OBSERVATIONS

Diabetic Ketoacidosis Associated With Orlistat Treatment

Orlistat is a drug frequently prescribed as an adjuvant in weight control therapy (1–2).

Orlistat inhibits gastric and pancreatic lipases in the lumen of the gastrointestinal tract to decrease the systemic absorption of dietary fat (1,2). In clinical trials, steatorrhoea and other gastrointestinal disorders are the most frequently reported side effects (3). Other reported adverse effects include hypertension (4) and depression (5). No cases of severe hyperglycemia or diabetic ketoacidosis (DKA) have been previously reported with this drug.

We report an 18-year-old Caucasian woman with type 1 diabetes for the past 3 years who had a progressive increase in weight, reaching 89 kg, and a height of 164 cm (BMI 33 kg/m^2). She was administered several weight-reducing regimens, but to no avail. One month before her hospitalization, she began taking, on her own, orlistat (120 mg three times per day) in addition to a low-calorie diet. This was accompanied by one to three watery bowel movements per day. She was progressively lethargic, and her insulin dose requirement increased from 86 to 98 U/day, in three preprandial injections of regular insulin with one evening dose of long-acting insulin. She had no other underlying illnesses and was not on any other medication. Her home blood glucose monitoring revealed progressive worsening of her diabetes control. On the day of presentation in the emergency room, she was complaining of severe lethargy, abdominal discomfort, nausea, and two episodes of vomiting. Laboratory data showed severe hyperglycemia (blood glucose 550 mg/dl), acidosis (pH 7.0), hyperosmolar state (Na 153 mEq/l, K 3.0 mEq/l, BUN 60 mg/dl, creatinine 1.8 mg/dl), severe ketosis (ketone bodies 40 mg/dl), and positive urinary ketones. She was afebrile (37.2°C), weighed 85 kg, had an HbA_{1c} 12%, and was dehydrated (~10% of her body weight). Orlistat was stopped, and the patient was started on intravenous hydration and insulin. The patient showed significant improvement over a period of 5 days. On discharge, she was back on her baseline insulin dosage of 82 U/day, and she was hemodynamically stable.

In this patient, orlistat, probably secondary to the watery stools, seemed to have progressively caused dehydration and a decrease in intravascular volume. Initially, this lead to insulin resistance and increased insulin requirements, followed by DKA. This is the first report of DKA precipitated by orlistat in a type 1 diabetic patient. We advise caution and close monitoring of patients with type 1 diabetes who are given orlistat for obesity management.

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Association Among Hyperinsulinemia, Family History of Diabetes, and Diminutive Stature in Normoglycemic Premenopausal Women

Several cross-sectional studies have detected an association between glucose intolerance (1,2) and type 2 diabetes (3–6) with diminutiveness particularly in women. Recently, a longitudinal study confirmed these data (7) but without explanations for the relationship.

Insulin is a hormone that participates actively in protein anabolism (8) during the growth phase, and insulin resistance (of genetic [9,10] or environmental [11] etiology) could be accompanied by a decrease in skeletal development resulting in a diminution of the final height attained. Hence, we tested the hypothesis that hyperinsulinemia or family history of type 2 diabetes is related to decreased stature.

Women attending the Outpatient Clinic of the Department of Internal Medicine of the Hospital Riotinto in Huelva, Spain were interviewed for recruitment into the study. Of the 3,024 women assessed, 230 fulfilled the following selection criteria: premenopausal, aged >17 years, nonusers of oral contraceptives, normoglycemic, and with normality of endocrine, metabolic, renal, and hepatic function. For statistical assessment of biometric and biochemical variables, the subjects were grouped, a posteriori, with respect to diminutive stature (<152 cm; 10th percentile of the overall study group). In the first phase, the values of basal insulin were assessed with respect to the presence or absence of normal height attainment. In the second phase, multivariate logistic and multiple linear regression analyses were used to test for associations between height and the anthropometric and biochemical variables measured. The following eight variables were introduced into the logistic multivariate analysis: age, basal insulinemia, basal glycemia, BMI (kg/m^2) and waist circumference as continuous variables,

