OBSERVATIONS

Screening for Adrenal Antibodies in Children With Type 1 Diabetes and Autoimmune Thyroid Disease

Type 1 diabetes is associated with other autoimmune diseases. Many diabetes centers routinely screen patients with type 1 diabetes for autoimmune thyroid disease (ATD). The presence of two autoimmune diseases raises the possibility of polyendocrine autoimmune disease. The association of autoimmune adrenal insufficiency, or Addison's disease, with type 1 diabetes is described in case reports dating back more than a century (1,2). Studies have illustrated shared HLA alleles (DQA1*0501, for example) among patients with type 1 diabetes, ATD, and Addison's disease (3,4). Pancreatic islet cell antibodies have been detected in 6.2% of patients with Addison's disease (5). Yet, it is unclear whether patients with type 1 diabetes should be routinely screened for Addison's disease.

Our study's objective was to determine whether routine screening for Addison's disease is warranted in children with both type 1 diabetes and ATD. Children were diagnosed with thyroid disease if they had thyroid peroxidase antibodies (TPOs >50 Ku/l) and/or were receiving thyroid hormone replacement for primary hypothyroidism. A population of children with type 1 diabetes but without thyroid disease was also screened. The study population consisted of 114 children with type 1 diabetes, 35 (25 girls and 10 boys) with thyroid disease (28 on L-thyroxine) and 79 (42 girls and 37 boys) without thyroid disease (normal thyroid-stimulating hormone and TPO <50 Ku/l). Adrenal antibodies were measured by standard immunofluorescent technique (Nova Century Scientific-Immco anti-adrenal slides), and TPOs were measured by an automated electrochemiluminescence immunoassay (Roche Elecsys 2010).

None of the children had signs or symptoms suggestive of Addison's disease. No adrenal antibodies were detected in the group with thyroid disease. In the group without thyroid disease, a teenage boy presenting with new-onset type 1 diabetes tested positive for adrenal antibodies. There was a known history of Addison's disease in the child's deceased mother. The child continues to be followed and has shown no clinical or biochemical evidence of adrenal insufficiency. The mean age of the children was 11.2 ± 3.7 years in the group with thyroid disease and 11.1 ± 3.7 years in the group without thyroid disease. The mean diabetes duration was 3.5 ± 2.5 and 4.2 ± 3.5 years in the groups with and without thyroid disease, respectively. The median TPOs in the group with thyroid disease was 331 (interquartile range 109–997) Ku/l.

We detected adrenal antibodies in only one of our children with type 1 diabetes, a child with a known family history of Addison's disease. The previous literature shows contradicting data in this regard. Although some studies have shown increased prevalence of adrenal antibodies and biochemical adrenal insufficiency in patients with type 1 diabetes (4,6–8), others have not shown any statistically significant increase in prevalence compared with healthy control subjects (9–11). Although most of these previous studies tend not to differentiate the patients with or without thyroid disease, one study of patients with type 1 diabetes did show an increased prevalence of adrenal antibodies (5.1 vs. 0.6%) in patients with thyroid antibodies compared with those without (7).

Measurement of the more specific and sensitive 21-hydroxylase antibody may have resulted in more positive results in our patients (4,12). However, Peterson et al. (12) found good correlation between the conventional immunofluorescent adrenal autoantibody and 21-hydroxylase antibody techniques.

We conclude that routine screening for Addison's disease in children with type 1 diabetes, regardless of thyroid status, does not appear warranted unless there is a strong clinical suspicion or family history of Addison's disease.

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Predictive Value of Autoantibodies to IA-2 for Insulin Requirements in Japanese Subjects With Type 1 Diabetes

GAD autoantibodies (GADAs) are frequently detected before the onset of diabetes and indicate the development of insulin dependency (1). Phosphatase-like protein IA-2 antibodies (IA-2As) in combination with GADA have been shown to improve the positive predictive value for type 1 diabetes (2). However, the presence of IA-2A and its clinical usefulness in Japanese type 1 diabetic patients have not been fully determined. Here we report the significance of serum antibodies to IA-2A and GADA to predict the insulin requirement in Japanese patients with type 1 diabetes.

We studied 101 Japanese patients with type 1 diabetes who fulfilled the classification of the American Diabetes Association (3). We included 47 men and 54 women, aged 41.3 ± 15.3 (mean ± SD) years, who had diabetes for 10.4 ± 9.6 years. Serum GADA and IA-2A levels were determined using a commercially available radioimmunoassay kit (RSR, Cardiff, U.K.) and ^{125}I-labeled human recombinant GAD65 and ICA512 on the basis of the first proficiency test of the Diabetes Autoantibody Standardization Program (4). The cutoffs were >0.4 units/ml for IA-2A and >1.3 units/ml for GADA.

Of the 101 Japanese type 1 diabetic patients assayed, GADA and IA-2A were detected in 60 (59%) and 37 (37%) patients, respectively. The mean dosage of daily insulin in all 101 subjects was 24 units. We classified subjects into two groups: high insulin dosing (≥24 units/day of insulin, n = 77) and low insulin dosing (<24 units/day of insulin, n = 24). Mean BMI did not differ significantly between these two groups (20.8 ± 2.9 vs. 21.9 ± 4.0 kg/m^2, P = 0.126). We observed no significant differences in GADA levels between these two groups (Fig. 1). In contrast, the IA-2A levels in the high–insulin dosing group were significantly higher than in the low–insulin dosing group (1.5 ± 2.8 vs. 0.3 ± 0.8 units/ml, $P < 0.05$) (Fig. 1). Moreover, by setting the cutoff point at 1.5 units/ml, the mean level of IA-2A in the high–insulin dosing group, all of the IA-2A–positive patients would require treatment with ≥24 units/day of insulin (Fig. 1). No cutoff point for GADA level could predict insulin dependency.

We found a significant difference in IA-2A levels, but not in GADA levels, between high– and low–insulin dosing groups. Our observations show that the presence of high-level IA-2As could be useful in predicting insulin requirements in Japanese type 1 diabetic subjects. A large-scale prospective study is required to verify this hypothesis.

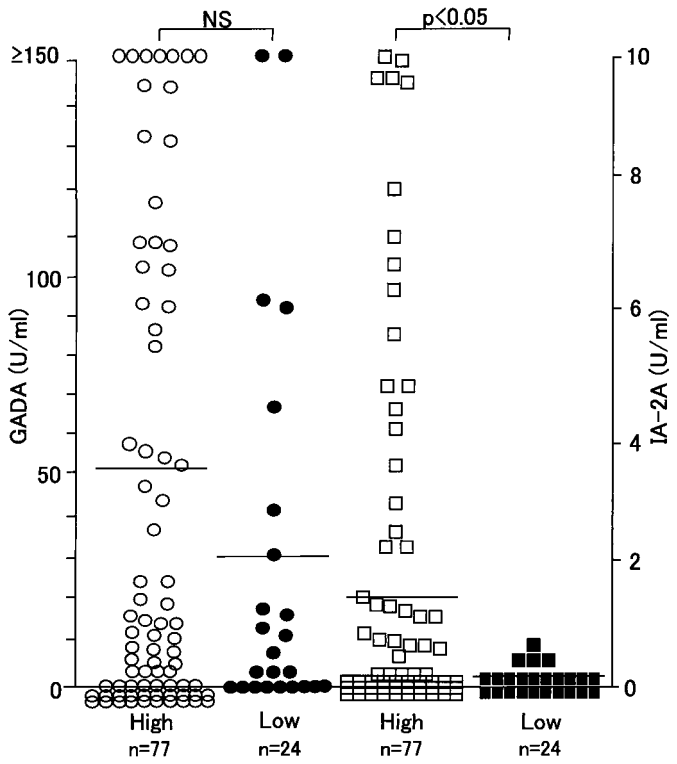

Figure 1—*GADA (○/●) and IA-2A (□/■) levels in type 1 diabetic subjects subdivided by insulin dosing. Japanese patients* (n = *101) were divided into high–insulin dosing (○/□; high, ≥24 units/day of insulin;* n = *77) and low–insulin dosing (●/■; low, <24 units/day of insulin;* n = *24) groups, as described in the text. Each line (—) represents the mean level of each group.*

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Prognostic Value of the Carotid Artery Intima-Media Thickness for the Presence and Severity of Coronary Artery Disease in Type 2 Diabetic Patients

Over the past decade, the measurement of carotid artery intima-media thickness (IMT) using high-resolution B-mode ultrasonography has emerged as one noninvasive method of choice for determining the anatomic extent of atherosclerosis and its progression and for assessing cardiovascular and stroke risk (1–4).

