to use statin therapy for diabetic patients without overt cardiovascular disease (CVD), the recommendation to treat "regardless of baseline LDL" might have extended beyond the evidence quoted. I find the recommendation's evidence rather weak, despite a similar recommendation elsewhere (2). For evidence on diabetic patients without overt cardiovascular problems, two studies are listed (3,4). Here is an abbreviated synopsis:

The Heart Protection Study (3) showed cardiovascular benefit of statin therapy for LDL >3.0 mmol/l similar to

<3.0 mmol/l. Only 49% of the study's diabetic subjects were free of overt CVD, and 19% had prior myocardial infarction.

The CARDS (Collaborative Atorvastatin Diabetes Study) (4) showed cardiovascular benefit of statin therapy for LDL >3.1 mmol/l or <3.1 mmol/l. Subjects were without CVD but had at least one of hypertension, retinopathy, proteinuria, or smoking.

I believe the more appropriate interpretation of these two studies is that cardiovascular benefits of the statin therapy on diabetic patients have been shown for LDL < or >3.1 mmol/l (or 3.0 mmol/l, depending on the study). However, the precise lower limit of LDL, where the cardiovascular benefits may or may not persist, has not been explored. Using a threshold of 3.0 mmol/l for LDL is not a replacement for using successively lower thresholds. Using an allegory may help. For example, one cannot claim that since antihypertensive therapy reduces cardiovascular events for patients with blood pressure of >160/100 mmHg, as well as <160/100 mmHg, antihypertensive medications should be used regardless of any baseline blood pressure. Our current ignorance of the lowest LDL threshold of statin's benefits should not be replaced by the statement that no lower limit to the benefit of LDL lowering exists. A recent study (5) not referenced in the position statement showed cardiovascular benefit of lowering LDL from 3.3 to 2.15 mmol/l, but again, it does not provide an answer as to whether unlimited lowering of LDL may cease to be useful (6).

Hence, I would recommend amending the statement, "For those over the age of 40 years, statin therapy to achieve an LDL reduction of 30–40%, regardless of baseline LDL levels, is recommended (A)." This can be replaced by "For those over the age of 40 years, without overt CVD or cardiovascular risk factors other than diabetes, statin therapy to lower LDL from >3.0 mmol/l to <3.0 mmol/l is advisable. The lowest baseline LDL where statin therapy might cease to be of benefit is currently unexplored and therefore unknown."

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Standards of Medical Care in Diabetes–2006

Response to Tseng

We appreciate Dr. Tseng's letter (1), as it identifies an error in our 2006 stated HDL cholesterol goals (2), when expressed in SI units, and allows us to comment further on our recommendation regarding the use of statins in those with type 2 diabetes.

Tseng is correct that the 2006 goals for HDL (2) should read 40 mg/dl (1.03 mmol/l) for men and 50 mg/dl (1.29 mmol/l) for women. We will make this change for the 2007 position statement.

Tseng also raises the issue that he does not feel that the evidence supplied supports our recommendation that "For those over the age of 40 years, statin therapy to achieve an LDL reduction of 30–40% regardless of baseline LDL is recommended." We are in disagreement on this point. While he is correct that in the Heart Protection Study (3), the cut point for LDL level was 3.0 mmol/l (116 mg/dl), they found that "lowering the LDL cholesterol from <3.0 mmol/l to <2.0 mmol/l (i.e., <116–<77 mg/dl) in people with diabetes reduces macrovascular disease" and concluded that "statin therapy should now be considered routinely for all diabetic patients at sufficiently high risk of such major vascular event, irrespective of their initial cholesterol concentrations." Similarly, while the cut point in the Coronary Artery Diabetes Study (4) was 3.1 mmol/l (120 mg/dl), the median LDL cholesterol on statin treatment was 2.0 mmol/l (77 mg/dl), and 25% had a concentration <1.7 mmol/l (66 mg/dl). The Coronary Artery Diabetes Study investigators also concluded that "no justification is available for having a particular threshold level of LDL cholesterol as the sole arbiter of which patients with type 2 diabetes should receive statins." Based on the above, we continue to feel our recommendation is appropriate and evidence based. Of note, we do review and revise the American Diabetes Association Clinical Practice Recommendations each year based on current evidence.