tobacco and alcohol use, and the family history of type 2 diabetes as dichotomous variables. The dependent variable was the presence or absence of height diminution. Multiple linear regression analyses were performed with these variables but with height entered as a continuous variable. Relative to the rest of the study group, the subjects of short stature were older ($P < 0.01$), had higher BMI ($P < 0.01$) and greater waist measurements ($P < 0.01$), and had higher baseline insulin levels ($P < 0.01$) as well as a family history of type 2 diabetes ($P < 0.01$). In a multivariate analysis, fasting insulin levels (odds ratio [OR] = 1.03; 95% CI = 1.01–1.05; $P < 0.02$) and a family history of type 2 diabetes (OR = 3.72; 95% CI = 1.40–9.96; $P < 0.01$) were the only variables associated with diminutive stature. These variables also correlated significantly with height (as a continuous variable) in the multiple linear regression analysis (regression coefficient of family history of type 2 diabetes = −3.040 [95% CI = −2.98 to −3.10], $P < 0.01$]; basal insulinemia = −0.05 [95% CI = −0.01 to −0.09], $P < 0.01$), irrespective of age, BMI, waist circumference, or basal glycemia.

Our principal findings indicated that women of diminutive stature have a higher prevalence of obesity and hyperinsulinemia and a higher percentage of family members affected with type 2 diabetes. As such, we propose that family history of type 2 diabetes and hyperinsulinemia are associated with short stature in normoglycemic premenopausal women and could explain the perceived association of decreased height and increased risk of type 2 diabetes.

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Regurgitation of Blood into Insulin Cartridges in the Pen-like Injectors

The pen-like injector for insulin is widely used by diabetic patients and improves their quality of life. However, an important disadvantage of this reusable injector is the possible contamination of biological materials (1). Macroscopic blood regurgitation into a cartridge is sometimes observed. In such a case, if the cartridges were to be used by another patient, this could result in the transmission of contagious diseases such as the hepatitis B virus. Therefore, we investigated the blood contamination in 146 cartridges used by diabetic patients by immunochromatography using anti-human hemoglobin antibody.

Hemoglobin was detected in 6 of 146 cartridges (4.1%). The quantity of the contaminated blood per cartridge was calculated to be over 0.3 μl. We carried out a simulative examination using three types of injectors. The injector punctured a rubber tube filled with dye solution. After 800 μl of insulin (2 U insulin serially 40 times for Novopen and 4 U insulin serially 20 times for Novopen III and Autopen) was injected without changing the needle under a hydrostatic pressure of 0 cm H_2O, the dye content in the cartridge was measured fluorometrically. Dye regurgitation was detected in 13 of 19 cartridges with Novopen, in 3 of 19 cartridges with Novopen III, and in only 1 of 19 cartridges with Autopen. Novopen showed the highest incidence of dye regurgitation compared with Novopen III (x^2 test; $P = 0.001$) and Autopen ($P < 0.0001$). The volume of regurgitated dye solution was 0.03–0.22 μl per cartridge. When the hydrostatic pressure in the rubber tube was elevated from 0 to 5, 10, 30, and 100 cm H_2O by lifting the reservoir of dye solution from a flat level to 100 cm in height, dye regurgitation occurred at each hydrostatic pressure and was independent of the hydrostatic pressure. Such regurgitation appears to be dependent on the devices used and possibly on the frequency of pressing.

In addition, a questionnaire was administered to 193 outpatients using insulin cartridges at four outpatient clinics when collecting the patients' used cartridges. Twenty of these patients reported noticing a reddened cartridge after insulin injection, and two patients reported sharing their insulin cartridges with other patients.

A study on viral transmission in chimpanzees reported that, if serum was positive for hepatitis B e antigen, injection of even 10^{-8} dilutions of the serum (10^{-5} μl) in chimpanzees could result in hepatitis B virus infection (2). Our findings indicate that the amount of blood or dye

regurgitated into cartridges would be sufficient to transmit hepatitis B virus infection. In fact, previous reports suggested that hepatitis B infection might be developed by dental use of pen-like injectors for local anesthesia (3,4). Of course, insulin cartridges contain anti-microbial agents (i.e., phenol or cresol) (5,6). However, these agents are effective only for killing bacteria, not viruses (7). Therefore, it is imperative that attention should be called to the careful use of cartridges as well as needles (8). Shared use of insulin cartridges must be prohibited to prevent the transmission of viral infections.

