OBSERVATIONS

The Biogun

A novel way of eradicating methicillin-resistant *Staphylococcus aureus* colonization in diabetic foot ulcers

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an ever-increasing problem facing the health service in the U.K. There is a need to develop new methods of combating MRSA. In the Manchester diabetic foot clinic, the prevalence of MRSA is ~40% of staphylococcal cultures. MRSA has been demonstrated to double the foot ulcer healing time (1). While the pathogenetic relevance of MRSA colonization remains debatable, MRSA even in clinically noninfected ulcers may take >6 months to disappear (2). The Dentron Biogun has been shown to ionize molecular oxygen and generate superoxide radical anions (O^{2-}) with a bactericidal effect against microorganisms. In vitro studies using the Biogun have shown it to be effective against a range of microorganisms, in particular MRSA.

In an open-label prospective pilot study, 15 consecutive diabetic patients without clinically infected foot ulcers but with MRSA colonization were treated with the Biogun. Treatment with the Biogun continued on a weekly basis until MRSA was eradicated or to a maximum of three treatments. Patients were considered to be clear of MRSA if they had three consecutive negative MRSA cultures, each at least 1 week apart. Of the 15 patients treated using the Dentron Biogun, we achieved successful eradication of MRSA colonization in 60%. There were no significant differences between the groups that had successful MRSA eradication and those that were unsuccessful in terms of age, type of diabetes, duration of diabetes, duration of foot ulceration, or the proportion with neuroischemic ulcers. The only factor that influenced the success of MRSA eradication was the ulcer size, which was significantly smaller (294.8 ± 104.6 vs. 843.3 ± 254.4 mm, $P < 0.05$) (2) in patients where MRSA eradication was successful. There was no significant difference for the duration that the foot ulcers were colonized with MRSA and the success of MRSA eradication. There were no significant side effects, with only one patient noticing a mild tingling sensation.

The most important factor in determining the success of the Biogun appears to be the size of the foot ulcer. We believe that the success rate may be improved by increasing the length and frequency of treatment or by improving the efficiency of delivering the charged ions over a greater surface area. With the rise in the prevalence of MRSA in the diabetic foot clinic and the known increased risk of developing bacteremia with its implication on resources, additional methods of MRSA eradication need to be developed. We suggest that the Dentron Biogun might represent a simple, effective, and, because it can be used repeatedly, inexpensive method for eradicating MRSA. The promising pilot data warrant further assessment in a properly designed randomized controlled trial.

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Higher Levels of HDL Cholesterol Are Associated With a Decreased Likelihood of Albuminuria in Patients With Long-Standing Type 1 Diabetes

Response to Molitch et al.

We read with great interest the article by Molitch et al. (1), concerning the association between high levels of HDL cholesterol and albuminuria in type 1 diabetes. We have found similar results in a group of 157 patients with long-standing type 1 diabetes but in relation to retinopathy, which seems to be a more objective marker of microangiopathy than albuminuria in diabetes. Retinopathy was assessed by two experienced ophthalmologists using direct ophthalmoscopy on dilated pupils, followed, if necessary, by fluorescein angiography. Pictures of the eye fundus were collected. We divided our patients into two groups, one with ($n = 118$) and one without ($n = 39$) retinopathy. Two assessed groups were identical with respect to age (42.3 ± 12.6 vs. 39.9 ± 12.5 years, $P > 0.05$) and duration of diabetes (26.5 ± 6.9 vs. 25.7 ± 6.5 years, $P > 0.05$). Similarly to Molitch et al. (1), HDL cholesterol levels were significantly lower in patients with diabetic retinopathy than in those that did not have any changes at fundus of the eye (1.49 ± 0.4 vs. 1.65 ± 0.42 mmol/l, $P = 0.039$). Higher levels of HDL cholesterol (≥1.6 vs. <1.6 mmol/l) were associated with a five-times–lower likelihood of diabetic retinopathy (OR 0.20 [95% CI 0.06–0.70], $P = 0.01$). Of patients with retinopathy, 55% had positive microalbuminuria. However, the majority of patients with retinopathy were treated with ACE inhibitors, which must have influenced this percentage.

Contrary to Molitch et al. (1), we have not found any differences in HbA_{1c} between patients with and without retinopathy (8.2 ± 1.4 vs. 8.1 ± 1.3%, $P > 0.5$). Our study suggests that high HDL cholesterol may, independently of glycemic control, prevent the development of microvascular complications in type 1 dia-

betes. These results could be related to antioxidant, antithrombotic, and anti-inflammatory properties of HDL particles (2). Interestingly, structural modifications of HDL mediated by various mechanisms, including glycation, oxidation, and enzymatic degradation, may affect their functional and atheroprotective properties (3). This may suggest that not only quantity but also quality of HDL particles play a role in the damage of endothelium.

Molitch et al. (1) and our studies confirm the hypothesis that the higher the levels of HDL cholesterol, the lower the risk of late diabetes complications.

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Integrating Pediatric Diabetes Education Into Routine Clinical Care

The Families, Adolescents and Children's Teamwork Study (FACTS)

The importance of optimal glycemic control for children and adolescents to prevent the long-term complications of diabetes is well recognized (1). Educational interventions that increase parental involvement in blood glucose monitoring and insulin dose adjustment have demonstrated beneficial effects in specialist centers (2,3). The Families, Adolescents and Children's Teamwork Study (FACTS) was developed to evaluate a family-centered, structured education program for children and young people that can be integrated into routine clinical care. The small group setting facilitates increased peer group contact for both children and parents and improves cost efficiency, allowing the program to be delivered within existing service provision.

The program combines skills training with increased parent-adolescent teamwork and consists of four small group (three to five families) sessions over 12 months. The first two skill-based sessions cover carbohydrate counting, blood glucose monitoring, and insulin dose adjustment, with the last two focusing on sharing parental/child responsibility (4). Each session takes place on the same day as the regular 3-monthly age-banded clinic visits.

All health professionals involved received training in the delivery of group education by an experienced health psychologist. Sessions were monitored to ensure that they were patient centered and interactive, in order to engage children, adolescents, and parents in self-management. Written information to reinforce the main topics discussed was provided at the end of each session. Changes to insulin regimes were made only when requested by parents or health professionals but not as part of the program.

