

OBSERVATIONS

Association Between Smoking, Hematological Parameters, and Metabolic Syndrome in Japanese Men

Cigarette smoking increases the risk for metabolic syndrome (1), and it may also affect hematological parameters (2). Because certain hematological parameters may be associated with metabolic syndrome (3), we have investigated whether the mode of association between smoking and metabolic syndrome varies according to hematological parameters.

Among individuals who had undergone a general health screening test between 1994 and 2003, 27,972 subjects (9,729 never smokers [52.8 ± 10.7 years], 7,242 former smokers [54.8 ± 9.9 years], and 11,001 current smokers [50.4 ± 9.8 years]) answered in full a questionnaire concerning their smoking habits and were enrolled in the current study. Metabolic syndrome was defined as the presence of three or more of the following: 1) fasting glucose ≥ 110 mg/dl, 2) blood pressure $\geq 130/85$ mmHg, 3) triglycerides ≥ 150 mg/dl, 4) HDL cholesterol < 40 mg/dl, and 5) BMI ≥ 25 kg/m². The interquartile cutoff points were 4,700, 5,500, and 6,600 cells/ μ l for white blood cell (WBC) count and 14.4, 15.1, and 15.7 g/dl for hemoglobin level.

Compared with the never smokers, the WBC count and hemoglobin level were significantly higher in the current smokers ($5,200 \pm 1,200$ vs. $6,400 \pm 1,800$ cells/ μ l, $P < 0.0001$, and 14.8 ± 1.0 vs. 15.2 ± 1.0 mg/dl, $P < 0.0001$, respectively). After adjusting for age and total cholesterol level, logistic regression analysis showed that current smokers had a higher incidence of metabolic syndrome with an odds ratio (OR) of 1.59 (95% CI 1.47–1.73) compared with never smokers. Compared with the lowest quartile (Q), the incidence of metabolic syndrome was significantly more frequent in the

higher quartiles of the WBC count (Q2, OR 1.73 [95% CI 1.54–1.95]; Q3, 2.50 [2.23–2.80]; and Q4, 3.80 [3.41–4.24]) and in those of the hemoglobin level (Q2, 1.65 [1.47–1.86]; Q3, 2.41 [2.15–2.70]; and Q4, 4.05 [3.63–4.53]).

The association between current smoking and metabolic syndrome was found to be statistically significant in lower quartiles of the WBC count (Q1, OR 1.40 [95% CI 1.10–1.79] and Q2, 1.36 [1.13–1.64]) but not in the higher ones (Q3, 1.02 [0.87–1.18] and Q4, 1.04 [1.89–1.21]). By contrast, the association between current smoking and metabolic syndrome was statistically significant regardless of the hemoglobin level (Q1, 1.50 [1.19–1.88]; Q2, 1.53 [1.27–1.84]; Q3, 1.43 [1.21–1.67]; and Q4 1.25 [1.09–1.43]). These results suggest that the association between smoking and metabolic syndrome may be heavily confounded by certain factors that increase the circulating WBC count.

NOBUKAZU ISHIZAKA, MD, PHD¹

YUKO ISHIZAKA, MD, PHD²

EI-ICHI TODA, RMS²

RYOZO NAGAI, MD, PHD¹

MINORU YAMAKADO, MD, PHD²

From the ¹Department of Cardiovascular Medicine, University of Tokyo Graduate School of Medicine, Tokyo, Japan; and the ²Center for Multiphasic Health Testing and Services, Mitsui Memorial Hospital, Tokyo, Japan.

Address correspondence to Dr. Nobukazu Ishizaka, Department of Cardiovascular Medicine, University of Tokyo, Hongo 7-3-1 Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: nobuishizaka-tyk@umin.ac.jp.

© 2006 by the American Diabetes Association.

References

1. Geslain-Biquez C, Vol S, Tichet J, Caradec A, D'Hour A, Balkau B: The metabolic syndrome in smokers: the D.E.S.I.R. study. *Diabetes Metab* 29:226–234, 2003
2. Whitehead TP, Robinson D, Allaway SL, Hale AC: The effects of cigarette smoking and alcohol consumption on blood haemoglobin, erythrocytes and leucocytes: a dose related study on male subjects. *Clin Lab Haematol* 17:131–138, 1995
3. Mardi T, Toker S, Melamed S, Shirom A, Zeltser D, Shapira I, Berliner S, Rogowski O: Increased erythropoiesis and subclinical inflammation as part of the metabolic syndrome. *Diabetes Res Clin Pract* 69: 249–255, 2005

Changing Incidence of Major Amputation for Diabetes in Novi Sad, Serbia and Montenegro, Between 1994 and 2004

The reduction in incidence of major amputation for diabetes is an accepted target of health care, but the extent to which this is being achieved is unclear (1). Assessment of the published literature is made especially difficult by the effect of population selection and by a rapid increase in the prevalence of known diabetes in most countries. For the most meaningful results, it follows that data should be derived from unselected and circumscribed populations and should be expressed in terms of the number in the community with diabetes (2).