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Does the Metabolic Syndrome Exist

Response to Grundy

A key question in the debate concerning the metabolic syndrome (1,2) is whether the risk accompanying it is more than the sum of its parts. Grundy (1) asserts that "risk factors are multiplicative, i.e., risk for ASCVD [atherosclerotic cardiovascular disease] from risk factors rises geometrically, not linearly, as the number of risk factors increases. Therefore, total risk is more than a summation of the individual factors." The study by Yusuf et al. (3) is offered to support this statement, but this study is a standardized case-control study of 27,098 participants in 52 countries representing several major ethnic groups to assess the relation between BMI, waist and hip circumferences, and waist-to-hip ratio to myocardial infarction overall and for each group. The metabolic syndrome is not even mentioned in the article.

In the same issue of *Diabetes Care*, Sunderström et al. (4) published a study evaluating the risk factors for cardiovascular death in >2,000 individuals followed for 30 years after being studied at age 50. More than 1,000 of them were reexamined at age 70 and followed for 9 more years. Sunderström et al. showed that the "metabolic syndrome did not predict cardiovascular mortality independently of its individual components at any age" and concluded that "the metabolic syndrome might be viewed as a clinically handy summary measure of nontraditional risk factors rather than as a strong biological entity." Thus, this evidence suggests that the answer to the key question posed above is that the risk of the metabolic syndrome for cardiovascular events is no more than the sum of its parts. Whether the metabolic syndrome serves an important function to alert physicians and patients of the importance of addressing these risk factors is a separate issue.

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Does the Metabolic Syndrome Exist?

Response to Davidson

In response to Davidson (1), who questions whether the metabolic syndrome conveys more risk for cardiovascular disease (CVD) than that contained in its risk components, I suggest that this debate is partly confused by ambiguity over the issues of prediction versus causation. The argument based on prediction contends that among the diagnostic components of the syndrome (elevated blood pressure, low levels of HDL cholesterol, high triglycerides, elevated glucose, and abdominal obesity), most of the predictive power is contained in blood pressure and HDL cholesterol. Therefore, in epidemiological studies, the short-term risk for CVD for the syndrome as a whole, assessed by current diagnostic criteria, does not substantially exceed the risk contained in two of its risk factors. Consequently, from a predictive perspective, the metabolism syndrome is really nothing more than a higher blood pressure and a lower HDL. The argument from causation holds that these predictors of risk do not necessary reflect the true causes of the risk. Indeed, there are other types of data to indicate that several risk factors of the syndrome, such as elevations in VLDL, a prothromobotic state and a proinflammatory state also contribute to risk. It is possible to say that for causation, robust predictors are confounded by other risk factors, some of which are not routinely measured. In fact, there is still uncertainty as to whether a low HDL cholesterol is truly a direct cause of CVD or is only a marker for risk. Further, clinical trials indicate that reducing blood pressure does not fully reverse the risk predicted by a higher blood pressure; hence risk associated with a higher blood pressure must be confounded by other factors. The clinical implications of this distinction between prediction and causation are considerable. At present, it cannot be assumed that treatments directed toward the predictors will produce the expected reduction in risk; rather, it is important to identify the true causes of CVD associated with the metabolic syndrome so that they can be better targeted for therapy.

A second line of debate is whether the risk factors of the metabolic syndrome, or indeed for all CVD, are additive or synergistic in their effect on CVD risk. Synergism in effect is referred to as multiplicative risk. Several epidemiological studies and the risk algorithms developed from these studies support the synergism associated with multiple risk factors. If multiple risk factors are synergistic in their effects, as epidemiology indicates, then the risk associated with multiple risk factors is greater than what would be obtained by simple addition of their individual effects.

Finally, the metabolic syndrome is a progressive condition. It typically worsens with advancing age. Hence, risk is compounded by aging. This means that risk predicted at any one time underestimates the long-term risk associated with the syndrome.