Families were randomly assigned to either the immediate (1st year) or delayed (2nd year) intervention. The delayed group acted as waiting list controls during the 1st year (i.e., attended only for routine clinical care) and attended the educational sessions in additional to routine clinical care during the 2nd year. Over the 2-year study period, 67 randomized subjects (55.5% male), mean (±SD) age 12.9 ± 2.1 years, attended the immediate (n = 33) or delayed (n = 34) intervention. The mean HbA_{1c} (A1C) at baseline was 9.1 ± 1.25% and mean duration of diabetes 4.9 ± 3.25 years. There were no significant differences between participants and nonparticipants in A1C, number of daily injections, or total daily dose of insulin at baseline.

Individuals attending the first two education sessions were more likely to increase their number of daily injections (attendees 44%, nonattendees 14%; P = 0.006). Interim analysis of change in A1C indicates that individuals who attended the two group sessions showed a reduction in A1C (mean drop 0.27%), whereas those who did not attend showed an increase in A1C (mean increase 0.26%); this difference nearly reached statistical significance (t = 1.60, df = 70, P = 0.058).

This is the only pediatric educational intervention that has been tested by two independent research groups and that has been shown suitable for both individual and group delivery. Although the effects on A1C are small, the ability to deliver the intervention not only to individual families in specialist units but also to small groups in a routine clinical setting makes this program relevant to other centers providing pediatric diabetes care.

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Retinopathy Predicts Future Cardiovascular Events Among Type 2 Diabetic Patients

The Valpolicella Heart Diabetes Study

We read with interest the recent article by van Hecke et al. (1) showing that diabetic retinopathy is associated with an increased risk of mortality and cardiovascular disease (CVD) incidence among type 1 diabetic patients.

Because the available data on associations between retinopathy and incident CVD in large population samples of type 2 diabetic patients are limited and conflicting (2–4), we would like to offer recent findings from our large observational study. We carried out a prospective, nested, case-control study in 2,103 type 2 diabetic outpatients, who were free of diagnosed CVD at baseline. More details of study design and methods have been published elsewhere (5).

During 5 years of follow-up, 248 participants (62% men; age 66 ± 4 years; diabetes duration 14 ± 3 years) subsequently developed nonfatal coronary heart disease (myocardial infarction and coronary revascularization procedures), ischemic stroke, or cardiovascular death. Using risk-set sampling, 496 control subjects, among those who remained free of diagnosed CVD during follow-up, were randomly selected in a 2:1 ratio, matched for age and sex to the case patients. At baseline, a single ophthalmologist diagnosed retinopathy after pupillary dilation, according to a clinical disease severity scale (6). Overall, 364 (48.9%) participants had retinopathy, 285 of whom had nonproliferative retinopathy and 79 proliferative retinopathy (as also confirmed by fluorescein angiography). After adjustment for age, sex, BMI, smoking history, plasma lipids, HbA_{1c}, and diabetes duration and treatment, those with nonproliferative (odds ratio 1.7 [95% CI 1.2–2.3]; $P < 0.001$) or proliferative (4.1 [2.0–8.9]; $P < 0.001$) retinopathy had a higher risk of incident CVD than those without retinopathy. Additional adjustment for hypertension (defined as blood pressure ≥130/85 mmHg or treatment) and macroalbuminuria (defined as urinary albumin-to-creatinine ratio ≥25 mg/mmol) considerably attenuated these associations, particularly among those with nonproliferative retinopathy (1.1 [0.7–1.5]; P = NS); the risk of incident CVD remained twofold greater, but statistically nonsignificant, among those with proliferative retinopathy (2.04 [0.9–5.8]; $P = 0.08$).

These results show that retinopathy is associated with a moderately increased risk of incident CVD among type 2 diabetic individuals, thus suggesting that retinopathy and CVD may have similar pathophysiological backgrounds. However, this association seems to be largely explained by occurrence of classical risk factors, especially hypertension and nephropathy. Thus, our data emphasize the importance of evaluating the CVD risk among diabetic patients with retinopathy; these patients could be candidates not only for aggressive treatment of their eye disease but also for blood pressure lowering, as well as aggressive treatment of underlying CVD risk factors.

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Prostatic Cancer, Hypogonadism, and Insulin Resistance

A case report

A 47-year-old Greek diabetic man presented with erectile dysfunction and a decrease in sexual desire. The patient had type 2 diabetes for the previous 8 years and was on treatment with rosiglitazone and metformin with strict glycemic control (HbA_{1c} 5.8%). No symptoms or signs of neuropathy were present. Hypogonadotrophic hypogonadism was found.

His plasma testosterone level was very low (100 ng/dl [reference range 300–1,000]) and there was no luetinizing hormone response to luetinizing hormone–releasing hormone (LHRH) test. Further work-up with a magnetic resonance imaging scan and hypophyseal function tests did not reveal any space-occupying lesions of the hypothalamic pituitary site.

The process led to the diagnosis of idiopathic hypogonadotropic hypogonadism. On further work-up, the patient was found to have a prostatic carcinoma. There was no evidence of metastatic disease (his plasma prostate specific antigen [PSA] level was 1.9 ng/ml).

Six years earlier, the patient was treated with finasteride for benign prostatic hypertrophy. A radical prostatectomy was performed and a poorly differentiated adenocarcinoma was found (Gleason grade 10, T3N1Mx).

Postoperatively his plasma testosterone rose to normal levels (530 ng/dl), and there was no need for diabetes medica-

tion, given that his fasting plasma glucose values never exceeded 6 mmol/l while only on diet.

His homeostasis model assessment of insulin resistance (HOMA-IR) (fasting serum insulin [μU/ml] × fasting plasma glucose [mol · l^{-1}/22.5]) was 1.8, and an oral glucose tolerance test performed with 75 g glucose was absolutely normal. His PSA value was 0.3 ng/ml.

After surgery there was very little change in body weight. His BMI before the operation was 26.6 kg/m^2 and after the operation 26.5 kg/m^2. This minimal change in body weight could not account for the observed euglycemia, nor could his diet given that it was virtually unchanged.

Combined androgen blockade therapy was initiated with goserelin acetate and bicalutimide. Three weeks later his plasma testosterone level fell well in the hypogonadotropic range (80 ng/ml) with a simultaneous, abrupt worsening of his glycemic control. Fasting plasma glucose ranged from 10 to 15 mmol/l and HOMA-IR rose to 15, indicating an insulin-resistant state. Again there was no significant change in his body weight; his BMI was 26.5 kg/m^2.