Novi Sad is the capital of the northern province of Vojvodina in Serbia and Montenegro. All patients with known diabetes in Novi Sad and the surrounding region are managed at one of three specialist centers situated at the Regional Health Centre and the Institute of Health Care. All non-traumatic amputations are undertaken within the Department of Vascular Surgery at the Regional Health Centre. The structure of these services enables total ascertainment of all major (transtibial and transfemoral) amputations, as well as precise definition of the numbers who have diabetes. Comprehensive record keeping was initiated in 1991 and was maintained until 1995, when it was interrupted by a period of major political and social upheaval. The city was heavily bombed in 1999, and it was only possible to return to routine data collection from 2004 onwards. Despite the events of the late 1990s, the total population and its constituent racial groups have been relatively constant.

In 1994 and 2004 the total populations of the region were 295,022 and 299,294, respectively, and the numbers with diabetes were 8,026 (2.7%) and 16,128 (5.4%), respectively. The number of first major amputations in 1994 and 2004 were 27 and 43, respectively. When expressed per 10⁵ total population, the incidence of first major amputation for diabetes increases from 9.16 to 14.4, but when expressed in terms of the at-risk (di-

abetic) population, the incidence decreases from 3.38 to 2.68 ($P = 0.013, \chi^2$). When data are expressed in terms of the total population, the benefit of changes in management may be obscured by the increasing prevalence of the disease.

Although the decrease in amputation incidence was only 20%, the actual incidence in 2004 was well within the range reported by other European centers. Since the magnitude of any such decrease is dependent on the baseline value, we suggest that rather than aim for a percentage reduction in incidence, future health care targets should specify an absolute value. Evidence from the published literature suggests that this should be of the order of 2 to 3 per 10^3 of those with diabetes or even lower.

DRAGAN S. TESIC, MD¹
 PAVLE PANTELINAC, MD¹
 SVETOLIK AVRAMOV, MD²
 VLADIMIR VUKOBRATOV, MD²
 JANKO PASTERNAK, MD²
 WILLIAM JEFFCOATE, MRCP³

From the ¹Clinic of Endocrinology, Diabetes and Metabolic Diseases, Institut for Internal Diseases, Clinical Centre, Novi Sad, Serbia and Montenegro; the ²Clinic of Vascular and Transplantation Surgery, Institut for Surgery, Clinical Centre, Novi Sad, Serbia and Montenegro; and the ³Department of Diabetes and Endocrinology, Foot Ulcer Trials Unit, City Hospital, Nottingham, U.K.

Address correspondence to Professor Dragan S. Tesic, Medical Faculty, Clinical Centre, Clinic of Endocrinology, Diabetes and Metabolic Diseases, Hajduk Veljkova 1-3, 21000 Novi Sad, Serbia and Montenegro. E-mail: drtesic@eunet.yu.

© 2006 by the American Diabetes Association.

References

1. Jeffcoate WJ, Van Houtum WH: Amputation as a marker of the quality of foot care in diabetes. *Diabetologia* 47:2051-2058, 2004

2. Van Houtum WH, Rauwerda JA, Ruwaard D, Schaper NC, Bakker K: Reduction in diabetes-related lower-extremity amputations in the Netherlands: 1991-2000. *Diabetes Care* 27:1042-1046, 2004

Decreased Insulin Secretion but Not Insulin Sensitivity in Normal Glucose Tolerant Thai Subjects

Reduced insulin secretion and insulin sensitivity has been demonstrated in normal glucose tolerant (NGT) subjects whose 2-h plasma glucose levels after an oral glucose tolerance test were 5.6-7.7 mmol/l compared with those with 2-h plasma glucose levels <5.6 mmol/l (1-3). These data are from high-risk ethnic subjects. Whether these data are true in Asians is uncertain.

We studied insulin secretion and insulin sensitivity in 51 NGT and 15 impaired glucose tolerant Thai subjects. Subjects were grouped according to 2-h plasma glucose levels after an oral glucose tolerance test into four groups (Table 1). Insulin sensitivity was determined by euglycemic-hyperinsulinemic clamp and expressed as glucose infusion rate. Insulin secretion was determined by homeostasis model assessment (HOMA) of steady-state β -cell function (%B) from a HOMA2 model (available at <http://www.dtu.ox.ac.uk/homa>) and adjusted with glucose infusion rate (HOMA%B_{adjusted}) to obtain the accurate result of insulin secretion. For statistical analysis, ANOVA was used for group comparison, and between-

group differences were compared using Bonferroni post hoc analysis.

As shown in Table 1, age, BMI, and waist circumference were significantly different between groups. Glucose infusion rate was also different between groups, but the difference disappeared after adjustment with age, BMI, and waist circumference. HOMA%B_{adjusted} of gr.IV was significantly lower than those of gr.I ($P = 0.003$) and gr.II ($P = 0.039$) but was not different from that of gr.III. The difference of HOMA%B_{adjusted} between groups could still be demonstrated after adjustment with age ($P = 0.005$).

This study demonstrated that insulin secretion adjusted for insulin sensitivity in NGT subjects started to decline progressively from 2-h plasma glucose >5.6 mmol/l. This study agrees with others (1-3). This is the first study in Asians where the declined β -cell function adjusted for insulin sensitivity is demonstrated in NGT subjects. These findings are in accordance with those from studies of other ethnic populations, including Mexican Americans, African Americans, Hispanics, and Caucasians, indicating that the results are not ethnic specific. It can be hypothesized that these high-normal oral glucose tolerance test subjects may have an increased risk of developing diabetes; therefore, lifestyle modification should be implemented early in this group as in impaired glucose tolerant subjects.