These multiple lines of evidence support my contention that the CVD risk accompanying the metabolic syndrome

cannot be causally explained by the factors contained in its current diagnostic criteria. The latter serves to identify the presence of higher risk condition but does not necessarily represent the sole targets of therapy for the condition.

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The Metabolic Syndrome (Emperor) Wears No Clothes

Response to Kahn

Kahn (1) pointed out that metabolic syndrome is associated with many uncertainties and inconsistencies, which could easily misdirect care, mislead patients, and lead to unnecessary health care costs. The risk of cardiovascular disease (CVD) associated with the syndrome is no greater than that explained by the presence of its components, and it is possible to create an almost infinite number of scenarios in which individuals who do not meet the diagnostic criteria for metabolic syndrome would be at greater risk of CVD than would those who do, as noted by Reaven (2).

What if, among the diagnostic components of metabolic syndrome, waist circumference, which is one of the anthropometric markers of obesity, was substituted by high-sensitivity C-reactive protein (CRP)? CRP is a sensitive marker of subclinical systemic inflammation and positively relates to leptin (3) and insulin resistance (4) and negatively relates to adiponectin (5), even in people with normal BMI (excluding those with diabetes). Reaven (2) pointed out that only about one-third of the most insulin-resistant individuals were actually obese, and the degree of correlation between insulin-mediated glucose uptake and BMI, waist circumference, and visceral obesity were almost equal. Neither abdominal obesity nor metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III criteria, were a significant independent risk factor for CVD in multiple regression analyses (6,7), while very low levels of CRP were useful for risk prediction among women with calculated 10-year Framingham risks <10% (8). Previously, we propose a CRP value of 0.65 mg/l as the cut point for metabolic syndrome (9) instead of ethnic-specific controversial cut points of waist circumference. Whether the new clothes fit the emperor should be revealed by reanalyses of existing epidemiological studies including CRP data.

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The Metabolic Syndrome (Emperor) Wears No Clothes

Response to Oda

The possible inclusion of C-reactive protein (CRP) in the metabolic syndrome algorithm highlights the problems of the construct itself. If the syndrome is supposed to be a predictive tool for future cardiovascular events, then we should indeed test the benefit of adding CRP, along with age, sex, race, adiponectin, homocysteine, etc. If the utility of the syndrome is to call attention to obesity, then there is no need for expensive laboratory tests. If the virtue is to predict diabetes, then a measure of glucose intolerance alone is better. If the syndrome is supposed to identify those with insulin resistance, then there are simpler ways to do so; however, measuring CRP might be helpful.

Dr. Oda (1) seems to have one purpose for the construct; others have different perspectives. The problem is that no one, not even the proponents themselves (2–4), have conveyed the exact utility of the syndrome and shown that it is better than or even equal to other approaches, and the critical issue, therefore, is why clinicians should even bother diagnosing metabolic syndrome in the first place.

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A Strong Dose-Response Relation Between Serum Concentrations of Persistent Organic Pollutants and Diabetes: Results From the National Health and Nutrition Examination Survey 1999–2002

Response to Lee et al.

Lee et al. (1) and *Diabetes Care* deserve praise for publishing what may be the first study worldwide to analyze, in a sample of a general population, serum concentrations of persistent organic pollutants (POPs) and plasma fasting glucose. The main implication of the study is that POPs stored in the adipose tissue may be a key player in the etiopathogenesis of type 2 diabetes. It is even rational to speculate that POPs might be, if not "the single factor" (2), then one factor linking some core components of the metabolic syndrome.

In the study by Lee et al. and other studies (3,4), it seems likely that a relationship exists between diabetes and POPs. Hence, patients, clinicians, and other health professionals may need to cope with the possible fact that on average, diabetic subjects have higher concentrations of POPs and may thus be more likely to suffer the adverse effects of POPs. The mechanistic, clinical, and public health implications of the study by Lee et al. are potentially high (1,3–5). However, several questions remain unanswered regarding the nature of the relationship between prevalence of diabetes and population distribution of POPs (6,7). Therefore, I would appreciate it if Lee et al. could address the following issues.