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Left Ventricular Hypertrophy and Diastolic Dysfunction in Mitochondrial Diabetes

Approximately 1% of diabetes is associated with a mitochondrial tRNA mutation at position 3,243, which was found in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Left ventricular hypertrophy (LVH) is often reported in MELAS (1).

We studied 12 type 2 diabetic patients with the mutation (DM-Mt3243). They were suspected of the mutation for maternally inherited diabetes or hearing impairment. The mutation was shown in the blood by a molecular test using *Apa*I. Echocardiography was performed in all of the DM-Mt3243 patients and compared with 184 ordinary type 2 diabetic patients. Between the two groups, age, sex, and diabetes duration were not different. Family history of diabetes in mothers was found in nine DM-Mt3243 patients (75%) and in 48 ordinary diabetic patients (26%). Hearing impairment was present in nine DM-Mt3243 patients. Blood pressures were not different. On echocardiograms, no patients with DM-Mt3243 showed wall motion abnormalities. Left ventricular internal dimensions were not different. DM-Mt3243 patients had greater left ventricular wall thickness (10.0 ± 1.5 vs. 9.0 ± 1.1 mm) and mass than ordinary diabetic patients ($P < 0.002$). LVH (>11 mm) was found in 4 DM-Mt3243 patients (33%) vs. 13 ordinary diabetic patients (7%) ($P < 0.01$). However, no individuals with DM-Mt3243 had marked LVH (>15 mm), such as hypertrophic cardiomyopathy (HCM). In pulsed Doppler of left ventricular inflow, DM-Mt3243 patients had longer deceleration time of *E* wave and greater *A*-to-*E* velocity ratios (1.24 ± 0.22 vs. 1.05 ± 0.21) than ordinary diabetic patients ($P < 0.005$).

Anan et al. (1) performed echocardiography in five MELAS patients and found LVH in two (40%). One patient had systolic dysfunction. In a follow-up study of six MELAS patients, an increase in left ventricular wall thickness was found in three patients, two of whom showed a decrease in systolic function. The 3,243 mutation would be a causative factor for LVH and may cause systolic dysfunction with progressive LVH. In marked LVH, abnormally increased mitochondria were shown. These abnormalities are considered a compensatory reaction to mitochondrial metabolic alterations.

In DM-Mt3243, six cases with HCM were reported, three of whom had systolic dysfunction (2–6). In such patients, much more abundant mutation was shown in myocardium than in blood (3). Abnormally increased mitochondria were also reported (5). LVH would be the feature of cardiac involvement in DM-Mt3243; however, there is no report to show prevalence and severity of LVH. Ueno and Shiotani (7) reported that 10 DM-Mt3243 patients had thicker left ventricular wall than 19 ordinary diabetic patients, but they did not show prevalence of LVH or the reasons why their patients had a molecular test. We showed that LVH was present in 33% of DM-Mt3243 patients, which is lower than the reported prevalence of MELAS (40%) (1). None of our DM-Mt3243 patients had marked LVH, such as HCM. Hence, LVH in DM-Mt3243 is less severe than in MELAS. Also, none of our DM-Mt3243 patients had systolic dysfunction. Because LVH in DM-Mt3243 is mild and systolic function is reported to correlate negatively with increased thickness in MELAS, systolic dysfunction would be uncommon. However, diastolic function was more severely impaired in DM-Mt3243 patients than in ordinary diabetic patients. Although diastolic dysfunction in DM-Mt3243 could be attributed to LVH, impaired mitochondrial ATP production may be contributing to diastolic dysfunction. Thus, DM-Mt3243 patients more often have LVH with diastolic dysfunction than ordinary diabetic patients. However, marked LVH, such as HCM, and systolic dysfunction are uncommon.