CHATCHALIT RATTARASARN, MD¹
 SUPAMAI SOONTHORNPAN, MD²
 RATTANA LEELAWATTANA, MD²
 WORAWONG SETASUBAN, MD²

From the ¹Department of Medicine, Division of Endocrinology and Metabolism, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; and the ²Department of Medicine, Division of Endocrinol-

Table 1—Clinical characteristics of subjects

	2-h plasma glucose (mmol/l) after OGTT				P
	NGT (n = 51)			IGT (n = 15)	
	gr.I (<5.6)	gr.II (5.6-6.7)	gr.III (6.7-7.8)	gr.IV (7.8-11.1)	
Sex (female/male)	5/10	12/11	8/5	6/9	NS
Age (years)	32.2 ± 1.2	34.1 ± 1.8	36.2 ± 2.9	45.1 ± 1.4*†‡	<0.0001
BMI (kg/m ²)	21.7 ± 0.9	23.1 ± 0.9	25.6 ± 1.0*	27.2 ± 0.8*†	<0.0001
Waist circumference (cm)	74.9 ± 2.7	75.6 ± 2.4	81.4 ± 2.6	91.8 ± 2.8*†	<0.0001
Glucose infusion rate (mg · kg _{FFM} ⁻¹ · min ⁻¹)	9.31 ± 0.82	9.43 ± 0.71	7.49 ± 0.51	6.04 ± 0.67*†	0.004
HOMA%B	127.9 ± 6.9	116.0 ± 8.6	129.0 ± 13.7	124.0 ± 12.2	NS
HOMA%B _{adjusted}	1150.9 ± 89.2	1012.2 ± 67.8	951.1 ± 111.1	690.9 ± 73.4*†	0.005

Data are means ± SE. HOMA%B_{adjusted} = HOMA%B × glucose infusion rate. * $P < 0.05$ compared with gr.I; † $P < 0.05$ compared with gr.II; ‡ $P < 0.05$ compared with gr.III. IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

ogy and Metabolism, Prince of Songkla University, HadYai, Songkhla, Thailand.

Address correspondence to Chatchalit Ratarasarn, MD, Division of Endocrinology and Metabolism, Department of Medicine, Ramathibodi Hospital, Rama VI Road, Bangkok 10400, Thailand. E-mail: racrt@mucc.mahidol.ac.th.

© 2006 by the American Diabetes Association.

References

1. Piche ME, Lemieux S, Perusse L, Weisnagel SJ: High normal 2-hour plasma glucose is associated with insulin sensitivity and secretion that may predispose to type 2 diabetes. *Diabetologia* 48:732-740, 2005
2. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo A: Beta-cell dysfunction and glucose intolerance: results from San Antonio Metabolism (SAM) Study. *Diabetologia* 47:31-39, 2004
3. Yeckel CW, Taksali SE, Dziura J, Weiss R, Burgert TS, Sherwin RS, Tamborlane WV, Caprio S: The normal glucose tolerance continuum in obese youth: evidence for impairment in β -cell function independent of insulin resistance. *J Clin Endocrinol Metab* 90:747-754, 2005

Could Blood Ketone Monitoring Be A Tool for Managing Gestational Diabetes Mellitus?

Nutritional management of gestational diabetes mellitus (GDM) is based on guidelines from diabetology societies (1). Ketonuria is often monitored, but clear management guidelines have not been established. Home-based methods of measuring ketonemia are available. We believe that it is important to evaluate the utility of this tool in GDM.

We measured ketonemia in a control population of pregnant women and a GDM population. Pregnant women were systematically screened for GDM between the 24th and 28th weeks (75-g oral glucose tolerance test [OGTT], World Health Organization guidelines). A total of 56 women (29.98 \pm 4.86 years of age, prepregnancy BMI 23.14 \pm 4.62 kg/m², weight gain 14.49 \pm 4.93 kg) with a normal OGTT and 49 women (31.35 \pm 5.39 years, prepregnancy BMI 25.96 \pm 5.91 kg/m², weight gain 9.25 \pm 5.52 kg) with GDM were included.

Each subject was monitored in accordance with the appropriate guidelines; in addition, the control subjects performed

glycemia and ketonemia self-monitoring three times a day (upon waking and before the midday and evening meals). GDM women were also asked to measure their postprandial glycemia. All subjects measured their fasting ketonuria.

Glycemia measurement was performed using test strips and a meter (Abbott), and capillary blood ketonemia measurement was performed using Optium β -Ketone test strips and the same meter (2). The replicate analysis resulted in CVs of 3.3%. The study protocol was approved by an ethics committee.