Treatment with metformin and rosiglitazone was reinstituted with a significant euglycemic response (fasting plasma glucose 5.5 mmol/l).

The presence of diabetes in the preoperative hypogonadal state, the remission of it in the immediate postoperative eugonadal phase, and the reappearance of insulin resistance after the institution of androgen deprivation treatment indicate that in this patient, the effect of testosterone was insulin sensitizing.

Marked hyperglycemia in prostatic cancer patients, after initiation of androgen deprivation therapy, has been reported in the literature with good response to pioglitazone (1). In the present case, prostatic carcinoma presented as hypogonadotropic hypogonadism. Schaeffer and Walsh (2) eloquently suggested that adenocarcinoma of the prostate should be considered in the differential diagnosis of hypogonadism based on the suppression of the hypothalamic-pituitary-testicular axis occasionally caused by this carcinoma. Undifferentiated prostatic carcinomas may yield normal PSA values, and this should be kept in mind when considering testosterone replacement therapy in men with hypogonadism. Another point of significance is that our patient was receiving rosiglitazone and peroxisome proliferator–activated receptor-γ ligands, which may modify PSA levels (3).

Based on the above information, it is clear that in diabetic patients presenting with sexual dysfunction, prostatic carcinoma should be considered in the differential diagnosis, regardless of the PSA level. Further research is needed to examine the possible relationship between testosterone and insulin resistance and the possible role of hyperinsulinemia in the course of prostatic carcinoma disease, given that in recent years it has become clear that there are multiple androgen-independent routes.

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A Case of Type 1 Diabetes Followed by Methimazole-Induced Hypersensitivity Syndrome

Viruses have generally been considered to be a major environmental factor in the etiology of type 1 diabetes. Drug-induced hypersensitivity syndrome (DIHS) is characterized by a severe drug eruption and multiorgan involvement, and reactivation of human herpesvirus-6 (HHV-6) may contribute to its pathology (1). This is the first reported case of type 1 diabetes followed by DIHS.

Recently, we have reported a case of DIHS induced by methimazole for Graves' disease (2). This patient developed type 1 diabetes during treatment of DIHS. Briefly, a 50-year-old Japanese male subject was diagnosed as having DIHS caused by methimazole in November 2003, based on the physical manifestations and laboratory findings including elevated anti–HHV-6 IgG titer. The administration of glucocorticoids gradually improved his clinical manifestations.

In December 2003, fasting plasma glucose was 4.9 mmol/l. His glycemic control, thereafter, gradually worsened despite treatment with nateglinide (270 mg/day). In March 2004, laboratory studies showed fasting plasma glucose to be 14.4 mmol/l; HbA_{1c}, 12.1%; fasting serum C-peptide, 0.35 ng/ml (normal range 0.5–2.73); and urinary excretion of C-peptide (which means integrated intrinsic insulin secretion), 17.24 mg/day (normal range 40–120). Basal level of serum C-peptide was finally undetectable. Anti-GAD antibody was 24.1 unit/ml (normal range <1.5). Response of serum C-peptide to glucagon was blunted. Thus, we diagnosed the patient as having type 1 diabetes. He started insulin injections immediately. His glycemic control gradually improved.

The coexistence of type 1 diabetes and Graves' disease is not infrequent. The onset age of type 1 diabetes in this case is fairly later, and anti-GAD antibody titer is relatively low, although type 1 diabetes with autoimmune thyroid disease was reported to be clinically characterized as high titer (609 ± 166 units/ml) of anti-GAD antibody and later-onset age (~30 years) compared with the general type 1 diabetic population (3). Therefore, these findings cannot exclude the possibility that the coexistence of type 1 diabetes and Graves' disease may be not incidental.

It is possible that viral infections such as coxsackie B4 virus and cytomegalovirus can trigger autoimmune reactions against pancreatic β-cells, which leads to type 1 diabetes. Molecular mimicry has been considered as a pathogenetic mechanism for autoimmune disease (4).

GAD65-reactive T-cells have been postulated to recognize the peptide derived by coxsackie B4 virus, leading to autoimmune type 1 diabetes (4). Furthermore, sequence homology between GAD65 and cytomegalovirus might participate in the onset of type 1 diabetes and stiff-man syndrome (5). Interestingly, HHV-6 is closely related to cytomegalovirus genomically and antigenically, and GAD65-reactive T-cells also recognize an epitope derived by HHV-6 (5), suggesting that reactivation of HHV-6 might contribute to the onset of autoimmune type 1 diabetes by the molecular mimicry.

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Favorable Effects of Early Insulin Secretion by Nateglinide on Postprandial Hyperlipidemia in Patients With Type 2 Diabetes

Severe postprandial hyperlipidemia is observed in and substantially contributes to the progression of atherosclerosis in type 2 diabetic patients, especially those with insulin resistance and compensatory hyperinsulinemia (1–4). As with postprandial hyperglycemia, increased lipid levels in type 2 diabetic patients peak late, and the magnitude of the increase is greater than that seen in healthy people (2,4). To determine whether early insulin secretion by nateglinide can suppress postprandial hyperlipidemia in type 2 diabetic patients, 20 Japanese patients (10 men and 10 women, [means ± SE] aged 56.4 ± 2.5 years, with BMI and HbA_{1c} 25.6 ± 1.2 kg/m^2 and 5.7 ± 0.1%, respectively) with newly diagnosed type 2 diabetes performed a 75-g oral glucose tolerance test and oral fat tolerance test (OFTT) twice. A 90-mg dose of nateglinide was administered immediately before fat loading in one of the two OFTTs. In the OFTT, each subject ingested 17 g fat/m^2 surface area (OFTT cream; Jomo Food Industry, Takasaki, Japan) (2). Plasma glucose and serum insulin, triglycerides, and remnant-like particles cholesterol (RLPC) concentrations were determined before and 30 min and 1, 2, and 4 h after fat loading.