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Acknowledgments— The authors would like to thank Masako Ohtomo of Tokyo Saiseikai Central Hospital for her secretarial assistance.

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Alterations in Insulin-like Growth Factor Binding Protein-1 and Sex Hormone Binding Globulin Levels in Type 1 Diabetic Adolescents With Microalbuminuria

Puberty is considered a critical period for the development of microvascular complications of diabetes. Recently, we documented that more pronounced progression of albuminuria occurs during puberty than before or after puberty (1). This supports the concept that endocrine changes of puberty can lead to early initiation or acceleration of diabetic kidney damage. Therefore, we attempted to investigate the relationship between incipient nephropathy and pubertal hormones in adolescents with diabetes.

A total of 26 type 1 diabetic patients were selected for this study. Subjects were classified into two groups according to the presence of incipient nephropathy: patients with persistent microalbuminuria (5 boys and 5 girls, albumin excretion rate [AER] 20 μg/min three times within 3 months, age 14.4 ± 3.0 years, diabetes duration 6.2 ± 2.5 year, and mean HbA_{1c} 8.4 ± 8.4%) and patients with normoalbuminuria (8 boys and 8 girls, AER <20 μg/min, age 14.1 ± 3.3 years, diabetes duration 6.0 ± 2.2 years, and mean HbA_{1c} 8.2 ± 2.7%). A group of healthy subjects were recruited as control subjects (5 boys and 5 girls, age 14.2 ± 3.1 years). All subjects were in puberty (Tanner stage ≥2), and had normal blood pressure. The three groups were matched for age and pubertal stage, and the diabetic group was matched for diabetes duration and mean HbA_{1c} since the onset of diabetes. BMI and height standard deviation scores did not differ among the study groups. Fasting serum levels for IGF binding proteins (IGFBPs)-1, -2, and -3, IGF-I, human growth hormone (hGH), sex hormone binding globulin (SHBG), estradiol, and testosterone were measured by radioimmunoassay (IGFBP-1, SHBG, hGH, and estradiol and testosterone: Diagnostic Systems Laboratories, Webster, Texas; IGF-I, IGFBP-2, and IGFBP-3: Mediagnost, Tübingen, Germany). AER was measured by immunonephelometric method (Orion Diagnostica, Espoo, Finland) from a timed overnight urine collection. For comparisons among groups, one-way analysis of variance was performed. Where overall significance was attained, differences between any two groups were tested by Wilcoxon's test. Multiple regression analysis was applied to assess relationships between AER and endocrine variables. IGFBP-1 was higher in microalbuminuric patients than in normoalbuminuric patients and in control subjects (median 85.3 [95% CI 72.1–98.5], $P < 0.003$ vs. 61.4 [49.1–73.3] and 55.0 [50.6–70.7] ng/ml, respectively). Patients with microalbuminuria had a lower IGF-I level than those with normoalbuminuria and control subjects (209.2 [151.0–243.1], $P < 0.01$, vs. 368.7 [280.1–403.0] and 412.0 [310.4–501.5] ng/ml, respectively). In the microalbuminuric group, basal hGH was higher than in the normoalbuminuric and control groups (12.8 [6.7–23.6], $P < 0.001$, vs. 7.2 [4.2–11.3] and 5.6 [3.3–9.1] μU/ml, respectively). SHBG was lower in microalbuminuric patients than in normoalbuminuric patients and control subjects (26.1 [22.0–33.9], $P < 0.01$, vs. 42.2 [33.0–58.6] and 55.2 [40.1–59.9] nmol/l, respectively. IGFBP-2, IGFBP-3, estradiol, and testosterone levels did not differ in the study groups, and no difference was found in the daily dose of insulin in the diabetic groups. Multiple regression analysis showed that IGFBP-1 ($r^2 = 0.23$, $P = 0.012$), SHBG ($r^2 = 0.20$, $P = 0.021$), hGH ($r^2 = 0.13$, $P = 0.030$), and HbA_{1c} ($r^2 = 0.12$, $P = 0.041$) were independently predictive for log AER as dependent variables. Together, these variables explained 68% of the variation of the AER ($r^2 = 0.68$, $P = 0.002$).