The two groups did not differ in terms of age, but BMI and weight gain were higher in the GDM than in the control group ($P < 0.01$). The mean ketonemia was lower in the control than in the GDM group (0.01 \pm 0.10 vs. 0.04 \pm 0.009 mmol/l, $P < 0.001$). Fasting ketonemia did not differ between the control and GDM groups (0.01 \pm 0.11 vs. 0.01 \pm 0.06 mmol/l, respectively). Ketonemia values measured before the midday and the evening meal were lower for control than for GDM patients (midday 0.01 \pm 0.08 vs. 0.05 \pm 0.11 mmol/l, $P = 0.002$; evening 0.02 \pm 0.09 vs. 0.05 \pm 0.10 mmol/l, $P = 0.005$).

A ketonemic episode was defined as the unbroken period during which each day is a part of a sliding 7-day interval containing $>25\%$ of height value. Of the control subjects, 6 (12%) experienced at least one ketonemic episode (average length 10.5 days) versus 23 (47%) in the GDM group (average length 13.8 days) (a total of 37 episodes).

For women with GDM, we are not currently in a position to conclude whether their ketonemia levels have clinical significance in terms of the pregnancy outcome or the health of the child. Ketonemia values differ from those recorded in control subjects, and this difference is not irrelevant. A study needs to be performed to be certain that higher ketonemia has a detrimental prognostic significance for fetal development.

Reports from the literature have focused exclusively on ketonuria. A negative correlation between ketonuria and intellectual quotient in children born to diabetic mothers has been reported (3,4). A relationship between high fasting ketonemia during the last trimester and delayed educational development has been suggested (5).

HENRI GIN, MD, PHD¹
ANNE VAMBERGUE, MD²

CLAUDINE VASSEUR, MD³
VINCENT RIGALLEAU, MD, PHD¹
PHILIPPE DUFOUR, MD²
AGNES ROQUES, MD³
PIERRE FONTAINE, MD, PHD²
THE GROUPE DIABÉTE ET GROSSESSE-ALFEDIAM

From the ¹University Medical Center, Bordeaux, France; the ²University Medical Center, Lille, France; and the ³University Medical Center, Angers, France.

Address correspondence to Prof. Henri Gin, Hôpital du Haut Lévêque, F-33604 Pessac, France. E-mail: henri.gin@chu-bordeaux.fr.

© 2006 by the American Diabetes Association.

References

1. American Diabetes Association: Gestational diabetes mellitus (Position Statement). *Diabetes Care* 26 (Suppl. 1):S103-S105, 2003
2. Byrne HA, Tiezen KL, Hollis S, Dornan TL, New JP: Evaluation of an electrochemical sensor for measuring blood ketones. *Diabetes Care* 23:500-503, 2000
3. Churchill JA, Berendes HW, Nemore J: Neuropsychological deficits in children of diabetic mother. *Am J Obst Gynecol* 105:257-268, 1969
4. Stehbins JA, Baker GL, Kitchel M: Outcome at ages 1, 3, and 5 years of children born to diabetic women. *Am J Obstet Gynecol* 127:408-413, 1977
5. Jovanovic L, Metzger BE, Knopp R, Conley MR, Park E, Lee YJ, Simpson JL, Holmes L, Aarons JH, Mills JL, the Diabetes in Early Pregnancy Study Group: The Diabetes in Early Pregnancy study: β -hydroxybutyrate levels in type 1 diabetic pregnancy compared with normal pregnancy. *Diabetes Care* 21:1978-1984, 1998

Blood Pressure Measurement in Diabetes Clinic

Are we paying enough attention?

The American Diabetes Association statement (1), "Care of Children and Adolescents With Type 1 Diabetes," outlines recommendations for management of hypertension in children with type 1 diabetes. Hypertension in children can be missed if appropriate norms are not used, and, as the authors state, "clinicians who care for children with diabetes often pay little or no attention to blood pressure." Here, we report results of a retrospective chart review of serial clinic

Downloaded from http://diabetesjournal.org/care/article-pdf/29/3/745/593586/2006000745.pdf by guest on 05 August 2024

blood pressure measurements among 217 youth with type 1 diabetes for ≥ 5 years. Hypertension was defined as systolic and/or diastolic blood pressure >95 th percentile for age, sex, and height at three consecutive clinic visits (2). Blood pressure was taken at each outpatient visit using an automated blood pressure device by trained medical assistants.

Sixty (28%) of 217 patients met the study diagnosis of hypertension (mean age 12.7 ± 3.2 years) after 5.7 ± 3.8 years of diabetes. These patients had higher systolic blood pressure z-scores (1.13 vs. 0.49, $P = 0.002$) and higher BMI z-scores (0.68 vs. 0.30, $P = 0.01$) at the time of diabetes diagnosis than did patients without hypertension. Only 21 of 60 (35%) had the diagnosis documented in the medical chart, and only 5 of 60 patients (8.3%) had therapy initiated specifically for treatment of hypertension. Spot-urinary albumin-to-creatinine ratios were categorized as normal ($<20 \mu\text{g}/\text{mg}$), high normal (≥ 20 but $<30 \mu\text{g}/\text{mg}$ on two of three measurements), and microalbuminuria ($\geq 30 \mu\text{g}/\text{mg}$ on two of three measurements). Seventeen (9%) of those with available data ($n = 190$) had microalbuminuria. This complication was more frequently addressed than hypertension, with 14 of 17 (82%) subjects being treated with ACE inhibitors. Patients who met study criteria for hypertension tended to have higher albumin-to-creatinine ratios. Of those patients with available data, 2 of 57 (4%) with elevated blood pressures had high-normal ratios and 8 of 57 (14%) developed microalbuminuria, while 0 of 133 with normal blood pressure had high-normal ratios and 9 of 133 (7%) developed microalbuminuria (P for trend <0.05).