In vitro and in vivo studies indicate that carotid artery IMT measurements obtained by ultrasonography correlate well with pathologic measurements, and numerous investigators (5) have demonstrated the reproducibility of this technique and the strong correlation between IMT and classic risk factors (male sex, aging, overweight, elevated blood pressure, high blood cholesterol, diabetes, and smoking). Many studies (6–8) have shown that the incidence of coronary artery disease (CAD) in diabetic patients is two or three times higher than that in nondiabetic control subjects. A few previous studies (9,10) have evaluated the association between IMT and CAD in diabetic patients. In all these studies, CAD was diagnosed from symptoms and clinical records rather than by coronary angiography. Yet it is not fully confirmed that IMT can be used as a predictor of CAD, even with its severly luminal coronary obstruction, in diabetic patients.

We investigated the association between carotid artery atherosclerosis, valued from the IMT and the presence of atherogenic plaques, and CAD (angiographic documentation: CAD was diagnosed by detection of >50% stenosis in one of the three major coronary arteries; evaluation with Gensini score: a scoring system for use in coronary artery angiography that can be used to determine the severity of coronary artery disease based on the degree of luminal obstruction [11]). From November 2002 to January 2003, high-resolution ultrasound examination (ATL–HDI 1500) was performed to check the carotid arteries (carotid bulb, internal, and external carotid arteries bilaterally), IMT (measured in millimeters), and for the presence of plaques (categories: homogeneous, heterogeneous, and ulcerative) in 21 patients with type 2 diabetes and CAD (group A) and 20 patients with type 2 diabetes and without CAD (group B). Demographic, biochemical, and clinical characteristics of the two groups were recorded [age, duration of diabetes, BMI, waist circumference, HbA_{1c}, hypertension, drug treatment, diabetes complications, total serum cholesterol, LDL cholesterol, lipoprotein(a), apolipoprotein (apo)-B, serum homocysteine, and smoking].

Statistical analysis was performed using Student's *t* test, Pearson χ^2, and Pearson coefficient correlation.

The number of men and women in the two groups was identical. CAD diabetic patients had higher lipoprotein(a) ($P = 0.018$), serum total homocysteine ($P = 0.026$), and smoking ($P = 0.008$). In all patients of group A and in both carotid arteries, IMT was significantly higher. Mean IMT (mean ± SD) was 1.14 ± 0.286 vs. 0.875 ± 0.195 mm ($P = 0.001$). There were no significant differences between the two groups regarding BMI, waist circumference, duration and treatment of diabetes, HbA_{1c}, hypertension, diabetes complications, serum total cholesterol, LDL cholesterol, HDL cholesterol, apo-B, triglycerides, or the number and constitution of the atherogenic plaques.

IMT was not associated with Gensini score ($P = 0.728$). In multivariate analysis, IMT was the only parameter that was found to be independent ($P = 0.02$). Using the receiver operating characteristic analysis, IMT values ≥0.925 mm were associated with a relative risk of 25 in regard to the presence of CAD.

In conclusion, our data demonstrate that *1*) IMT measured by a simple, rapid, low-cost method for image processing, which can be performed directly during scanning of the carotid arteries, is a prognostic indicator for CAD in diabetic patients; and *2*) there is no correlation between IMT and CAD regarding the coronary arteries luminal obstruction. However, it is possible to have severe CAD without coronary arteries luminal obstruction (unstable plaque). The lack of correlation of the extent of obstruction, judged angiographically on the basis of evident luminal obstruction, is consistent with the biological nature of plaque accumulation seen with type 2 diabetes (hence frequently negative stress tests despite abluminal disease that sets the stage for acute coronary syndromes).

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Test Strips for Blood Glucose Monitors Are Not Always Accurate

Self-monitoring of blood glucose is essential for managing diabetes. Over 30 different blood glucose monitors cleared by the U.S. Food and Drug Administration (FDA) are available to consumers. The FDA relies solely on data provided by manufacturers for clearance. Few physicians or diabetic patients are aware that blood glucose monitor test strips that are exposed to humidity and/or excessive temperature give falsely elevated results. Manufacturers know this, and the information they provide to patients obfuscates the problem; furthermore, the FDA does not require the reporting of environmental effects on accuracy.

On more than one occasion, I administered excessive insulin based on results from the last few test strips from vials of 50 that had been opened for <1 month. I determined that the test strips were inaccurate by comparing them to new ones using glucose control solutions. I contacted the manufacturer, but representatives would provide no data on environmental effects. A Medline search showed no studies on this subject. *Health Devices* evaluates blood glucose monitors periodically but has never performed environmental testing.

The FDA requires manufacturers to report whenever they become aware of information that reasonably suggests that one of its devices *1*) has or may have caused or contributed to a death or serious injury or *2*) has malfunctioned and that the device or a similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. This information is available at the FDA website in the Manufacturer and User Facility Device Experience Database (MAUDE) (1). A search showed 691 reports for the test strips and 316 for the blood glucose monitor I used, many from health care providers. Many involve instances where the blood glucose monitor indicated high glucose levels, while symptoms were consistent with severe hypoglycemia. Hypoglycemia was confirmed by emergency medical services or in emergency departments. Manufacturers frequently respond to FDA inquiries with the statement "glucose controls were not used on the system."

This is disingenuous, as the manufacturers are well aware that few diabetic patients use glucose control solutions. A personal survey of 24 pharmacies shows that 15 carry no solutions and 5 only one brand for one monitor because they don't sell any. One recent study evaluating how well diabetic patients use blood glucose monitors reported that only 29 of 111 used glucose control solutions, often outdated and only rarely, and that most did not know what they were for (2).

The frequency and subject of MAUDE reports are not uniform across blood glucose monitors. Those using individually wrapped test strips, especially those containing a desiccant, have few reports, while those using test strips stored in vials account for most. (This is complicated because the two largest-selling devices both use vials with 50 test strips.) Studies addressing test strip reliability are lacking and urgently needed.

A human factors evaluation of one monitor marketed with a videotape beginning "It's as easy as 1, 2, 3" found that it requires 52 substeps to use properly (3). The authors conclude, "It is not appropriate to blame the user for making an error when the root cause of the error may really be the design of the system itself." Glucose monitors that are easier to use and that alert the user when the test strips should be discarded need to be designed. The medical community and regulatory agencies must insist on it.

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Sirolimus-Induced Interstitial Pneumonitis in an Islet Transplant Recipient

Islet transplantation can now result in markedly improved metabolic control for a subset of individuals with "brittle" type 1 diabetes. Yet, the immunosuppression required to prevent allograft rejection may come at a high price. We report the first case of an islet transplant recipient with sirolimus-induced interstitial pneumonitis.