Alterations in the growth hormone/IGF axis are well documented in adult diabetic patients with renal involvment (2), but very few data are available in pediatric patients. Recently, one study described high IGFBP-1 levels (3) and another study demonstrated low SHBG levels in relation to microalbuminuria in adolescent patients (4). This is the first observation in microalbuminuric pubertal patients to show simultaneous alterations in both binding protein systems, suggesting the role of high IGFBP-1 (resulting in decreased bioactivity of IGF-I and increased

hGH secretion via feed back mechanism) and/or low SHBG levels (reflecting enhanced tissue effect of androgens) in the initiation of diabetic renal damage in this period of life.

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Acknowledgments— This work was supported by a research grant (T-11/120/1996) from the Scientific Council of the Hungarian Ministry of Health.

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Ethics in Diabetic Clinical Trials

It is time for the diabetes community to take action regarding the conduct of clinical trials on diabetic patients in the U.S.

The Declaration of Helsinki, an international document that describes ethical principles to be used in clinical investigations, states that "In any medical study, every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method" (1). I believe that many of the placebo-controlled trials currently being performed to assess new oral diabetic therapies do not meet this ethical standard. Comparing an experimental drug with a placebo is perfectly ethical when no proven effective therapy exists and when the risk-to-benefit ratio needs to be assessed. However, when effective therapy exists, the use of placebo control subjects does not meet the ethical standard. In these situations, the efficacy and safety of the experimental medication should be tested by blindly randomizing one group to the experimental drug and the other group to an existing drug that has been shown as effective and safe.

Few would argue that using placebo for a short period of time in type 2 diabetic subjects is usually safe. Before the general utilization of HbA_{1c} in clinical trials, when almost all diabetic drugs showed maximal efficacy within a few days, clinical trials were of short duration, and the use of placebo was unlikely to be harmful to the diabetic subject. However, when differences in A_{1c}'s need to be assessed, clinical trials must be at least 3 months duration. In addition, if the therapy being used before the study is long-lasting, a washout period must also be included, which will further prolong the period of exposure to hyperglycemia. Furthermore, when drugs such as the thiazolidinediones, which may not be fully effective for as long as 3 months, are used to assess differences in diabetes control, clinical trials need to be at least 6 months duration.

As investigators, how long can we ethically permit hyperglycemia to continue in diabetic subjects randomized to placebo therapy? Indeed, 6 months of hyperglycemia will have an adverse effect on the quality of life, and could possibly be long enough for microvascular complications that would not have occurred with better glycemic control to occur. Undoubtedly, prolonged hyperglycemia has the potential to exacerbate macrovascular disease with increased platelet aggregation, postprandial hyperlipidemia, lower plasminogen activator inhibitor activity, higher fibrinogen levels, increased clotting factors, glycosylation of LDL particles, and more.

Another breach of ethical standard occurs in the conduct of studies designed to examine the efficacy of therapies for symptomatic diabetic distal symmetrical polyneuropathy. In most studies, a washout period of 3 weeks or more is required. Consequently, many patients cannot tolerate the symptoms and drop out. Thus, the studies are conducted on patients with mildly symptomatic neuropathy, and a positive study only proves that the drug is effective in mild diabetic neuropathy. Further pain and suffering for patients who survive the washout period can be inflicted by placing them on a placebo. In these studies, the efficacy of the experimental drug would more humanely and efficiently be tested by adding either the drug or the placebo to the patient's existing therapy, which would be consistent throughout the study.

Therefore, as advocates for our patients and as investigators who are responsible for the welfare of diabetic subjects in clinical trials, we should encourage the Federal Drug Administration and the pharmaceutical industry to avoid (whenever possible) the use of placebo-controlled trials when a proven effective and safe alternative therapy is available.