Our analysis is retrospective and relies upon casual blood pressures, which may overestimate the true rate of hypertension. Nonetheless, our data indicate that adolescents with type 1 diabetes may develop blood pressure in the hypertensive range, and as suggested by the recent American Diabetes Association statement, this blood pressure may not be routinely recognized. This represents missed opportunities to confirm hypertension with repeat auscultatory measurement and/or 24-h ambulatory blood pressure monitoring and to intervene with lifestyle modification/pharmacologic therapy, all with the hope of preventing future micro- and macrovascular complications. Routine blood pressure assessment using appropriate age-, sex-, and height-

dependent norms is an essential component of every visit to the diabetes clinic.

JAMIE R. WOOD, MD¹
MARY ANN O'RIORDAN, MS¹
BETH A. VOGT, MD¹
MARK R. PALMERT, MD, PHD^{1,2}

From the ¹Department of Pediatrics, Case School of Medicine, Rainbow Babies and Children's Hospital, Cleveland, Ohio; and the ²Department of Genetics, Case School of Medicine, Rainbow Babies and Children's Hospital, Cleveland, Ohio.

Address correspondence to Jamie R. Wood, MD, Pediatric and Adolescent Unit, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215. E-mail: jamie.wood@joslin.harvard.edu.

© 2006 by the American Diabetes Association.

References

1. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, Deen L, Grey M, Anderson B, Holzmeister LA, Clark N: Care of children and adolescents with type 1 diabetes (ADA Statement). *Diabetes Care* 28:186–212, 2005
2. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents: Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. *Pediatrics* 98:649–658, 1996

COMMENTS AND RESPONSES

Recommendations for Management of Diabetes During Ramadan

Response to Al-Arouj et al.

Al-Arouj et al. (1) have made recommendations for fasting during the holy month of Ramadan for Muslim diabetic patients. The recommendations were drafted by an expert panel of diabetologists from around the globe, and it represents a landmark for practicing clinicians who look after diabetic Muslims. The recommendations were based on expert opinion rather than evidence-based scientific research, which, as the panel pointed out, is lacking in this area. These

provisional recommendations await well-designed research aimed specifically at seeing whether fasting is beneficial or harmful to patients with type 1 diabetes.

Type 1 diabetic patients are often advised not to fast by physicians. The nature of type 1 diabetes makes fasting hazardous. Thus, type 1 diabetic patients are put in the category of very high risk in the recommendations. Evidence-based scientific data will definitely help physicians caring for such patients to decide whether to advise patients with type 1 diabetes strongly or half-heartedly about fasting.

Patient education regarding fasting during the holy month of Ramadan is badly needed. Research in this area is also deficient. In a recent study, only 33% of our diabetic patients received general advice on fasting during Ramadan (2). Morbidity related to fasting has been reported to be quite high. The rates of severe hypoglycemia and hyperglycemia were alarmingly high in the Epidemiology of Diabetes and Ramadan study, a population-based large epidemiological study that spanned 13 countries with sizeable Muslim populations (3). Such a high rate of fasting-related morbidity was reported earlier in a small study by Uysal et al. (4). Education of patients is the cornerstone of safe fasting, which is needed on both an individual and large-scale level, and this is the responsibility of diabetes care team members.

Diabetic patients with established renal disease run substantial risk of complications by fasting and rightly the recommendations put them in the high-risk category. The great majority of those patients have major comorbidities and are taking many drugs, including insulin and sulfonylurea agents, which make them prone to severe hypoglycemia. We feel that these patients need to be singled out more specifically in the guidelines as such groups, even those who receive renal replacement therapy, often insist on fasting (A.A.A.-A., unpublished observations). Fasting for prolonged periods, especially in hot climates, may impose negative impacts on renal function from hypovolemia and dehydration. The mainstay of management of those patients is targeted toward arresting the progression of their underlying renal disease, and fasting during Ramadan should not be recommended.

Another group that deserves special consideration is adolescent patients with type 1 diabetes. These patients should not be encouraged to fast, as recurrent severe

hypoglycemia may have grave consequences, especially on neurobehavioral development (5–7). We feel that this group should have been pointed out categorically.

Finally, we commend the efforts of the expert panel, which took the painstaking task of drafting these long-awaited recommendations. Taking the issue of Ramadan and diabetes further warrants randomized controlled studies to explore the perceived benefits and expected risks of fasting, which will provide the scientific platform for future updated recommendations. Only when this is coupled with mass educational campaigns to patients with diabetes will the expected benefits from fasting be fulfilled.

TARIK A. ELHADD, MD
ABDULLAH A. AL-AMOUDI, MD

From the Department of Medicine, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia.

Address correspondence to Dr. T.A. Elhadd, MD, Department of Medicine, King Faisal Specialist Hospital and Research Center, Jeddah 21499, Saudi Arabia. E-mail: tarikelhadd58@gmail.com.