When nateglinide was not administered (Nate−), triglycerides and RLPC continued to increase during OFTT, while no significant changes in plasma glucose or insulin were noted. In OFTT with nateglinide administration (Nate+), increases in triglycerides and RLPC after fat loading were significantly lower than in Nate− by ANOVA ($P < 0.001$). The average increments of triglycerides and RLPC from baseline to 4 h were 1.1 mmol/l and 0.31 mmol/l in Nate− and 0.46 mmol/l (−58%, $P < 0.01$) and 0.05 mmol/l (−84%, $P < 0.01$) in Nate+, respectively. Plasma glucose levels in Nate+ were gradually decreased by 1.6 mmol/l on average after 2 h. Insulin levels in Nate+ peaked after 30 min and then decreased to below baseline level by 4 h. Furthermore, in Nate−, the regarding rates of increase for triglycerides and RLPC during OFTT had significant correlations with Σinsulin during the oral glucose tolerance test ($r = 0.63$ and 0.72, respectively), which is a surrogate measure for insulin resistance, while in Nate+, there were no significant correlations among them.

Early insulin secretion following nateglinide administration was thus proved to inhibit postprandial hyperlipidemia in type 2 diabetic patients. Improvements in insulin resistance over a short period of time seem to exert substantial influence on lipid parameters. Insulin secretion patterns appear to play a major role in postprandial hyperlipidemia as well as hyperglycemia.

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Transient Diabetes Associated With Withdrawal of Lithium Therapy

We describe a patient with bipolar disease who developed diabetic ketoacidosis following discontinuation of long-term lithium treatment. Diabetes resolved completely after 7 months of insulin therapy. Transient diabetes in this patient could have been precipitated by withdrawal of lithium therapy.

A 26-year-old white male was admitted to our hospital with vomiting and abdominal pain. He suffered from bipolar disorder and had been on lithium treatment for 3 years. Six weeks before presentation, he had discontinued lithium due to persistent tremors and 2 weeks afterward developed excessive thirst and polyuria. He had no personal or family history of diabetes and was not receiving any other medications. On arrival, his BMI was 24 kg/m^2 and he was dehydrated and acidotic (pH 7.11), with ketonuria and hyperglycemia (blood glucose 33 mmol/l). We diagnosed diabetic ketoacidosis and treated him accordingly with intravenous fluids and soluble insulin. He rapidly improved and was discharged on twice-daily biphasic insulin. HbA_{1c} (A1C) was 7.2% 1 month later. Subsequently, he experienced repeated hypoglycemic spells, which led to cessation of insulin after 7 months. At this stage, A1C was 5.4% and oral glucose tolerance test was normal, with adequate insulin and C-peptide responses to a glucose load. GAD and islet cell antibodies were negative. After 3 years off treatment, his A1C has remained <5.5%.

We considered several explanations for the unusual profile of diabetes in this patient. The initial presentation was suggestive of type 1 diabetes, but the remitting course makes this diagnosis unlikely. Although prolonged remission may occur in early type 1 diabetes, this honeymoon period is unlikely to last 3 years. Atypical type 2 diabetes, characterized by ketosis at onset and subsequent remission, has been described in African patients but not in whites (1). Nonetheless, the negative antibodies and subsequent insulin independence in this case favor type 2 diabetes as the more likely diagnosis.

The onset of diabetes followed discontinuation of lithium, thus suggesting that lithium withdrawal precipitated diabetes. The effects of lithium on carbohydrate metabolism are complex, and improvement and worsening of glucose tolerance have both been observed in patients receiving lithium (2,3). Studies in rats show that lithium exerts antidiabetic effects by increasing glycogenesis, either through an insulin-sensitizing action or through direct activation of enzymes involved in hepatic glycogenesis (3). An intriguing possibility in this case, therefore, is that diabetes was masked by lithium treatment and precipitated by its withdrawal. To the best of our knowledge, this is the first report of diabetes occurring in association with lithium withdrawal. Clinicians should be vigilant to similar cases that may provide insights into atypical presentations of diabetes.

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Association of hGrb10 Genetic Variations With Type 2 Diabetes in Caucasian Subjects

The genes contributing to type 2 diabetes are mostly unknown (1). Grb10 is an adapter protein that, in target tissues (2,3), interacts with the insulin receptor (3–9), thus affecting downstream signaling (10–12) and insulin action (2,7,10–16). We tested the hypothesis that variants in the Grb10 gene modulate the risk for type 2 diabetes, one of the most frequent outcomes of insulin resistance.

Resequencing of coding and immediately flanking sequences of hGrb10 (17,18) identified six single nucleotide polymorphisms (SNPs), five of which had a minor allele frequency >5%. Based on their physical location and their mutual linkage disequilibrium, these five SNPs (i.e., rs1800504, rs2715128, rs2072235, rs4947710, and rs3807550) could be grouped into two clusters. The rs1800504 and rs4947710 SNPs (each belonging to different clusters) were analyzed for association with type 2 diabetes in 764 diabetic patients and 323 unrelated control subjects from the east coast of central Italy (19,20). No significant association with type 2 diabetes was observed for rs1800504 (data not shown). By contrast, the genotype distributions of rs4947710 (i.e., G/G, G/A, and A/A) were significantly different between case and control subjects (87.2, 12.3, and 0.5% vs. 61.9, 35.8, and 2.3%, respectively, $P < 0.0001$), with A allele carriers showing a reduced risk of type 2 diabetes (unadjusted odds ratio 0.239 [95% CI 0.17–0.33], $P = 0.0001$; age-, sex-, and BMI-adjusted odds ratio 0.235 [95% CI 0.15–0.36], $P = 0.0001$). A potential biological relevance of rs4947710 was suggested by an in silico analysis (ESEfinder; available at http://exon.cshl.edu/ESE/), which indicated that the G-to-A substitution of rs4947710 may cause the disruption of a putative consensus motif for the human Ser/Arg-rich proteins SF2/ASF.

To replicate this association, we studied 731 type 2 diabetic case and 358 nondiabetic control subjects, all being Caucasians from the Boston area (20). In contrast to what was observed in the Italian population, the genotype distributions of rs4947740 were similar in case and control subjects (G/G = 83.9%, G/A = 15.2%, and A/A = 1.0% and G/G = 86.0%, G/A = 14.0%, and A/A = 0.0%, respectively, $P = 0.15$).