A 59-year-old woman with type 1 diabetes since age 7 years became insulin independent after two islet infusions. She developed a gradually worsening, nonproductive cough 68 weeks after transplantation. At that time, her medication consisted of sirolimus, tacrolimus, filgrastim, aspirin, pravastatin, magnesium, calcium, nitrofurantoin, and levetiracetam. Chest auscultation and a radiograph were both unremarkable. Nitrofurantoin was discontinued because it has been associated with chemical pneumonitis. Computer tomography imaging 3 months after onset of her symptoms revealed patchy, nonsegmental air space disease in the basilar segments of both lower lobes and the superior segment of the left lower lobe. Pulmonary function tests showed a restrictive pattern. The patient had a mild fever and marked fatigue in addition to the worsening cough. A bronchial lavage showed a frail mucosa but no evidence for an infectious process. Empiric quinilone therapy was administered for a total of 14 days with no clinical improvement. The erythrocyte sedimentation rate steadily increased to a maximum of 100 mmHg/h, while the white blood cell count remained low (2.87 K/μl). Drug-induced pneumonitis was suspected. Faced with a diagnostic lung biopsy vice discontinuing sirolimus, the patient opted for the latter. We did not introduce an alternative immunosuppressive regimen due to the patient's clinical course, one complicated by myelosuppression, hypertension, hyperlipidemia, and other drug-induced complications. Instead, we initiated treatment with long-acting insulin anticipating islet allograft rejection. All drug-related symptoms resolved within 2 weeks, and both the computer tomography findings and the pulmonary function tests normalized within 3 months. The patient reverted to insulin dependency, but strikingly, she continues to display endogenous insulin secretion (C-peptide of 1.1 ng/ml) 9 months after discontinuing all immunosuppression.

Approximately 50 cases of sirolimus-induced pneumonitis have been reported, including at least one death (1–4). Most have been renal allograft recipients, but individuals with lung, liver, and heart transplants have also been affected. In most individuals, sirolimus trough concentrations ranged between 15 and 30 ng/ml. The occurrence of interstitial pneumonitis in our patient is inconsistent with the presumed sirolimus dose effect because her trough levels were maintained between 6 and 10 ng/ml. The precise etiology underlying sirolimus-induced pneumonitis remains unknown, but it has been speculated that sirolimus might expose cryptic pulmonary antigens, triggering a lymphocytic alveolitis and interstitial pneumonitis (3).

We conclude that sirolimus-induced pneumonitis can occur at low trough levels and should be considered in the differential diagnosis of an islet transplant recipient presenting with similar symptoms.

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No Deterioration in Glycemic Control in *HNF-1α* Maturity-Onset Diabetes of the Young Following Transfer From Long-Term Insulin to Sulphonylureas

Maturity-onset diabetes of the young (MODY) accounts for ~1% of diabetes in the U.K. It is characterized by autosomal dominant inheritance of young-onset diabetes that is not insulin dependent. MODY is frequently misdiagnosed as type 1 diabetes and treated immediately with insulin due to its presentation with marked hyperglycemia in slim adolescents/young adults (1–4). With diagnostic molecular genetic testing now well established, it is possible to make a definitive diagnosis of specific genetic subtypes of MODY (5).

HNF-1α mutations account for ~65% of U.K. MODY (MODY 3) cases. Patients with a mutation in *HNF-1α* are sensitive to the hypoglycemic action of sulfonylureas (6). This suggests that patients with *HNF-1α* MODY started on insulin from diagnosis could transfer to a sulfonylurea, as described in isolated cases (1,2). However, there have been no systematic studies. *HNF-1α* MODY is characterized by β-cell dysfunction that deteriorates over time (7,8), which leads to some concern over taking patients off insulin, particularly after a prolonged period on this treatment.

We aimed to assess the short-term safety and effectiveness of transferring patients with *HNF-1α* mutations on insulin from diagnosis to sulfonylureas. The characteristics of the eight U.K. Caucasian patients were median age 34 years (range 17–48), median age of diagnosis 14 years (range 8–17), and median time on insulin 20 years (range 4–35); four patients had been on insulin for >27 years. The me-

dian dose of insulin was 0.5 U/kg (range 0.1–2.2). Insulin was stopped, and gliclazide 20 mg was started and rapidly increased to a maximum dose of 160 mg b.d. unless good control was achieved or the patient suffered hypoglycemia. Patients monitored blood glucose levels four times daily initially and tested their urine for ketones. Telephone support was provided by our national team based in Exeter, U.K., and local support was provided in four cases by MODY link nurses (9). HbA_{1c} was measured on insulin and after at least 2 months on sulfonylureas (median 6 months [range 2–11]).

All patients were able to discontinue insulin and were maintained on sulfonylureas without developing ketonuria or marked hyperglycemia. There was heterogeneity in response with the majority of patients (6 of 8) showing an improvement in control. The median reduction in HbA_{1c} following transfer to sulfonylureas was 0.8% (range −2.5 to 3.2) ($P = 0.26$). The median dose of gliclazide was 80 mg daily (range 20–320). Only one patient had a marked deterioration in HbA_{1c} (3.2%) on transfer to sulfonylureas. She had a long duration (35 years) of diabetes and may have coinherited type 2 diabetes genes from her father (who had type 2 diabetes), which can result in a more severe phenotype (10). All patients reported improvements in quality of life as a result of stopping insulin. The longest any of these patients has been off insulin is 18 months (range 7–18).

We conclude that transferring insulin-treated *HNF-1α* MODY patients to sulfonylureas was safe in the short term, even when patients have been on prolonged insulin treatment, and is not associated with a deterioration of control in most patients. Although the improved glycemic control seen in most patients may be partly attributed to increased blood glucose monitoring and/or attention from health care professionals, this could only be seen if treatment with sulfonylureas was effective. Sulfonylurea therapy should be considered in patients with *HNF-1α* MODY on insulin from diagnosis, but this should be closely monitored. This emphasizes the clinical utility of performing diagnostic molecular genetic testing. These preliminary short-term data need to be repeated in larger series with long-term follow-up. Many of these patients may require insulin again in the future.

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Type 1 Diabetes and Multiple Sclerosis

Together at last

Last year, Marrosu et al. (1) reported an increased prevalence of type 1 diabetes among Sardinian individuals with multiple sclerosis and their first-degree relatives. The study was accompanied by a commentary (2) indicating that these autoimmune disorders were "an unlikely alliance" because the HLA haplotype that increases risk for multiple sclerosis (DRB1*15-DQA1*0102-DQB1*0602) protects against type 1 diabetes. To the authors' knowledge, there have been no published studies of an increased risk of multiple sclerosis for individuals with type 1 diabetes or their families.

Could the association between type 1 diabetes and multiple sclerosis be unique to Sardinia, where the rates of these two disorders are among the highest in the world? Indeed, multiple sclerosis is associated with DRB1*0405-DQA1*0501-DQB1*0301 and DRB1*0301-DQA1*0501-DQB1*0201 in Sardinia (3) and not DRB1*15-DQA1*0102-DQB1*0602, as it is elsewhere in the world. The DRB1*0301-DQA1*0501-DQB1*0201 haplotype is also associated with type 1 diabetes and other autoimmune diseases, such as celiac disease and autoimmune thyroid disease, which are also highly prevalent in Sardinia. Thus, perhaps the association

between type 1 diabetes and multiple sclerosis observed in Sardinia is due to its unique HLA haplotype distribution (4).

Alternatively, the "unlikely alliance" hypothesis, which represents the current thinking of many researchers, may have biased us to the point that we failed to look for a possible association between type 1 diabetes and multiple sclerosis. Indeed, we plead guilty to this charge. However, examination of data collected for our Familial Autoimmune and Diabetes (FAD) Study revealed, for the first time, a highly significantly increased prevalence of multiple sclerosis in adults with type 1 diabetes and their first-degree relatives.