© 2006 by the American Diabetes Association.

References

1. Al-Arouj M, Bouguerra R, Buse J, Hafez S, Hassanein M, Ibrahim MA, Ismail-Beigi F, El-Kebbi I, Khatib O, Kishawi S, Al-Madani A, Mishal AA, Al-Maskari M, Nakhhi AB, Al-Rubean K: Recommendations for management of diabetes during Ramadan. *Diabetes Care* 28:2305–2311, 2005
2. Elhadd TA, Bissar LS, AlGhamdi SM, Bashir M, Alulaqi N, Al Amoudi A: Low education provided to patients with diabetes for fasting the holy month of Ramadan: a questionnaire survey (Abstract). In *187th American Endocrine Society Annual Meeting, San Diego, California, 4–7 June 2005*. Chevy Chase, MD, The Endocrine Society
3. Salti I, Benard E, Detournay B, Bianchi-Biscay M, Le Brigand C, Voynet C, Jabbar A, EPIDIAR Study Group: A population-based study of diabetes and its characteristics during the fasting month of Ramadan: results of the Epidemiology of Diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care* 27:2306–2311, 2004
4. Uysal AR, Erdogan MF, Sahin G, Kamel N, Erdogan G: Clinical and metabolic effects of fasting in 41 type 2 diabetic patients during Ramadan (Letter). *Diabetes Care* 21:2033–2034, 1998
5. Frier BM, Deary IJ: Severe hypoglycemia and cognitive impairment in diabetes. *BMJ* 313:767–768, 1996
6. Gold AE, Deary IJ, Jones JW, O'Hare JP, Reckless JPD, Frier BM: Severe deterioration in cognitive function and personality in five patients with longstanding diabetes: a complication of diabetes or consequences of treatment? *Diabet Med* 11: 499–505, 1994
7. Ryan CM: Neurophysiological consequences and correlates of diabetes in childhood. In *Neurophysiological and Behavioural Aspects of Diabetes*. Holmes CS, Ed. New York, Springer, 1994, p. 58–84

Recommendations for Management of Diabetes During Ramadan

Response to Al-Arouj et al.

In their otherwise fine article concerning recommendations for the management of diabetes during Ramadan, Al-Arouj et al. (1) perpetuate an ingrained, but mistaken, view of the glycemic response to different kinds of ingested carbohydrates. Their recommendations of eating foods containing complex carbohydrates at the predawn meal and simple carbohydrates at the sunset meal is based on their stated assumption that digestion and absorption of the former is delayed and faster for the latter. These assumptions have been challenged by clinical research. For instance, Wahlqvist et al. (2) showed in normal subjects and one type 2 diabetic patient that glucose appearance in the circulation was independent of saccharide chain length. Hydrolysis is so rapid in the gastrointestinal tract that the rate of glucose absorption from ingested monosaccharides (glucose) and polysaccharides (starch) was equivalent.

Therefore, one might expect that the amount of simple carbohydrate in the diet might not have much impact on postprandial glucose excursions. This was studied by measuring the effect of different proportions of simple and complex carbohydrate in meals in which total carbohydrate remained constant at 50% in type 2 diabetic patients (3). Three different ratios of complex to simple carbohydrates were evaluated: 80:20, 50:50, and 20:80. Glucose and insulin concentrations were measured hourly all day long, as was urinary glucose collected throughout the day. The results were similar in all three diets with small, but statistically significant, increases in plasma and urinary glucose levels in the diet containing 80% complex carbohydrate compared with the other two. It should be emphasized that all of the simple carbohydrate was from naturally occurring sugar in fruits, vegetables, and dairy products. No refined sugars were added to any of the diets. These results may be due, in part, to the fact that the natural sources of simple carbohydrate contained more fiber than foods furnishing the complex carbohydrate. However, it is now accepted that meals containing sucrose, incorporated into foods or desserts or even sprinkled onto cereal, do not lead to higher postprandial glucose excursions in either type 1 or type 2 diabetic patients (4–6). The latter observations are obviously independent of fiber. Thus, the type of carbohydrate, i.e. simple or complex, does not influence postprandial glycaemic excursions.

MAYER B. DAVIDSON, MD

From Charles R. Drew University, Los Angeles, California.

Address correspondence to Mayer B. Davidson, MD, Clinical Center for Research Excellence, Charles R. Drew University, 1731 East 120th St., Los Angeles, CA 90059. E-mail: madavids@cdrewu.edu.

© 2006 by the American Diabetes Association.