In conclusion, a significant association between the hGrb10 rs4947710 SNP (whose biological function on differential splicing is suggested by in silico analysis) and type 2 diabetes was found in Caucasian subjects from Italy but not in those from the U.S. Lack of replication of genotype-phenotype associations is not an

uncommon event in the study of complex disorders (21–23) and can arise from the original result being a false-positive because of bias or chance or from the second result being a false negative because of insufficient power. Such explanations, however, do not seem to account for our conflicting findings. The population of the original study was relatively homogeneous, making the possibility of population stratification remote, and the *P* value for association with type 2 diabetes was highly significant, making chance an unlikely explanation of the association finding. The replication study had close to 100% power to detect the odds ratio observed in the original study. Thus, lack of replication in our study is likely to result from differences in the genetic and/or environmental background of the populations studied, highlighting the need for large, collaborative studies providing sufficient power to investigate gene-gene and gene-environment interactions and their differences among populations.

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Metformin-Induced Pancreatitis

A possible adverse drug effect during acute renal failure

About 2% of episodes of acute pancreatitis are caused by drugs (1). Phenformin was repeatedly associated with acute pancreatitis (1), but only two case reports highlighted a possible causative role for metformin (2,3). In one case, acute pancreatitis occurred for the coexistence of correct metformin treatment and acute renal failure (2); in the other, metformin overdose was deemed responsible (3).

A 61-year-old woman with diabetes and hypercholesterolemia presented after 5 days of vomiting, followed by oliguria and epigastric pain. At home, the therapy of 3 g/day metformin and 80 mg/day fluvastatin was continued, despite symptoms. Laboratory investigations showed metabolic acidosis with normal lactate, creatinine 13 mg/dl, amylase 270 units/l (normal range 30–110), lipase 1,813 units/l (23–300), and white blood cells 9,000/mm^3 (80% neutrophils). Acute pancreatitis was confirmed by computed tomography. No recognized cause of acute pancreatitis was identified (hypertriglyceridemia, hypercalcemia, alcoholism, gall stones, virus, or trauma). Drugs were suspended, and a treatment of insulin and intravenous fluids normalized amylase, lipase, and blood gases. The patient was discharged with stable creatinine levels of 2.7 mg/dl. She was reexposed to fluvastatin for 1 month, but no symptoms were reported.

Available evidence suggests that acute pancreatitis was caused by metformin accumulation, resulting from a combination of drug overdose and acute renal failure, in turn triggered by vomiting in a patient with concealed renal insufficiency. Because renal failure is a contraindication to metformin, rechallenge was performed only for fluvastatin (1), with negative results. In this case, the association drug/event is considered "probable" (4).

In the presence of appropriate doses and normal renal function, metformin-induced acute pancreatitis was never reported. However, when glomerular filtration rate (GFR) is <60 ml/min, metformin accumulates and adverse effects, mainly lactic acidosis, may occur (5,2). Our and previous observations (2,3) suggest to include acute pancreatitis among the possible metformin-induced adverse events precipitated by renal failure.

A GFR <60 ml/min with normal serum creatinine (concealed renal failure) increases the risk of adverse reactions from hydrosoluble drugs in elderly diabetic patients (6). We reanalyzed the data of hospitalized elderly from the Gruppo Italiano di Farmacovigilanza nell'Anziano study (1993–1998). Of 145 diabetic patients given metformin, 28 subjects had concealed renal failure (mean daily dose 808 ± 303 mg), while the other 28 patients had both reduced GFR and increased creatinine values (mean daily dose 686 ± 470 mg). These patients are at risk of acute renal failure, with critical metformin accumulation and ensuing toxicity, including acute pancreatitis.

Metformin is a precious antidiabetic drug (5). Nonetheless, acute pancreatitis can arise in patients with renal insufficiency. GFR should be carefully monitored in older diabetic patients taking metformin.

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COMMENTS AND RESPONSES

Change in HbA_{1c} as a Measure of Quality of Diabetes Care

The Diabetes Quality Improvement Project established performance indicators that were adopted by The National Committee for Quality Assurance in the Diabetes Physician Recognition Program (DPRP) (1,2). The HbA_{1c} (A1C) factors heavily in the scoring system, accounting for 15 of a possible 80 points. To achieve full credit, <20% of a random sampling of patients may have an A1C >9.0% and at least 40% must be <7.0%. This methodology may bias against diabetes consultants who are referred patients in worse control. Improvements in A1C may more readily reflect quality of care. The American Diabetes Association recommends an A1C of <7.0% (3) and in previous guidelines set ≥8.0% as a level whereupon "additional action is suggested" (4). The Diabetes Control and Complications Trial (DCCT) demonstrated that a decline in the A1C of 1% reduced microvascular complications by 30% or more (5). Therefore, poor control and clinically meaningful improvements may be defined by an A1C of ≥8% and −1%, respectively. The purpose of the present study is to evaluate change in A1C as a marker of quality of care.

Patients from one physician were evaluated, and all were referred from other providers. A1C data were collected prospectively in new patients from 1 January 2003 through 31 December 2004.

Data were included if the baseline A1C (collected the day of the consult or within 90 days prior) was ≥8.0%, and at least one subsequent A1C, performed after 3 months, was measured. A third A1C was collected in patients who had been seen for ≥6 months at the time of data collection. The mean ± SD A1C was calculated for each of the three time points, and a *t* test was performed to determine statistical significance between levels.

A total of 96 patients met the entry criteria. Of these, 54 (56%) had a third data point. The remainder had not yet been followed long enough at the time of data collection ($n = 32$) or did not adhere to follow up ($n = 9$). The mean A1C at entry was 10.36 ± 1.66%. The mean first and second follow-up A1C levels were 8.06 ± 1.68 and 7.68 ± 1.38%, respectively. Changes from entry to first and second A1C were both statistically significant ($P < 0.001$). Seventy-four percent of patients at first follow-up A1C and 80% at the second demonstrated an A1C decline of ≥1%.

In this brief observation, the majority of patients who were referred for endocrine consultation to evaluate and treat poor diabetes control showed clinically meaningful improvements in A1C. In evaluating quality of care, the DPRP looks at a cross section of randomly chosen patients. In a consultation practice, the diabetes specialist may accumulate many poorly controlled patients. Therefore, the impression is that quality of care is poor. Moreover, provider recognition may be less likely under the current scoring system. Yet, the DCCT demonstrated that reductions in microvascular complications, in particular retinopathy, can be seen with sustained A1C reductions even if the target of <7% is not achieved (5). Change in A1C may be a useful marker for quality of care given by diabetes consultants and can be used as an adjunct to the current DPRP standards, especially if longer-term data are used.