The FAD Study focused on the clustering of type 1 diabetes, autoimmune thyroid disease, and rheumatoid arthritis in a cohort of adult type 1 diabetic subjects diagnosed before age 17 years and seen at Childrens' Hospital of Pittsburgh between 1950 and 1964. Self-report data on the existence of other autoimmune disorders in type 1 diabetic subjects and their siblings and parents were also collected. Seventy-six percent of the eligible probands and 83% of their siblings and parents participated. We recruited 94 nondiabetic control families for comparison.

Two percent of the females with type 1 diabetes and 0.5% of their sisters reported multiple sclerosis. No cases of multiple sclerosis were observed among male probands or male siblings, and multiple sclerosis was totally absent in the control families. Published prevalence rates for multiple sclerosis in the U.S. ranged from 0.06 to 0.17% (~0.1% on average) for female adults. Thus, we observed a 20-fold increase in the prevalence of multiple sclerosis in our type 1 diabetic women ($P = 0.003$). Nondiabetic sisters had a fivefold higher risk of multiple sclerosis compared with the general population, which was not statistically significant.

We therefore conclude that adult women with type 1 diabetes are at an enormously increased risk of multiple sclerosis, and that the answer to questions about the clustering of these disorders is that they are "together at last." Further epidemiologic studies are needed to confirm our findings. Genetic studies are also required to evaluate the DRB1*0301, DRB1*0405, and DRB1*15 extended haplotypes for common alleles at other loci that may contribute to the familial clustering of multiple sclerosis and type 1 diabetes.

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Serum Amylase and Lipase in Diabetic Ketoacidosis

Increased amylase and lipase occurs 16–25% of the time in diabetic ketoacidosis (DKA) (1). Acute pancreatitis can present or coexist with DKA and aggravate its severity (2). Nonspecific elevations of amylase in DKA have been reported (3), although increased serum lipase is assumed to indicate actual pancreatic involvement. Two cases of DKA are described in which elevated enzymes were seen without clinical or radiographic evidence of acute pancreatitis.

The first patient was a 74-year-old female with a 32-year history of type 1 diabetes who presented with DKA. Although she had no abdominal pain or tenderness, her amylase and lipase levels were elevated and peaked at values of 1,024 units/l (normal range 17–100 units/l) and 3,455 units/l (normal range <53 units/l), respectively. The enzymes declined precipitously to normal with rehydration and insulin administration. Calcium was 11.7 mg/dl (8.5–10.5) and parathyroid hormone was 232 pg/ml (10–65). It was felt that hypercalcemia due to primary hyperparathyroidism caused acute pancreatitis, precipitating DKA. However, computed tomography (CT) did not show any pancreatic inflammation. The patient had a sestamibi neck scan and underwent successful parathyroidectomy. Several months later she had another episode of DKA but was normocalcemic. The serum amylase was 781 units/l, and lipase was 972 units/l. Transaminases and triglyceride levels were normal. She did not exhibit any abdominal complaints or pancreatic inflammatory changes on CT. Endoscopic retrograde cholangiopancreatography revealed a normal hepatobiliary tree and pancreatic duct. The enzymes normalized with resolution of DKA.

The second patient was a 23-year-old white female with type 1 diabetes who presented with dehydration and DKA. She had an undetectable serum alcohol level and normal calcium, hepatic, and lipid profiles. The amylase level peaked at 406 units/l, and lipase peaked at 2,404 units/l. The patient denied abdominal pain and tenderness on physical examination. Ultrasound of the liver and gall bladder was unremarkable, and CT did not show any inflammation, enlargement, or other changes in the pancreatic area. At an office visit 10 days after discharge, her lipase and amylase levels were normal at 32 and 41 units/l, respectively.

The clinical diagnosis of acute pancreatitis rests on the presence of abdominal pain and associated increases of amylase and lipase, while CT scan is recognized as the gold standard for confirmation. The prevailing opinion is that absolute enzyme elevations greater than

three times normal indicate pancreatic involvement (4). Although this may be true in many situations, the above cases and recent studies (1,2) support the notion that such elevations without actual pancreatic involvement may be nondiagnostic in the presence of DKA, as evidenced by absence of abdominal findings and CT scan abnormalities. However, it should not be overlooked that acute pancreatitis can sometimes accompany or precipitate DKA.

The source of elevated enzymes in DKA without acute pancreatitis remains unclear. Subtle injury to the pancreatic acinar cells may liberate them into the circulation. Another possibility is an extrapancreatic origin triggered by the dysmetabolic state, like release of salivary gland amylase, or its accumulation secondary to suboptimal excretion in the urine (3). Increase in lipase may be due to release of nonpancreatic lipolytic enzymes into the bloodstream from sources such as the stomach, liver, small bowel, tongue, esophagus, etc. (5). Some authors have suggested that hyperlipasemia may be related to assay inaccuracy in such cases (6).

In conclusion, significant but nonspecific elevations of amylase can be seen in DKA. Elevated lipase, traditionally thought to be more specific for pancreatitis, may also accompany DKA and does not necessarily denote concomitant pancreatic inflammation. Hyperlipasemia may therefore be less reliable for diagnosing acute pancreatitis in this setting.

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Rosiglitazone Lowers Blood Pressure and Increases Arterial Compliance in Postmenopausal Women With Type 2 Diabetes

Diabetes is associated with stiff large arteries, which plays an important role in the pathogenesis of vascular disease (1) and is the primary cause of mortality and morbidity with type 2 diabetes. Similarly, after menopause, women experience a dramatic increase in large artery stiffness and the rate of cardiovascular disease (2). Thiazolidinediones modulate glucose homeostasis (3) and exhibit a number of potential antiatherogenic actions (3), the collective effects of which remain to be fully elucidated in humans.

We therefore investigated whether rosiglitazone, the second member of the thaizolidinediones group, would improve blood pressure and arterial compliance, measured by distensibility index (4), in postmenopausal women with type 2 diabetes. In a randomized, double-blind, placebo-controlled study, 31 women with established diabetes diagnosed 1–12 years prior were tested before and after 12 weeks of treatment with 4 mg rosiglitazone daily ($n = 21$) or matching placebo ($n = 10$). Eighty percent of the women continued their use of metformin, a sulfonyurea, or both throughout the trial. Glycemic control, lipids, blood pressure, and distensibility index were assessed. Rosiglitazone reduced fasting plasma glucose (from 9.40 ± 1.7 to 7.1 ± 0.9 mmol $\cdot l^{-1} \cdot l^{-1}$, mean ± SEM; $P = 0.001$), HbA_{1c} (from 7.6 ± 0.7 to 6.4 ± 0.4%; $P = 0.001$), brachial systolic blood pressure (from 124 ± 10 to 112 ± 9 mmHg; $P = 0.003$), central systolic blood pressure (from 118 ± 9 to 111 ± 7 mmHg; $P = 0.02$), diastolic blood pressure (from 71 ± 4 to 65 ± 3 mmHg; $P = 0.004$) and mean arterial pressure (from 91 ± 6 to 84 ± 4 mmHg; $P = 0.001$), while lipid levels were unchanged. Rosiglitazone increased distensibility index (from 0.106 ± 0.02 to 0.134 ± 0.03 arbitrary compliance units; $P = 0.01$) and reduced pulse pressure (from 54 ± 7 to 50 ± 7 mmHg; $P = 0.08$). There were no significant changes in lipid profiles with rosiglitazone treatment. The placebo had no effect on any of the variables measured. All women maintained >90% compliance with no adverse events reported.

The main findings of this study are that for postmenopausal women with type 2 diabetes rosiglitazone improves glycemic control, reduces blood pressure, and increases compliance of large proximal arteries. Strict glycemic control delays the onset and moderates the progression of vascular complications (5), which may in part explain the increases in arterial compliance and reductions in blood pressure with rosiglitazone; however, it is possible that rosiglitazone improves cardiovascular parameters independently of glycemic changes. A reduction in blood pressure and an increase in large proximal artery compliance may reduce the risk of coronary artery disease (1). Long-term studies are required to determine whether these observed effects are sustained. In conclusion, rosiglitazone is an effective treatment to improve glycemic control and reduce the risk of cardiovascular disease in postmenopausal women with type 2 diabetes.