References

1. Al-Arouj M, Bouguerra R, Buse J, Hafez S, Hassanein M, Ibrahim MA, Ismail-Beigi F, El-Kebbi I, Khatib O, Kishawi S, Al-Madani A, Mishal AA, Al-Maskari M, Nakhhi AB, Al-Rubean K: Recommendations for management of diabetes during Ramadan. *Diabetes Care* 28:2305–2311, 2005
2. Wahlqvist ML, Wilmshurst EG, Richardson EN: The effect of chain length on glucose absorption and the related metabolic response. *Am J Clin Nutr* 31:1998–2001, 1978
3. Hollenbeck CB, Coulston AM, Donner CC Williams RA, Reaven GM: The effects of variations in percent of naturally occurring complex and simple carbohydrates on plasma glucose and insulin response in individuals with noninsulin-dependent diabetes mellitus. *Diabetes* 34:151–155, 1985
4. Hollenbeck CB, Coulston AM, Reaven GM: Effects of sucrose on carbohydrate and lipid metabolism in NIDDM patients. *Diabetes Care* 12(Suppl. 1):62–66, 1989
5. Mann JI: Simple sugars and diabetes. *Diabet Med* 4:135–139, 1987
6. Bantle JP: Clinical aspects of sucrose and fructose metabolism. *Diabetes Care* 12(Suppl. 1):56–61, 1989

Recommendations for Management of Diabetes During Ramadan

Response to Elhadd and Al-Amoudi and to Davidson

We thank Elhadd and Al-Amoudi (1) for their comments and interest in our article (2). Like them, we are also concerned by the very high rate of severe hypoglycemia and hyperglycemia in patients with diabetes who fast during Ramadan. We agree with them that patients with renal disease may have increased risk of hypoglycemia and that adolescent patients with poor glycemic control or recurrent hypoglycemia may also represent high-risk patients for developing hypoglycemia during fasting.

We thank Davidson (3) for his remarks. Our intent in recommending the addition of complex carbohydrates to a mixed meal at predawn was to keep a sustained increase in the appearance of glucose in the circulation to avoid hypoglycemia. We agree that initiation of hydrolysis of carbohydrates and the rate of appearance and the level of glucose soon after ingestion of simple or complex carbohydrates are fairly similar (4,5). However, these studies suggest that following the ingestion of complex carbohydrates, the day-long glucose concentrations (4) and the area under the curve for glucose (5) are larger for complex carbohydrates. Similar to these findings, Wolsdorf et al. (6) found that ingested uncooked starch behaves as a reservoir for continuous release of glucose compared with the absorption of ingested dextrose that occurs over a shorter period of time. Finally, and most importantly, ingestion of simple carbohydrates in the absence of additional protein or fat at Ifat (the breaking of the fast) enables rapid absorption of glucose when blood glucose levels are apt to be at their nadir, levels that could explain the relatively higher rates of hypoglycemia in the pre-Ifat period (7).

IMAD M. EL-KEBBI, MD¹
 MAHMOUD ASHRAF IBRAHIM, MD²
 FARAMARZ ISMAIL-BEIGI, MD, PHD³

From the ¹Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; the ²Egyptian Diabetes Center, Cairo, Egypt; and the ³Division of Clinical and Molecular Endocrinology, Case Western Reserve University, Cleveland, Ohio.

Address correspondence to Mahmoud Ashraf Ibrahim, MD, Egyptian Diabetes Center, 19 Nasouh St., Zeitoun, Cairo, Egypt 11321. E-mail: mahmoud@arab-diabetes.com.

© 2006 by the American Diabetes Association.

References

1. Elhadd TA, Al-Amoudi AA: Recommendations for management of diabetes during Ramadan (Letter). *Diabetes Care* 29: 744-745, 2006
2. Al-Arouj M, Bougeurra R, Buse J, Hafez S, Hassanein M, Ibrahim MA, Ismail-Beigi F, El-Kebbi I, Khatib O, Kishawi S, Al-Madani A, Mishal AA, Al-Maskari M, Nakhli AB, Al-Rubean K: Recommendations for management of diabetes during Ramadan. *Diabetes Care* 28:2305-2311, 2005
3. Davidson MB: Recommendations for management of diabetes during Ramadan (Letter). *Diabetes Care* 29:745, 2006
4. Hollenbeck CB, Coulston AM, Donner CC, Williams RA, Reaven GM: The effects of variations in percent of naturally occurring complex and simple carbohydrates on plasma glucose and insulin response in individuals with non-insulin-dependent diabetes mellitus. *Diabetes* 34:151-155, 1985
5. Wahlqvist ML, Wilmshurst EG, Richardson EN: The effect of chain length on glucose absorption and the related metabolic response. *Am J Clin Nutr* 31:1998-2001, 1978
6. Wolsdorf JI, Plotkin RA, Laffel LM, Crigler JF Jr: Continuous glucose for treatment of patients with type 1 glycogen storage disease: comparison of the effects of dextrose and uncooked starch on biochemical variables. *Am J Clin Nutr* 52: 1043-1050, 1990
7. Akram J, De Verga V, the Ramadan Study Group: Insulin lispro (Lys(B28), Pro(B29)) in the treatment of diabetes during the fasting month of Ramadan. *Diabet Med* 16: 861-866, 1999

The Effect of Rosiglitazone on Overweight Subjects With Type 1 Diabetes

Response to Strowig and Raskin

The recent report by Strowig and Raskin (1) raises the intriguing issue as to whether some type 1 diabetic patients may benefit from a supplementary insulin sensitization approach to their management. As our and other stud-

ies have shown that an estimate of insulin sensitivity (eGDR) is strongly predictive of mortality (2), coronary artery disease events (3), coronary calcification (4), and overt nephropathy (5) in type 1 diabetes, we would strongly endorse further pursuit of this approach.