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Ed. note: *We believe that Dr. Bell has raised an important issue, and we have requested responses from representatives of the industry, the Federal Drug Administration (FDA), the FDA Advisory Committee members, and an ethicist. These responses will be published in a later issue.*

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Erythromycin Administration Before Sleep is Effective in Decreasing Fasting Hyperglycemia in Type 2 Diabetic Patients

Previously, we reported that orally administered erythromycin, an agonist of the gastrointestinal hormone motilin (1,2), decreased fasting blood glucose and HbA_{1c} levels and increased the early phase of insulin secretion in type 2 diabetic patients; this was determined by intravenous glucose tolerance test. Intravenous infusion of erythromycin also elevated insulin secretion and lowered blood glucose during infusion in type 2 diabetic patients and in normal control subjects. The enhancement of glucose-stimulated early insulin secretion, which is important in maintaining postprandial glucose levels within limits, could lead to the improvement of glycemic control (3). The gastrointestinal motor effect of motilin seems to take action through cholinergic mechanisms during the interdigestive state, and the insulin secretagogue action of motilin and erythromycin is thought to be mediated by vagal-cholinergic muscarinic pathways (4,5). This time we investigated whether erythromycin could stimulate basal insulin release and improve glycemic control when administered at 400 mg before sleep in 30 type 2 diabetic patients. After 1 month of treatment using this method, we found that there was a significant increase in fasting insulin level (34.0 ± 5.8 vs. 42.0 ± 5.8 pmol/l, $P < 0.01$), although this significant change in insulin had not been observed with the administration of 200 mg three times per day in the previous study (3). We also found a more significantly marked decrease in fasting blood glucose when using this method (11.0 ± 0.6 vs. 8.2 ± 0.5 mmol/l, $P < 0.0001$) rather than when administering erythromycin 200 mg three times per day (11.2 ± 0.8 vs. 9.7 ± 0.5 mmol/l, $P < 0.05$).

The improved value of fasting blood glucose was almost twice as much as the value in the previous study (3). HbA_{1c} levels were also significantly improved compared with the control subjects (erythromycin 8.3 ± 0.2 vs. 7.8 ± 0.2%, $P < 0.0001$, and control subjects 8.4 ± 0.3 vs. 8.3 ± 0.2%). Interestingly, in most of the patients (25 of 30 patients, 83.3%), there was an improvement in bowel movements and/or constipation by taking erythromycin before sleep. There were two patients who had hypoglycemic attacks early in the morning, but no other side effects, such as liver dysfunction, were observed. It was reported that erythromycin improved impaired gastric emptying with severe diabetic gastroparesis (6). When administered before sleep, erythromycin may enhance cholinergic tone in the interdigestive state and increase the frequency of bowel movements while influencing insulin secretion.

Surprisingly, the administration of erythromycin before sleep initiated reduced fasting blood glucose, perhaps because of the stimulation of the basal insulin level and the improvement of bowel movements. Taking erythromycin four times per day, including before sleep, would be a more effective way to improve glycemic control and constipation that may be caused by diabetic autonomic neuropathy.

With this additional data, we should consider erythromycin derivatives that lack antibacterial activity not only as gastroprokinetic agents, but also as antidiabetogenic agents.

Table 1—*Clinical characteristics and effects of erythromycin (400 mg before sleep) or a placebo on glycemic control in type 2 diabetic patients*

	Erythromycin		Placebo	
	Before	1 month after	Before	1 month after
Age (years)	55.5 ± 2.4		54.0 ± 2.8	
Sex (M/F)	12/18		10/12	
Duration of diabetes (years)	8.0 ± 1.0		7.0 ± 1.0	
Oral hypoglycemic agents (yes/no)	30/0		2/10	
BMI (kg/m^2)	24.5 ± 1.2	24.2 ± 1.0	24.7 ± 1.2	24.5 ± 1.4
HbA_{1c} (%) (range 4.3–5.8)	8.3 ± 0.2	7.8 ± 0.2*	8.4 ± 0.3	8.3 ± 0.2
Fasting blood glucose (mmol/l)	11.0 ± 0.6	8.2 ± 0.5*	10.7 ± 0.4	11.0 ± 0.5
Fasting serum insulin (pmol/l)	34.0 ± 5.8	42.0 ± 5.8†	32.4 ± 5.5	31.9 ± 4.6

Data are means ± SD or *n*. *$P < 0.0001$ vs. pretreatment values; †$P < 0.01$.