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Type 2 Diabetes and the Naaman Syndrome

Evidence-based medicine strongly supports lifestyle changes for the prevention and treatment of type 2 diabetes, but are they accepted by patients, doctors, and health care providers or considered trivial compared with drug treatment?

The case reminds us of the biblical story of Naaman, the leper, landlord of the Syrian king. When he heard that Eli'sha, the prophet, might heal him, he moved from Syria to the door of Eli'sha with silver and gold to pay for his cure. He thought Eli'sha would do something extraordinary and impressive. Instead, Eli'sha simply sent a servant to tell him to wash in the Jordan. Naaman was furious and went back: such a long journey to Israel to hear that he merely had to wash! That would expose him to ridicule. Later, he reconsidered the advice, dipped himself in the Jordan, and his leprosy disappeared.

If we consider Naaman's cure independently of God's intervention, the story indicates that ordinary therapeutic measures, of apparently low value, may be more effective than complicated and expensive treatments. We propose to name after Naaman the scarce consideration given to diet and exercise in the prevention and cure of type 2 diabetes.

First, only a few patients are willing to comply with lifestyle changes as much as they would fulfill pharmacologic prescriptions. Behavioral changes are only apparently easy to achieve, but it was also not easy for Naaman to accept a treatment that might be useless. Structured programs based on education, cognitive approaches, and reinforcement methods are effective in promoting adherence to dietary recommendation and physical exercise (1), but most patients claim that they have no time to spend in these activities, not to mention extra time for exercise.

Second, physicians need specific training to lead patients into behavioral modifications. But are they really willing to adjust to this requirement? Academic curricula provide no room for communication abilities and group management, and physicians are fearful of losing their role when involved in educational programs, which are scarcely considered and poorly remunerated. Most doctors still believe that their duty is to offer prescriptive treatment to the increasing number of diabetic patients. There is no time left for cognitive approaches.

Finally, diabetes units need different facilities and staff, including psychologists and exercise physiologists, to carry out a comprehensive educational task. This results in objections from hospital boards, who are keener on funding technological developments. It is time for health care providers to redirect resources to behavioral strategies, which are extremely cost-effective in the long term, considering the cost of diabetes and its late complications.

In conclusion, Naaman syndrome is a widespread condition: patients, doctors, and health care providers need to eliminate it for an effective prevention and treatment of type 2 diabetes.

"Then went he down, and dipped himself seven times in Jordan . . . and he was clean" (2nd Kings 5:14).

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Deficiency in the Detection of Microalbuminuria by Urinary Dipstick in Diabetic Patients

Microalbuminuria is considered a marker of diabetic nephropathy. Early detection of microalbuminuria allows for early intervention with the goal of delaying the onset of overt diabetic nephropathy.

The aim of this study was to compare the analysis of urinary albumin and creatinine by both Microalbustix and Clinitek microalbumin urinary dipsticks compared with high-performance liquid chromatography (HPLC) analysis.

Diabetic patients attending the Endocrine Clinic at Austin & Repatriation Medical Center, Heidelberg, Australia, were studied (56% normoalbuminuric, 34% microalbuminuric, and 10% macroalbuminuric by immunoturbidimetry). Albumin and creatinine concentrations were determined in 24-h urine samples by Microalbustix and Clinitek microalbumin dipsticks using a Clinitek 50 Autoanalyzer (Bayer, Elkhart, IN) and by HPLC, as previously described (1). Urinary creatinine concentration was also determined using a Hitachi 971 Autoanalyzer.

Using an upper limit of normal of <30 mg/l for albumin concentration, 56 of 115 and 48 of 98 urines were normal by Microalbustix and Clinitek microalbumin, respectively, and also by HPLC analysis. The Microalbustix and Clinitek microalbumin gave false-negative results (<30 mg/l) for 20 of 115 (17.4%) and 16 of 98 (16.3%) urines, respectively. There were 21.0% false-negative results for diabetic urines measured by immunoturbidimetry compared with HPLC analysis. In urine tested by HPLC from nondiabetic volunteers, 73 of 106, 32 of 106, and 1 of 106 had albumin concentrations of <10,

10–30, and 30–80 mg/l, respectively. There were 3.7% false negatives for albumin concentration in nondiabetic urines measured by immunoturbidimetry compared with HPLC analysis. These results demonstrate that HPLC analysis does not overestimate albumin concentrations since results similar to conventional immunoturbidimetry were obtained for nondiabetic urine. The differences obtained for diabetic urine are due to changes in albumin processing in the diabetic state that are undetectable by immunochemical assays (2).

Using an upper limit of normal for the albumin-to-creatinine ratio (ACR) of <30 mg/g, 34 of 115 and 29 of 98 urines were normal by Microalbustix and Clinitek microalbumin, respectively, and by HPLC analysis. The Microalbustix and Clinitek microalbumin gave false-negative results (<30 mg/g) for 42 (36.5%) and 42 (42.9%) urines, respectively, compared with HPLC analysis (>30 mg/g). There were 36.3% false-negative results for diabetic urines measured by immunoturbidimetry compared with HPLC analysis. For the 106 nondiabetic volunteers, 100 of 106 and 6 of 106 were found to have ACRs <30 mg/g and 30–300 mg/g when albumin concentration was measured by HPLC. There were 0% false negatives for ACR in nondiabetic urine measured by immunoturbidimetry compared with HPLC analysis.

Development of a quantitative test for urinary albumin is difficult. Intact albumin filtered by the kidney is biochemically modified, resulting in the excretion of a complex mixture of <1% intact albumin and >99% albumin-derived fragments <10kDa (2). Conventional immunoassays and dye binding methods cannot detect albumin-derived fragments (2,3), and a proportion of the intact albumin excreted has also been shown to be immunounreactive (1,4). Immunoassays measure active epitope in urine; however, this epitope may not be exclusively associated with intact albumin (1–4). HPLC analysis of urinary albumin is able to detect both intact immunoreactive and intact immunounreactive albumin (1) and is priced <$10 per urine sample. All other available methods for measuring urinary albumin cannot detect albumin fragments.

Microalbustix and Clinitek microalbumin dipsticks exhibit poor sensitivity in detecting early changes in the kidney that result in microalbuminuria. Both dipsticks were similar, which is not surprising. They are based on the same sulfonephthalein dye binding method that does not detect albumin-derived fragments (3) because an inhibitor is present in the dipstick formulation that inhibits urinary protein fragments binding to it (5). The American Diabetes Association recommends that semiquantitative or qualitative screening tests for microalbuminuria have a detection rate for abnormal samples of >95% for patients with microalbuminuria to be useful for screening (6). However, in 2002 the American Diabetes Association could find no published study that fulfilled these criteria for qualitative (or semiquantitative) dipstick tests (6).

A satisfactory screening test for microalbuminuria needs to be at least as sensitive as a laboratory method. Subsequent laboratory testing can eliminate false positives, but false negatives could result in the delay of beneficial early treatment that may stop or reverse the progression to overt diabetic nephropathy.