1) What is the direction of the relationships with the poverty income ratio? For example, in Table 1, did wealthier individuals have lower concentrations of DDE and higher concentrations of PCB153 after adjusting for confounders?

2) Many of the estimates (e.g., in Table 2) were adjusted for age, sex, race, income, lipids, BMI, and waist circumference. This is coherent with several aims (e.g., to "isolate" the effect of POPs from that due to obesity, age, race, or income). However, adjusting by BMI and waist circumference may also be an overadjustment, since fat intake is the most common source of exposure to POPs (1,5) and since the body burden of some of these lipophilic chemicals, but not all and not always, increases with increasing BMI (8,9). Thus, crude or less adjusted odds ratios (ORs) would also be relevant for determining the prevalence of diabetes in people with specific concentrations of POPs. Could the authors provide some crude ORs?

3) The finding that there was no association between obesity and diabetes among subjects with nondetectable levels of POPs is highly surprising and calls for additional results to be presented. A figure may be warranted.

4) Also crucial is what we may call "the changes in BMI-POPs relationship." Could the authors please comment on the possible influence upon BMI measurements of the cross-sectional design of the study? Could they suggest possible consequences upon findings of weight gain and weight loss in diabetic and nondiabetic participants?

5) High-prevalence ORs were found for the summary or composite of the six POPs with the highest concentrations. Are the results similar if the joint effects of multiple POPs are assessed through alternative methods?

6) Finally, the authors state that "reverse causality is unlikely." Indeed, evidence supporting the hypothesis that diabetes increases accumulation of POPs seems scarce (4). Do the authors know of studies on the toxicokinetics of POPs in diabetic subjects demonstrating that they accumulate POPs more than nondiabetic subjects?

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A Strong Dose-Response Relation Between Serum Concentrations of Persistent Organic Pollutants and Diabetes: Results From the National Health and Nutrition Examination Survey 1999–2002

Response to Porta

We thank Dr. Porta (1) for his interest in our study (2). As our study was cross-sectional, a possibility of reverse causality needs to be carefully evaluated. The most critical issue he raised is weight changes, which were not considered in our report. Body weight loss increases both serum and adipose tissue concentrations of persistent organic pollutants (POPs) (3,4), and diabetic patients are advised to attempt weight loss as a nonpharmacologic intervention. Conceivably, the strong relation between POPs and prevalence of diabetes could be explained by weight loss among diabetic patients. The National Health and Nutrition Examination Survey collected information on body weight 1 and 10 years before examination. Additional adjustment for weight change over the past 1 or 10 years attenuated the original odds ratios (ORs) to 12.8, 10.8, 26.5, and 26.7 or 9.1, 6.7, 16.0, and 15.8. BMI itself may be another important issue in relation to the possibility of reverse causality because BMI could be inversely related to clearance of POPs (4) and since diabetic patients are more obese. Thus, diabetic patients may increase accumulation of POPs in their body. However, one study reported no significant difference between the average elimination rates of diabetic and nondiabetic individuals (5). In addition, we adjusted for both BMI and waist circumference. Thus, decreased elimination does not appear to explain our finding.

We agree that one of the most surprising results would be that the prevalence of diabetes itself was quite low and that obesity was not associated with diabetes among subjects with very low levels of POPs, suggesting that POPs contained in the adipose tissue, not obesity, may be a key to diabetes. Some of our findings may be criticized due to the cross-sectional design. However, the lack of association between obesity and diabetes among subjects with very low levels of POPs is unlikely to be a cross-sectional bias. Although *Diabetes Care* does not allow figures in response letters, the requested figure depicting the interaction between obesity and POPs can be drawn from our publication and looks very persuasive.

Regarding Dr. Porta's other questions, wealthier individuals (higher poverty income ratio) had lower concentrations of DDE but higher concentrations of PCB153. ORs adjusted only for age were 14.4, 18.3, 45.5, and 47.0, with little change on further adjustment for sex and race/ethnicity. Several methods of combining the six POPs yielded conclusions similar to those we presented.

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