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Acknowledgments— This work was supported in part by Grants-in-Aid for Scientific Research (A) 08559012 and Grant (C) 09671057 from the Ministry of Education, Science, Sports and Culture of Japan (to A.I.).

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Lifestyle, Obesity, and Insulin Resistance

The prevention of diabetes is an urgent worldwide public health concern. The period preceding onset of type 2 diabetes is typically characterized by obesity and insulin resistance induced by overeating and physical inactivity. In the 1970s, Belloc and Breslow (1) presented evidence that physical health is associated with the following seven favorable habits: sleeping 7–8 h, eating breakfast almost every day, avoiding eating between meals, maintaining a desirable weight with respect to height, participating in active sports, limiting alcohol intake, and avoiding smoking cigarettes. We studied the relationships between unhealthy habits and the presence of obesity and insulin resistance.

Subjects consulting the health care center at the First Red Cross Hospital of Kyoto from 1998 to 1999 were recruited. The protocol was approved by the ethics committees of our hospitals. A physical examination, routine biochemical screening tests, and a 75-g oral glucose tolerance test including plasma insulin measurements were performed. We studied 453 subjects (321 men and 131 women, aged 53 ± 10 years). Subjects were free from diabetes and had a BMI of 23.4 ± 3.0. Data were gathered from a self-administered questionnaire completed by all subjects. Habitual patterns were deduced from answers on the questionnaire concerning eating (time spent eating a meal and regularity of meals, including breakfast) and sleep (bedtime and duration of sleep). Obesity was defined as BMI ≥25 kg/m^2. Insulin resistance was determined using the *R* value of the homeostasis model assessment (HOMA) of Matthews et al. (2) and was defined as an HOMA-IR ≥2.0. Logistic regression was used to evaluate associations between lifestyle data and obesity or insulin resistance.

Subjects who ate quickly had 1.8 times the risk for obesity and 1.5 times the risk for insulin resistance compared with subjects who ate more slowly (Table 1). Irregularities in the amount of meals eaten daily (e.g., eating more or fewer than three meals a day or eating between meals) was also associated with increased risk for both obesity and insulin resistance. Skipping breakfast was relatively common among men and carried an increased risk of obesity. As for sleep, sleeplessness beyond midnight and sleeping <6 h were both significant risk factors for obesity, whereas only insufficient amounts of sleep was a significant risk factor for insulin resistance.

Breslow's seven favorable habits appeared to show promise for the prevention of type 2 diabetes as well as for the promotion of overall physical health. In our study, erratic eating, skipping breakfast, eating between meals, and insufficient sleep (<6 h) were associated with obesity and insulin resistance. Whereas caloric restriction and physical exercise have obvious importance, we stress that actively promoting healthy habits concerning eating and sleeping should be considered for the prevention of obesity and insulin resistance. Individual lifestyle patterns should be analyzed to identify situations in which altering personal habits can counteract obesity, prevent type 2 diabetes, and promote overall good health.

Table 1—*Association between lifestyle and obesity or insulin resistance*

	Obese versus nonobese		HOMA-IR ≥2.0 versus HOMA-IR <2.0	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Eating rapidly (*n* = 209) versus normally (*n* = 244)	1.78 (1.17–2.70)	0.007	1.53 (1.05–2.23)	0.027
Eating meals irregularly (*n* = 152) versus regularly (*n* = 301)	2.18 (1.42–3.34)	0.0004	1.60 (1.08–2.38)	0.020
Skipping breakfast (*n* = 67) versus eating breakfast (*n* = 376)	2.19 (1.27–3.75)	0.005	1.75 (1.04–2.96)	0.037
Bedtime after midnight (*n* = 205) versus before midnight (*n* = 245)	1.64 (1.08–2.50)	0.021	1.31 (0.90–1.90)	0.164
Sleeping <6 h (*n* = 42) versus ≥6 h (*n* = 395)	1.98 (1.03–3.82)	0.041	2.17 (1.10–4.26)	0.025

Insulin resistance was defined as a value ≥2.0 for HOMA-IR, the *R* value for the homeostasis model of Matthews (2), which was calcuated as fasting blood glucose concentration (mmol/l) × fasting plasma insulin concentration (mU/l)/22.5.