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Change in HbA_{1c} as a Measure of Quality of Diabetes Care

Response to Spitz

We thank Dr. Spitz (1) for his letter commenting on the Diabetes Physician Recognition Program (DPRP) criteria regarding HbA_{1c} (A1C) levels. The DPRP criteria were changed in 2000 to coincide with those used in the Health Plan Employer Data and Information Set (HEDIS) program. More recently in 2004, a decision was made to include two measures for A1C, LDL, and blood pressure. In the case of LDL, the change reflected the HEDIS measure, National Cholesterol Education Program guidelines, and the American Diabetes Association recommendation. In the case of A1C and blood pressure, changes were based on current American Diabetes Association recommendations. Using two measures (which some refer to as good and poor control) allows a more comprehensive assessment of how well a group of patients is doing as this approach encourages both attention to persons in relatively poor control as well as allowing ongoing assessment of how the provider is doing in regard to meeting the stated guideline. For example, if only "% of patients with A1C >9%" were used, movement of patients from 9.1 to 8.9% would yield significant improvement, yet most would argue that little had changed. Using measures of "% >9%" and "% <7%", however, would show that little had changed. If patients were moved from an A1C of 9.1 to 6.9%, using only the 9% measure would yield the same results as in the first case, but using both measures the rather significant change would be clearly indicated. Using both measures allows one to see continuing improvement over time as the "% >9%" should continue to decrease and the "% <7%" should continue to increase.

Dr. Spitz suggests that it would be useful (and more fair to those who are referred patients who are not doing well in regard to A1C) to add a measure based on improvement in A1C. The suggestion is well worth considering and has been reviewed in the past by experts in both diabetes as well as measurement. One obvious problem in having a change in A1C measure is that doctors caring for patients who are at goal would appear to not be doing well using this measure, as no improvement would be needed or likely seen. As well, the goal of using measures to document how a population of patients is doing over time would not be part of this metric. Simply awarding points for A1C improvement would create some potential unfairness as well, as it is generally much easier to get a patient doing poorly to reduce his/her A1C 1% (from 10 to 9%, for example) than a patient doing relatively well (to reduce the A1C from 8 to 7%). Secondly, all A1C improvements are not equal in regards to clinical benefit, as an improvement of 1% in A1C offers a different benefit if the change is from 7 to 6% vs. 12 to 11%, for example. Finally there is the problem of setting the time frame for the change and having to review charts for multiple values, not just the most recent.

Dr. Spitz is of course correct that any improvement in A1C is a positive change. The data he cites for his practice are very impressive in regards to the reduction in A1C levels he has achieved. We feel that the current measures, used accurately, fairly capture this aspect of diabetes care, and adding a new measure for A1C change is not likely to add substantial new information to the program. However, we feel it is worthwhile to bring this to the current DPRP advisory committee for discussion at their next meeting.

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Proposal for the Reconsideration of the Definition of Gestational Diabetes

Response to Omori and Jovanovic

I read with interest the letter by Omori and Jovanovic (1) in the October 2005 issue of *Diabetes Care* and have the following comments.

In the Clinical Practice Recommendations from 2002 to 2005 (2–5), you will find the following statements.

"A fasting plasma glucose level >126 mg/dl (7.0 mmol/l) or a casual plasma glucose level >200 mg/dl (11.1 mmol/l) meets the threshold for the diagnosis of diabetes, if confirmed on a subsequent day, and precludes the need for any glucose challenge."

Although these two patient populations (i.e., patients with gestational diabetes mellitus [GDM] and patients with diabetes diagnosed during pregnancy) were not formally separated in relation to patient outcome or risk of congenital malformations, we, in our institution, have adopted the policy of labeling these pregnant women, who have blood glucose levels in the diabetic range, as "diabetic patients first discovered during pregnancy." This labeling would be even further substantiated if the index case was discovered during the first trimester.

The second point is the surprising finding in the Japanese study of having the highest frequency of both GDM and type 2 diabetes in the first trimester and the lowest in the third trimester, which is against the classical teaching and against the fact that insulin resistance, and consequently the frequency and incidence of GDM, is highest in the third trimester. This reversed incidence of GDM in different trimesters of pregnancy needs to be further analyzed and explained.

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Proposal for the Reconsideration of the Definition of Gestational Diabetes

Response to Dawood

We thank Dawood for his comments (1) concerning our letter (2), in which we reported the results of our two populations (from Japan and California). Our results underscore the need for a unique diagnosis for those women with moderate to severe hyperglycemia and/or other evidence of long-standing diabetes complications, and thus the label of gestational diabetes mellitus (GDM) is not adequate to identify the urgent need for more intensive surveillance and treatment than would otherwise be available for gestational diabetic women.

Dawood is correct; the American Diabetes Association (ADA) would not label our cohorts as having "type 2 diabetes" because their blood glucose concentrations did not reach the criteria of the ADA guidelines or position statements. The point is that regardless of whether these pregnant women are called type 2 diabetic women or, as Dawood suggests, "diabetic patients first discovered during pregnancy," it is a matter of semantics. The bottom line is that these women would receive better care if they were not thought to have merely GDM. It is time to reconsider the definition of GDM.

Dawood's second question was related to our lowest prevalence of GDM in the third trimester (first trimester: 33 of 250 [13.2%]; second trimester: 32 of 417 [7.7%]; and third trimester: 37 of 749 [4.9%]). In our Japanese cohort, our observation is based on the protocol that administers the oral glucose tolerance test in only those pregnant women with risk factors, not the population of pregnant women in general without risk factors for diabetes. The risk factors for diabetes have the highest likelihood of identifying those women who have diabetes already in the first trimester. The third-trimester increase in prevalence of GDM that Dawood questions only occurs in women without risk factors, when the pregnancy per se has the strongest impact on glucose intolerance, not age, obesity, history of glycosuria, glucose intolerance, hypertension, or delivery of a previous infant with macrosomia.

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The Effect of Monochromatic Infrared Energy on Sensation in Subjects With Diabetic Peripheral Neuropathy: A Double-Blind, Placebo-Controlled Study

Response to Clifft et al.