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Extreme Altitude Mountaineering and Type 1 Diabetes

The Cho Oyu Alpinisti in Alta Quota Expedition

The American Diabetes Association states that all levels of physical activity can be performed by people with type 1 diabetes who do not have complications and are in good blood glucose control (1). Extreme altitude mountaineering, defined as climbing at altitudes in excess of 5,000 m, creates physiological demands, especially in type 1 diabetic subjects, who might experience impaired pulmonary function (2). We present the metabolic control and symptoms of mountain sickness during the 2002 Alpinisti in Alta Quota (ADIQ) Expedition to Cho Oyu, which is the sixth highest Himalayan peak. Six subjects with type 1 diabetes and 10 matched nondiabetic individuals participated in the expedition. The type 1 diabetic subjects were free of long-term diabetes complications and experienced climbers; they were in good metabolic control before the expedition. The glucose profiles at time 0800, 1000, 1200, 1400, 1800, 2000, and 2200 and the insulin requirement were assessed. The 3-hydroxybutyrate concentration on capillary blood was also determined at 0800 and 2000. Retinopathy and albumin excretion rate were assessed before and after the expedition. One of 6 type 1 diabetic subjects and 3 of 10 control subjects ascended to the top of Cho Oyu (NS between groups).

The Lake Louise Scoring System (3) showed no difference between type 1 diabetic and nondiabetic subjects in their susceptibility to symptoms of altitude

sickness. None of the type 1 diabetic subjects developed fresh retinal hemorrhages. No differences were observed in urinary albumin excretion rate. There was a worsening of HbA_{1c} during the expedition in both control and type 1 diabetic subjects (5.4 ± 0.1% vs. 7.9 ± 06%, $P <$ 0.01). During the ascent to the Cho Oyu, there was a progressive increase in daily insulin requirement (from 38 ± 6 units/day at 0 m to 51 ± 6 at 4,200 m, $P <$ 0,001). A significant rise in the capillary glucose concentration at 0800, 1000, 2000, and 2200 was also observed. On the day the type 1 diabetic subject reached the top of the Chou Oyu, he had an insulin requirement of 56 units/day (34 units/day at sea level) and a mean plasma glucose concentration of 198 mg/dl. No changes in the daily glucose coefficient of variation were observed. No significant changes in the 3-hydroxybutyrate capillary concentration were observed at 0800 or 2000. In conclusion, we found that uncomplicated type 1 diabetic subjects can cope with extreme altitude mountaineering; however, this activity leads to a worsening of metabolic control. Moreover, our results suggest that all diabetic patients who want to deal with this activity need to be extremely trained to handle glucose monitoring and to vary dietary and insulin needs accordingly.

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Acute Angle Closure Glaucoma Following Rapid Correction of Hyperglycemia

Chronic hyperglycemia, associated with diabetes, leads to many ocular complications. The effects on the eye of rapidly correcting acute hyperglycemia, however, are less well appreciated.

A 59-year-old man with no prior history of diabetes presented to our hospital with several weeks of polyuria, polydipsia, and blurred vision. He had last seen an ophthalmologist 3 years previously when, in addition to his known hyperopia, he was diagnosed with bilateral cataracts; intraocular pressures (IOPs) were normal at that time, and corrected visual acuity was 20/50 in oculus dexter (OD) and 20/20 in oculus sinister (OS).

Laboratory data on presentation included 118 mmol/l serum sodium, 5.7 mmol/l potassium, 54 mg/dl BUN, 1.6 mg/dl creatinine, and a normal anion gap of 10. The serum glucose was 1,550 mg/dl. Calculated serum osmolality was 340 mosm/kg.

On physical examination, the subject was classified as overweight (BMI 37.4 kg/m^2). He appeared dehydrated and was tachycardic with stable blood pressure. Conjunctiva were injected bilaterally without exudates, and extraocular movements were normal. The remainder of the physical examination was unremarkable.

A diagnosis of hyperglycemic hyperosmolar syndrome was made. The patient was hydrated with 3.5 l normal saline i.v. over the first 3 h. He then received 10 units regular human insulin i.v. and 10 units s.c. His plasma glucose levels decreased from 1,520 to 1,050 mg/dl over 5 h with intravenous hydration alone before falling precipitously from 1,050 to 322 mg/dl over the next hour following administration of insulin.

At that point, the patient began to complain of increasing pain OD with a right frontal headache. His right conjunctiva was now markedly injected, and his visual acuity was reduced OD with inability to count fingers. His visual acuity OS was close to the baseline of 20/25. IOPs were 59 mmHg OD and 35 mmHg OS, and a diagnosis of acute angle closure glaucoma was made. He was treated with timolol, brimonidine, dorzolamide, pilocarpine, and prednisolone eye-drops. Within 2 h, his IOP began to decrease to 51 mmHg OD and 21 mmHg OS. Oral Acetazolamide was begun. Two hours later, IOP fell further to 39 mmHg OD and 18 mmHg OS, and the patient's eye pain improved. By the following morning, his IOP was within normal limits at 21 mmHg OD and 19 mmHg OS.

There are several putative mechanisms as to why hyperglycemia might contribute to angle closure glaucoma. The lens is freely permeable to glucose and does not require insulin for glucose penetration (1). Hyperglycemia leads to an increased level of glucose within the aqueous humor that in turn leads to elevated lens glucose levels. Aldose reductase within the lens converts the glucose to sorbitol, which increases lens hypertonicity, leading to water influx and lens swelling (2).

Although the lens is freely permeable to glucose, once acute hyperglycemia has been corrected, and normoglycemia restored, the osmotic changes within the lens do not immediately correct. Studies with amphibian lenses have not only shown significant changes in lens swelling during hyperglycemia but also further lens swelling when euglycemia is restored (3). This sequence, termed "double osmotic shock," is explained by the fact that as blood glucose levels normalize, further water is drawn into the lens by the differential level of glucose in the lens compared with the surrounding aqueous fluid. The enlarged lens can acutely obstruct the canal of Schlemm and lead to increased IOP.

Fortunately, acute angle closure glaucoma following rapid correction of acute hyperglycemia is exceedingly rare in clinical practice (4,5). Our case is remarkable because of the clear temporal relationship between development of acute eye pain and the rapid drop in plasma glucose levels. Clinicians should be aware of the potential to precipitate angle closure glaucoma during rapid correction of hyperglycemia.

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Clinical Worth of Adiponectin Levels in Obesity and Glycemic Control of Japanese Type 2 Diabetic Patients

Low levels of adiponectin in plasma have recently been implicated in the development of obesity, insulin resistance, and type 2 diabetes in mice and humans (1–4). We examined a role of adiponectin as a clinical examination in obesity and type 2 diabetes and raise a question of clinical worth of evaluating adiponectin levels in the management of type 2 diabetic patients.

In the first group, 39 Japanese subjects with type 2 diabetes, including 19 men and 20 women matched for age, HbA_{1c}, and plasma glucose levels, were assessed in a cross-sectional analysis. Plasma adiponectin levels were determined in type 2 diabetic subjects with normal BMI (21.6 ± 0.3 kg/m^2, n = 22 [11 men and 11 women], 63 ± 1 years) and those who were overweight (26.3 ± 0.3 kg/m^2, n = 17 [8 men and 9 women], 64 ± 2 years). These subjects were treated by diet therapy alone before assessment. No significant differences in plasma adiponectin levels were observed in type 2 diabetic subjects who were nonobese (adiponectin 5.9 ± 0.4 μg/ml) and overweight (6.2 ± 0.5 μg/ml). These results indicate that plasma adiponectin levels are not an indicator of mild obesity in type 2 diabetic patients.