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Use of Antidiabetic Plants in Morocco and Québec

In the western world, we are witnessing a vastly growing and renewed interest in complementary and alternative medicines. In particular, the herbal medicine market has exploded, evolving from an esoterical and marginal phenomenon (herbal shops and health food stores) to a

mass consumer market (pharmacies and department stores). With this increasing interest in phytomedicines, more individuals will explore the possibility of using herbal medicines to complement conventional antidiabetic therapy, as is already the case in certain minority cultures (1,2). Therefore, we carried out an ethnopharmacological survey of the antidiabetic plants most frequently recommended by herbalists, naturopaths, and other traditional practitioners. We compared results obtained in Morocco, where phytotherapy is commonly used in traditional medicine, and in Québec, where the use of medicinal plants is still marginal but follows the North American explosive trend. To obtain the most precise information on the frequency of use of antidiabetic medicinal plants, we asked individuals to list, in decreasing order of importance, the four to five plants most often recommended or sold for the treatment of diabetes. We found profound differences between Québec and Morocco.

Indeed, only *Trigonella foenum graecum* (fenugreek) was among the top ten most recommended antidiabetic plants in both surveys, appearing first in Morocco and second in Québec. Fenugreek is well known for its traditional use as an antidiabetic plant (3–5). It contains several hypoglycemic and hypolipidemic constituents and has been the object of clinical trials confirming its beneficial action in diabetes (3,4).

In Québec, *Vaccinium spp.* (blueberry) received first place. The European bilberry *Vaccinium myrtillus* improves the microvascular and lipid perturbations associated with diabetes (3,6). However, its cousin, *Vaccinium angustifolia*, the Canadian blueberry, has not received such scientific attention and may be an interesting candidate antidiabetic plant to study. Several of the other top ten most common antidiabetic plants in Québec are already known for their hypoglycemic activity, including *Taraxacum officinale* (dandelion), *Gymnema sylvester* (gymnema), *Glycyrrhiza glabra* (licorice), *Syzygium cumini* (jambul), *Opuntia streptacantha* (prickly pear), and *Panax ginseng/P. quinquefolium* (ginseng) (3–5).

In contrast, the most commonly recommended antidiabetic plants of the Morocco survey are less often the objects of published scientific study, despite their long history of traditional medicinal use. Aside from fenugreek and *Lupinus albus* (white lupin), which are known antidiabetic plants, *Globularia alypum* (globularia) (7) and *Nigella sativa* (nigella) (8) have recently been shown to exert interesting hypoglycemic effects in animal models of diabetes. Other commonly used plants were *Artemisia herba alba* (artemisia), *Origanum compactum* (oregano), and *Vitis vinifera* (red vine).

In conclusion, our ethnopharmacological survey has revealed several interesting candidate antidiabetic plants, particularly the Canadian blueberry and certain plants of Mediterranean origin commonly used in Morocco, such as globularia and nigella. However, it remains important to determine the safety and efficacy of these claimed antidiabetic plants and to understand their mode(s) of action. In that context, it is crucial for government and other granting agencies to support collaborative research efforts aimed at establishing the clinical efficacy of candidate antidiabetic plants and elucidating their mode(s) of action.

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Acknowledgments— The authors gratefully acknowledge the financial support of the Fonds International de Coopération Universitaire–FICU (Agence Universitaire de la Francophinie).

This study was part of a larger scale comparative survey on the use of medicinal plants in Morocco and Quèbec. The results of this study are detailed in a paper recently presented to the *Journal of Ethnopharmacology*.

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Erratum

Clark C: What we can learn from Argentina (Editorial). *Diabetes Care* 23:1721–1722, 2000

The first sentence of the last paragraph in the first column should state: "The protocol for such a program was developed by Dr. Juan José Gagliardino, Dra. Marta Sereday, Dr. Manuel Martí, and Dr. Isaac Sinay—then president of SAD—and me, as adviser." The author regrets the omission of Drs. Sereday and Martí in the original publication.