The recent paper by Clifft et al. (1) concludes that monochromatic infrared energy (MIRE) is no better than placebo MIRE in restoring sensation in the lower extremities of subjects with diabetes. We would like to suggest an alternative conclusion.

First, the subjects were treated with a MIRE device that delivered photo energy and therapeutic heat at a lower level than has been used in other clinical studies. Treatment times per session were also only 66% of those reported by Leonard et al. (2). As a result, each subject received ~50% less photo energy than used in the Leonard protocol. The clinical effect of phototherapy treatment is time dependent. In and of itself, this difference in treatment protocol may account for the authors' inability to obtain results similar to those reported by Leonard et al. (2).

Second, while many subjects who cannot sense the larger 6.65 Semmes-Weinstein monofilament (SWM) at any site are unlikely to obtain sensation to the 5.07 SWM during a course of 12 treatments, it is possible that sensation to an intervening monofilament (for example, a 5.65 monofilament) may actually occur (2,3). These data were omitted from the article.

Third, subjects were selected solely on ". . . self-diagnosed. . ." diabetes and their inability to detect the 5.07 SWM at one of four sites on either foot. It is likely that a number of the subjects did not have diabetic peripheral neuropathy, since many exhibited sensory loss in only one limb and/or at only one site. The selection and treatment of subjects was further confounded by the fact that while some subjects received active treatment on one extremity and placebo treatment on the other, some received active or placebo treatment on both extremities.

Finally, the authors neither used a forced-choice method of SWM testing nor required the patient to specify the location at which they sensed the SWM; these are preferred testing methodologies using the SWM as it was used in other studies (2,3). Since it is well known that subjects responding to a SWM may specify a location other than that which is actually being touched, the SWM data obtained may be less accurate than it could have been, possibly explaining the apparent improvement in the placebo-treated limbs.

We believe that the reported conclusion may be attributed to the variance of the treatment dosage (amount of photo energy delivered). Additionally, it is important that utmost care is required in properly administering an SWM test to maximize the reliability of the data obtained.

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The Effect of Monochromatic Infrared Energy on Sensation in Subjects With Diabetic Peripheral Neuropathy: A Double-Blind, Placebo-Controlled Study

Response to Burke

We thank Dr. Burke (1) for his thoughtful comments and critical review of our research study (2). In responding to his comments, we have addressed each of his stated concerns in order.

First, regarding the level of photo energy delivered, the manufacturer preset our active monochromatic infrared energy (MIRE) units to deliver the recommended 6–8 bars of energy or 1.95 J · cm^{-2} · min^{-1} for 30 min (total energy of 58.5 J/cm^2), whereas the MIRE units used in the Leonard study (2) delivered 1.3 J · cm^{-2} · min^{-1} for 40 min (total energy of 52.0 J/cm^2). Therefore, our subjects received slightly more photo energy per treatment than subjects in Leonard's study, contrary to Dr. Burke's comments.

Second, we analyzed our data in the same manner as the only other placebo-controlled study (3) to have a more meaningful analysis. However, in our active MIRE group, sensation decreased at 46 of 139 test sites, improved at 54 of 139, and did not change at 39 of 139. In the placebo group, sensation decreased at 28 of 140 sites, improved at 74 of 140, and did not change at 38 of 140.

Third, all subjects in our study had received a diagnosis of diabetes and were being medically managed by their physicians. Peripheral neuropathy was confirmed by monofilament testing, which is standard practice and used by other researchers (3,4). A few subjects in each group were insensitive to the 5.07 monofilament at one of four test sites, but there was no significant difference between groups in mean number of sites sensitive to the 5.07 monofilament at baseline. In regard to Dr. Burke's comments about group assignment, it is not clear to us why he believes that our results were con-

founded by the fact that some patients had one leg randomized to receive active MIRE and the other leg randomized to receive placebo MIRE. In the majority of subjects, both legs received the same treatment, but, in any case, we have no reason to question the value of random assignment. In addition, all subjects in the Leonard study (3) had one leg in the active group and the other leg in the placebo group.

Finally, when peforming monofilament testing, we used the "yes-no" method of testing, which is equally accurate and faster than the "forced-choice" method (4). We concur with Dr. Burke that only valid and reliable testing methods should be used.

While it is disappointing to discover that a promising new treatment may not be effective, patient treatment should be based on credible evidence. We hope that more randomized, placebo-controlled studies are conducted to either support or refute the results of our study and to help determine the rightful place of MIRE in the treatment of patients with peripheral neuropathy.

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Ischemia Imaging and Plaque Imaging in Diabetes: Complementary Tools to Improve Cardiovascular Risk Management

Response to Raggi et al.

Here we respond to the review by Raggi et al. (1). We are concerned that the stated aims have not been fulfilled.

The American Heart Association (2) and the U.S. Preventative Task Force (3) have strongly discouraged coronary heart disease (CHD) screening in asymptomatic subjects with diabetes. Only one small randomized study has shown benefit from revascularization in asymptomatic subjects with diabetes screened for CHD (4). This study needs to be replicated in larger groups with rigorous analysis of the psychological and physical benefits and cost effectiveness. Screening guidelines should remain conservative until further studies show clear evidence of clinical benefit. Raggi et al. present no data to validate the algorithm presented in Fig. 1 in their review; this is based on opinion only.

Although subjects with diabetes may be at high CHD risk even when myocardial imaging for ischemia is negative, we would disagree with the statement that this lends support to the concept of refining risk stratification in diabetes using plaque imaging techniques. For instance, using carotid intima-media thickness in asymptomatic diabetic patients to identify candidates for angiography will lead to many invasive tests in which the likelihood of finding significant CHD is low. Some of these patients will have luminal atherosclerosis, but current CHD prevention guidelines in diabetes mandate aggressive medical therapy regardless of the results of additional investigation. A lower threshold for angiography based on carotid intima-media thickness for instance could result in angioplasty for lesions that are not producing symptoms, that are moderate in stenosis severity, and for which there is no known survival benefit of angioplasty over medical therapy alone. More information on this debate will be available when the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) study reports.

Finally, the authors fail to make a clear distinction between subjects with and without CHD symptoms. Revascularization may be justified at low thresholds in symptomatic patients, whereas screening of asymptomatic subjects should be reserved for limited situations (2,3). We share the authors' desire to develop a better strategy to manage asymptomatic patients with diabetes and CHD, but how to do this remains unclear.