In the second group, a total of 14 Japanese type 2 diabetic subjects who were treated with antidiabetic agents without pioglitazone were evaluated prospectively. Of the 14, 8 subjects (4 men and 4 women, 62 ± 2 years) displayed better glycemic control, whereas 6 subjects (5 men and 1 woman, 65 ± 1 years) displayed worse glycemic control during the management. Decreases in HbA_{1c} and plasma glucose levels were not associated with elevations in plasma adiponectin levels (BMI 24.7 ± 1.1 to 25.0 ± 1.1 kg/m^2, HbA_{1c} 8.6 ± 0.2 to 7.1 ± 0.2% [$P < 0.05$], glucose 187 ± 17 to 128 ± 14 mg/ml [$P < 0.05$], and adiponectin 5.2 ± 0.9 to 5.1 ± 0.8 μg/ml). In addition, elevations in HbA_{1c} were not associated with decreases in plasma adiponectin levels. Rather, we observed that the elevations in HbA_{1c} levels were associated with elevations in adiponectin levels (BMI 23.0 ± 0.8 to 23.2 ± 0.6 kg/m^2, HbA_{1c} 7.6 ± 0.2 to 8.0 ± 0.1% [$P < 0.05$], glucose 176 ± 17 to 175 ± 32 mg/ml, and adiponectin 5.5 ± 1.4 to 7.2 ± 1.0 μg/ml [$P < 0.05$]). These findings indicate that adiponectin levels are not directly related to glycemic control in type 2 diabetic patients.

Moreover, in the third group of randomized subjects with type 2 diabetes (n = 9 [5 men and 4 women], age 56 ± 2 years) without any antidiabetic drugs, fasting plasma adiponectin levels were not negatively correlated with BMI, HbA_{1c}, fasting plasma glucose and insulin levels, or 2-h glucose levels after 75-g glucose ingestion, whereas plasma leptin levels were positively correlated with BMI (r = 0.598, $P < 0.01$).

These findings indicate that plasma adiponectin levels are unlikely to be a clinical indicator of mild obesity and glycemic control in Japanese type 2 diabetic patients. The clinical worth of adiponectin levels in the management of type 2 diabetes warrants further examination in the future.

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Prevalence of the Metabolic Syndrome in Middle-Aged Men and Women

Whereas the global epidemic of type 2 diabetes is now well characterized (1), data on the occurrence of the metabolic syndrome in populations are limited (2–5). The lack of an accepted internationally agreed definition has impeded epidemiological work on the prevalence and antecedents of this syn-

drome. Two definitions of the syndrome have been proposed, one by the World Health Organization (MSWHO) (6), and one in the U.S. Third Report of the National Cholesterol Education Program, Adult Treatment Panel, 2001 (ATP III) (4).

We have estimated and compared the prevalence of the metabolic syndrome according to both criteria in a cross-sectional study involving a group of 1,018 subjects aged 50–69 years of Irish ethnic origin. Participants were recruited from a primary care setting using stratified random sampling with a response rate of 69.9%. Details of the sample recruitment, the study questionnaire, anthropometric and physical measurements, and measurements of glucose and lipids have been described (7). Data on all variables required to define the metabolic syndrome according to both criteria were available for 890 participants.

The prevalence of the metabolic syndrome according to the WHO definition was 21.0% (95% CI 18.7–24.1%) and 20.7% (19.1–24.4%) according to the ATP III definition. A total of 13.1% (10.9–15.3) met the criteria for both syndromes and 28.5% (25.6–31.4) for one or both. The prevalence of the WHO definition of metabolic syndrome was higher in men (24.6%) than in women (17.8%), whereas prevalence of metabolic syndrome defined by ATP III was similar in men and women (21.8 vs. 21.5%). The prevalence of the syndrome increased with age: WHO: 15.2% in those aged 50–59 years to 24.3% in those aged 60–69 years; ATP III: 16.4% in those aged 50–59 years to 24.3% in those aged 60–69 years. The level of agreement between the two definitions of the syndrome was only moderate (κ statistic = 0.53, 0.46–0.60).

In summary, approximately a quarter of middle-aged men and women met one or both of the current criteria for the metabolic syndrome. However, there is only moderate agreement between the two definitions of the syndrome. There is an urgent need for a single internationally agreed definition of the metabolic syndrome.

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COMMENTS AND RESPONSES

Amputation and Mortality in New-Onset Diabetic Foot Ulcers Stratified by Etiology

Response to Moulik, Mtonga, and Gill

We have read the article by Moulik, Mtonga, and Gill (1) with much interest. Their findings are that increased mortality associated with foot ulceration is not influenced by underlying risk factors, namely peripheral neuropathy and peripheral vascular disease, and that it is only influenced by the age of the patient at presentation. There are points in this study regarding the method, the presentation of outcomes data, and the conclusion that we would like to highlight, and we would be grateful for a response from the authors.

A patient presenting with a new ulcer may have a history of ulceration. The period from first ulceration could therefore be potentially much longer than that measured in this group of patients presenting with new foot ulcers. Does the term "new onset" refer, therefore, to those patients with no history of ulceration or to those with current ulceration of short duration? The identification of significant vascular disease in patients with diabetic foot ulceration cannot be based solely on the detection of foot pulses because this is unreliable (2). More accurate evaluation requires a second method of assessment, such as the calculation of the ankle-brachial or toe-brachial pressure index and color duplex imaging (3). In the conclusion, it is noted that the high rates of morbidity and mortality in those patients with no identifiable ischemia or neuropathy were likely due to failure to detect underlying disease. Indeed, the amputation rates in this group were much higher than those of the neuropathic group and approached those of the ischemic group. Was further information obtained on the vascular status of the nonischemic patients who subsequently required amputation?

The data on the 5-year mortality rates in the groups appear inconsistent. In the article, Table 1 shows the number and percentage of deaths as 21 (25%) vs. 20 (46%) for the neuropathic and ischemic groups, respectively. The 5-year mortality figures in Table 3, however, show values of 21 (45%) and 20 (56%), respectively. It is unclear why these figures are different. If the Table 3 figures are incorrect, then the age-related adjustment may be invalid and ischemic disease would remain a significantly greater risk factor for subsequent mortality than neuropathy. This is further reinforced by the high number of deaths associated with vascular disease and would then be consistent with the significantly higher amputation rates seen in patients with ischemia versus neuropathy alone.

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Amputation and Mortality in New-Onset Diabetic Foot Ulcers Stratified by Etiology

Response to Williams, Price, and Harding

We offer many thanks to Williams, Price, and Harding for reading our article (1) with interest and for their comments regarding our study in this issue of *Diabetes Care* (2). In response to the specific points raised, we provide the following replies.

1) Patients with new-onset ulcers developing within the past 1 month were included in the study. Our records did not include whether these patients had previous ulcers that had healed completely. This may have been the case, but we feel only in a small minority of cases.

2) The study data were collected during initial assessment by a diabetologist/chiropodist in a diabetic foot clinic. The absence of two or more foot pulses on palpation is widely used as a diagnostic criterion for peripheral vascular disease and is used by many diabetologists (3). The use of ankle-brachial systolic pressure index is often misleading in diabetes. Color duplex scanning was done only in patients referred for vascular surgical assessment, and the data were not presented. As mentioned in the article, we presented data on simple clinical tests that can be performed in any hospital or community foot clinic and reflect common clinical practice.

3) Table 1 represents the total number of patients and absolute mortality statistics. Patients were recruited in the study over 5 years and thus had varying lengths of follow-up. To adjust for this, 5-year mortality rates were derived by Kaplan-Meier analysis and presented in Table 3 and Fig. 3. These would of course be different from the absolute mortality statistics and are not inconsistent.

The high mortality rates of patients with atherosclerotic vascular disease are well known. Atherosclerosis is more common with increasing age. This study points out that all diabetic patients with foot ulcers are at high risk, but those with vascular disease have a higher 5-year mortality, part of which could be due to the increased prevalence of atherosclerotic vascular disease with age. Similar comments have been made in other studies (4).

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Patients on Atypical Antipsychotic Drugs: Another High-Risk Group for Type 2 Diabetes

Response to Lean and Pajonk

The potential contribution of antipsychotic medication to the risk of diabetes in patients with severe mental illness has received significant attention in the psychiatric literature (1). In a recent review in *Diabetes Care*, Lean and Pajonk (2) claim to have summarized the "evidence for a causal link" between certain atypical antipsychotics and diabetes. However, their argument relies largely on spontaneous reports and retrospective, or uncontrolled, studies that are not suited to address causation. Furthermore, recent controlled prospective studies raise doubts about the authors' suggestion of a "direct metabolic effect" for drugs such as olanzapine.

The authors use case reports to argue for differential "diabetogenic potential of the atypical antipsychotics" (in Table 1 of their article) and claim that risperidone "appears to have the least propensity to cause diabetes." They did not cite studies by Koller et al. (3) and Hedenmalm et al. (4) documenting additional cases of diabetes, including cases of diabetic ketoacidosis and death, in patients taking risperidone. Neither did they point out that spontaneous reporting of adverse events is poorly suited to establishing disease incidence (5) and thus relative risk. Three pharmacoepidemiology studies are referenced in the article (6–8) that report lower diabetes risk among risperidone users. Other studies in which risperidone use was associated with a higher risk are not discussed (9–11). Perhaps more importantly, none of the studies directly comparing patients treated with different atypical antipsychotics reported statistically significant differences in rates of new diabetes, suggesting that diabetes risk is

comparable among the various agents represented in these studies.

In discussing potential mechanisms of drug-induced diabetes, Lean and Pajonk reference studies by Cagliero (12) and Newcomer (13) as evidence that olanzapine and clozapine adversely affect glucose metabolism and insulin sensitivity. Such conclusions are weakened by the fact that both studies were cross-sectional and without randomization to treatment. Using the hyperinsulinemic-euglycemic clamp method in a randomized prospective clinical trial (14), we found no significant differences in insulin sensitivity in normal individuals treated with olanzapine, risperidone, or placebo. A study in schizophrenia patients likewise did not show differences in insulin sensitivity comparing olanzapine, risperidone, and typical antipsychotic treatment cohorts (15). To assess changes in glycemic control during antipsychotic treatment, we analyzed our own clinical trial database (>5,000 patients in randomized controlled studies) and have not seen significant differences in the rates of new diabetes when olanzapine cohorts were compared with placebo or haloperidol or risperidone treatment groups (16) (Lilly data on file). Likewise, there were no significant differences among these groups in the number of patients exceeding potentially meaningful cutoffs in casual blood glucose values (e.g., ≥126, 140, 160, or 200 mg/dl) (17).

The article by Lean and Pajonk does make the important point that patients with severe mental illnesses such as schizophrenia are at increased risk for diabetes and that this association predated the introduction of newer antipsychotic drugs. Higher diabetes prevalence, irrespective of antipsychotic treatment choice, was also seen in the study by Sernyak et al., which they cite (6). According to Lean and Pajonk, this study showed that "there was a significant association between the development of diabetes and prescription of quetiapine, clozapine, and olanzapine but not risperidone." They fail to report that this was only true when the atypical antipsychotic cohorts were individually compared with the cohort taking older "typical" antipsychotics. In fact, Sernyak et al. report that the prevalence of diabetes among younger antipsychotic users (typical and atypical) was over five times the expected rate in the general population. Because risperidone users made up >40% of this group and the odds ratios for diabetes were not significantly different between risperidone and the other atypical agents (based on overlapping CIs), it seems clear that patients treated with risperidone are not protected from developing diabetes. The important point is that this group of patients represents a high-risk group regardless of the antipsychotic used. This risk is related, at least in part, to characteristics inherent in this population (16). Whether the medications add to this underlying risk has not, in our opinion, been established.

Serious mental illnesses, such as schizophrenia, are debilitating and difficult to treat. Clinicians need an accurate picture of the relative risks and benefits of available treatment options. Unfortunately, the incomplete presentation of the data by Lean and Pajonk will only worsen the confusion. Additional, well-designed research is needed to provide the clarity and confidence clinicians and their patients deserve.

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Olanzapine is marketed by Eli Lilly.

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Patients on Atypical Antipsychotic Drugs: Another High-Risk Group for Type 2 Diabetes

Response to Hardy and Breier

Our review in *Diabetes Care* (1) described the understanding of schizophrenia and diabetes and antipsychotic medication in relation to how it emerged from the published literature when we wrote the article. New results will change the emphasis in a balanced review, and delays between literature search, writing, and publication may exacerbate this phenomenon. We did not seek to prove causation or to quantify the links between specific atypical antipsychotics and the onset of type 2 diabetes. However, we presented evidence that patients with schizophrenia receiving antipsychotic drug therapy are at elevated risk of type 2 diabetes. Hardy and Breier (2), in their letter in this issue of *Diabetes Care*, make several points that we would like to address.

First, they question the quality of the studies that we review, stating that they "are not suited to address causation." Our review of over 50 years of literature included studies of variable quality but this richness would not satisfy modern criteria for systematic reviews. Most of that literature was not specifically designed to evaluate risks of diabetes. Epidemiologic methods can assess the comparative strength of association between a disease (in this case, diabetes) and potential factors that may influence the disease (in this case, the use of certain antipsychotics). These types of studies do not claim to demonstrate causation but are primarily for hypothesis generation to highlight an emerging issue to address in further research.

Second, Hardy and Breier state that we "did not cite studies by Koller and Hedenmalm" (3,4). The study by Koller et al. (3) was published after the cutoff date for our review article. In addition, both of these studies rely on databases (Food and Drug Administration's MedWatch and World Health Organization, respectively) of spontaneously reported adverse events. Hardy and Breier correctly indicate in the following sentence that spontaneous reports are poorly suited to establishing disease incidence. Our review article only mentions case reports and spontaneously reported events as beacons that support the more rigorous epidemiologic and clinical studies.

Third, Hardy and Breier question why we did not discuss three other studies in which risperidone use was associated with a higher risk (5–7). Buse et al. (5) and Lee et al. (6) were published after the review article was complete, and Lee et al. (6) was published in a non–peer-reviewed journal. There are two concerns with the methodologies used in Lage et al. (7) and Lee et al. (6). Because concomitant medications were not controlled for, differences in the use of other diabetogenic agents between the risperidone and olanzapine groups were unknown and could have biased the results. Comparisons to an untreated control population were not completed, so the studied populations may have had a higher or lower propensity to develop diabetes. The study by Buse et al. (5) was only based on a prescription database, without access to medical information on the underlying disease states. Antipsychotics are used for diagnoses other than schizophrenia, so there are numerous potential confounding factors that cannot be controlled in the analyses.

Fourth, Hardy and Breier state that "none of the studies. . . reported statistically significant differences in rates of new diabetes." In fact, in five more recently published studies (8–12), risperidone was significantly less likely to be associated with new-onset diabetes than olanzapine. However, four of these studies were published after the cutoff date for the review article (the study by Koro et al. [10] was included in our review).

Finally, they (reasonably) comment that the conclusions we drew from two studies (13,14) were "weakened by the fact that both studies were cross-sectional and without randomization to treatment." Instead, they refer to studies by Beasley et al. (15) and Newcomer et al. (16) using the hyperinsulinemic-euglycemic clamp method. However, these studies were performed in normal volunteers, not schizophrenics, and the duration of treatment with the antipsychotic (2–3 weeks) may have been inadequate to induce glucoregulatory changes. Although a regression analysis was done for age, this did not include weight, concomitant drugs, and family history of diabetes. It is not clear that the hyperinsulinemic-euglycemic clamp performed in the two-step manner used in these studies would be able to assess hepatic insulin insensitivity as we noted in dogs because tagged glucose was not given. In Ader's dog experiments (17), peripheral glucose uptake was also normal.

We stand by the conclusions that we drew in our review article at the time of its writing. Patients with schizophrenia and on antipsychotic drugs should be considered a high-risk group for type 2 diabetes. There are almost certainly differences in the relative hazards (including weight gain) with different antipsychotic drugs, which need to be evaluated in studies specifically designed for that purpose.

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