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Ischemia Imaging and Plaque Imaging in Diabetes: Complementary Tools to Improve Cardiovascular Risk Management

Response to Rutter and Nesto

We read with interest the letter by Rutter and Nesto (1) in reply to our review article; however, we believe we had already addressed several, if not all, of the concerns they express. In fact, we made the following statements in our study. *1*) "Our goal was to verify whether existing data support the use of these techniques (ischemia and atherosclerosis imaging) in isolation or as complementary tools for improved risk prediction" (not necessarily management!). *2*) "Continued research will be needed to confirm that the integration of several imaging modalities improves clinical outcome in a cost effective manner." *3*) "Figure 1 is an algorithm with. . . an attempt to integrate ischemia and atherosclerosis imaging. . . based on personal opinion." *4*) "Whether all asymptomatic diabetic patients should be tested remains debatable and unlikely to be financially affordable for society. To make asymptomatic screening more affordable at least one of the following conditions should be present. . ."

The tone of our writing was more one of hope for improvement in risk assessment than a call for unnecessary expenditure. Unfortunately, the prevailing argument used by Drs. Rutter and Nesto, that atherosclerosis imaging leads to unnecessary invasive diagnostic and interventional procedures, is a bit trite and not supported by substantial literature. On the contrary, some of us have shown that the performance of calcium screening in symptomatic patients at low-intermediate pretest probability of disease reduces the rate of normal cardiac catheterizations (hence unnecessary) and increases the number of "necessary" procedures, with a net 30–35% saving compared with a traditional diagnostic pathway (2). It was far from our intention to instruct physicians on doing unnecessary procedures; it was our desire to educate the readers as to what is currently known regarding coronary artery disease imaging in diabetes. The summary is that ischemia imaging is useful in some subgroups of diabetic patients, but it fails to completely define risk in a sizable portion of individuals and for any prolonged period of time. The enormous burden of disease inherent in diabetes deserves, therefore, better risk assessment. Evidence is accumulating that atherosclerosis imaging may help this task progress. Large amounts of calcium or an increased intima-media thickness actually adds useful prognostic information in diabetes (3,4), and absence of calcium is a good marker of low risk in diabetic and nondiabetic patients alike (3). Our appeal is for a conscientious application of imaging techniques while we learn more about their risk and benefit, as we use them daily.

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Cut Points of Waist Circumference

Response to Sone and Colleagues

Sone and colleagues (1,2) adopted Japanese criteria of abdominal obesity (waist circumference ≥85 cm in men and ≥90 cm in women) for the diagnosis of metabolic syndrome. These Japanese criteria of abdominal obesity were proposed by the Examination Committee of Criteria for Obesity Disease in Japan set up by the Japan Society for the Study of Obesity (3). They proposed waist circumferences of 85 cm in men and 90 cm in women as equivalent values for visceral fat area (VFA) of 100 cm^2. However, these cut points of waist circumference resulted from the inappropriate presupposition that VFA is linearly proportional to waist circumference. They determined the values by linear regression lines without revealing the sensitivities and specificities of these cut points. In fact, the dots in their VFA–waist circumference graphs were not scattered along linear lines, though VFA and waist circumference correlated well (3). If they had determined the cut points of waist circumference by receiver operating characteristic curves as they did to determine the cut points of BMI and VFA and determined the cut points of VFA separately by sex, the cut points of waist circumference might have been equivalent to Asian criteria (≥90 cm in men and ≥80 cm in women). For example, Shiwaku et al. (4) reported that optimal cut points of waist circumference were 82 cm for men and 73 cm for women in Japan. If the Examination Committee calculated areas under receiver operating characteristic curves, waist circumference might reveal to be a poor discriminator of VFA especially in women. After all, waist circumference is a marker of abdominal (central) obesity not of visceral obesity, which is assessed by VFA using computer tomography scanning, exposing subjects to X-ray irradiation. Therefore, Sone et al. should reanalyze their data using Asian criteria of waist circumference (≥90 cm in men and ≥80 cm in women) before reaching conclusions on the prognostic significance of metabolic syndrome defined with both National Cholesterol Education Panel (1) and International Diabetes Federation (2) criteria in Asian diabetic patients.

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Cut Points of Waist Circumference

Response to Oda

We are grateful for Dr. Oda's comments (1) on our recent reports (2,3) regarding the utility of waist circumference cutoff values in clinical risk assessments for cardiovascular disease. We agree with his point that the current Japanese criteria for abdominal obesity (85 cm for men and 90 cm for women in waist circumference) (4) are problematical, notwithstanding their adoption by the International Diabetes Federation (IDF) (5) and the American Heart Association (AHA) (revised version by the National Cholesterol Education Program [NCEP]) (6) in their definitions of metabolic syndrome.

We recalculated the risk of metabolic syndrome, as defined by the IDF and the NCEP, for cardiovascular events applying the Asian cutoff for waist circumference (90 cm for men and 80 cm for women) (7) and found that the hazard ratio (HR) of metabolic syndrome in female diabetic patients improved to some extent but that waist circumference alone was still not predictive for cardiovascular disease. In female patients, the HR of NCEP–metabolic syndrome for stroke improved to become significant (2.68 [95% CI 1.20–5.97]), and the HR of NCEP–metabolic syndrome and IDF–metabolic syndrome for combined cardiovascular events (either of coronary heart disease or stroke) also improved to become significant (2.02 [1.13–3.62] and 1.91 [1.07–3.42], respectively) using the Asian waist cutoff. The HRs for male patients did not change significantly under this modification. Consequently, modifying the IDF and the NCEP definitions by substituting the Japanese for the Asian cutoff value significantly improved the prognostic implications for female Japanese patients with type 2 diabetes, although it is notable that the HRs were still lower than those obtained using the World Health Organization definition (3).

An important limitation to the waist cutoff data (both Japanese [4] and Asian [7]) is that the values were determined from cross-sectional observations rather than from prospective cohort studies. Before undertaking any further discussions on the most appropriate cutoff value for waist circumference, further large-scale prospective studies are necessary to determine whether waist circumference per se is in fact a significant risk factor for cardiovascular events and/or mortality in East Asian diabetic and nondiabetic populations.

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