The eGDR measure is based on a regression equation (with terms for waist-to-hip ratio, hypertension status, and HbA_{1c}, i.e., eGDR = 24.39 - 12.97 [waist-to-hip ratio] - 3.39 [hypertension] - 0.60 [HbA_{1c}]) derived from 24 hyperinsulinemic-euglycemic clamp studies and has an r² of 0.63 for measured glucose disposal rate (6). As eGDR might therefore be a useful identifier of those who would benefit from thiazolidinedione therapy, it would be helpful to know if eGDR predicted response to rosiglitazone therapy in terms of HbA_{1c} in the Strowig and Raskin (1) study. In addition, was there any difference in change of waist circumference (or waist-to-hip ratio) by treatment group, consistent with the observation (7) that weight gain with rosiglitazone is mainly peripheral rather than central? Finally, it is notable that lipid concentrations were not generally affected by rosiglitazone therapy in contrast to blood pressure. This is similar to our eGDR studies wherein lipids did not help to predict glucose disposal rate, but hypertension status did (6). Do these dual observations thus suggest that in type 1 diabetes insulin resistance is more strongly linked to blood pressure than to lipids?

TREVOR J. ORCHARD, MD, MMEDSCI

From the Department of Epidemiology, Diabetes and Lipid Research, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address correspondence to Trevor J. Orchard, MD, MMedSci, Department of Epidemiology, Diabetes and Lipid Research, Graduate School of Public Health, University of Pittsburgh, 3512 Fifth Ave., Pittsburgh, PA 15213. E-mail: tjo@pitt.edu.

T.J.O. has received grant/research support from GlaxoSmithKline.

© 2006 by the American Diabetes Association.

References

1. Strowig SM, Raskin P: The effect of rosiglitazone on overweight subjects with type 1 diabetes. *Diabetes Care* 28:1562-1567, 2005
2. Olson JC, Erbey JR, Williams KV, Becker DJ, Edmundowicz D, Kelsey SF, Sutton-Tyrrell K, Orchard TJ: Subclinical atherosclerosis and estimated glucose disposal



References

1. Strowig SM, Raskin P: The effect of rosiglitazone on overweight subjects with type 1 diabetes. *Diabetes Care* 28:1562–1567, 2005
2. Orchard TJ: The effect of rosiglitazone on overweight subjects with type 1 diabetes (Letter). *Diabetes Care* 29:746–747, 2006
3. Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ: Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* 49:626–632, 2000
4. Strowig SM, Avilés-Santa ML, Raskin P: Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and troglitazone in type 2 diabetes. *Diabetes Care* 25:1691–1698, 2002
5. Strowig SM, Avilés-Santa ML, Raskin P: Improved glycemic control without weight gain using triple therapy in type 2 diabetes. *Diabetes Care* 27:1577–1583, 2004

Comparison of the Effects of Vitamins and/or Mineral Supplementation on Glomerular and Tubular Dysfunction in Type 2 Diabetes

Response to Farvid et al.

Recently, Farvid et al. (1) reported on the effects of dietary supplementation of physiologic doses of vitamins and/or minerals on urinary albumin excretion rate (UAER)/urinary protein excretion rate (UPER), blood pressure, and lipid profile. Although not mentioned in the article, data on blood pressure and lipids have previously been reported elsewhere (2,3).

The main finding is a significant reduction in UAER of ~66% in the group receiving both minerals and vitamins. Although Farvid et al. claimed this to be the primary end point, it was only measured once as albumin-to-creatinine ratio in morning spot urine at baseline and after 3 months. Repeated measurements (usually at least three) are always required to obtain valid data and correct diagnosis of persistent micro- and macroalbuminuria due to a coefficient of variation of 30–50%. There is a marked discrepancy be-

rate as predictors of mortality in type 1 diabetes. *Ann Epidemiol* 12:331–337, 2002

3. Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KY, Smithline Kinder L, Ellis D, Becker DJ: Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 26:1374–1379, 2003
4. Dabelea D, Kinney G, Snell-Bergeon JK, Hokanson JE, Eckel RH, Ehrlich J, Garg S, Hamman RF, Rewers M: Effect of type 1 diabetes on the gender difference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study. *Diabetes* 52:2833–2839, 2003
5. Orchard TJ, Chang Y, Ferrell R, Petro N, Ellis D: Nephropathy in type 1 diabetes: a manifestation of insulin resistance and multiple genetic susceptibilities? Further evidence from the Pittsburgh Epidemiology of Diabetes Complication Study. *Kidney Int* 62:963–970, 2002
6. Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ: Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* 49:626–632, 2000
7. Carey DG, Cowin GJ, Galloway GJ, Jones NP, Richard JC, Biswas N, Doddrell DM: Effect of rosiglitazone on insulin sensitivity and body composition in type 2 diabetic patients. *Obes Res* 10:1008–1015, 2002 [erratum in *Obes Res* 10:following TOC, 2002]

The Effect of Rosiglitazone on Overweight Subjects With Type 1 Diabetes

Response to Orchard

Our report (1) on the effect of rosiglitazone on overweight subjects with type 1 diabetes showed that rosiglitazone-treated subjects with a BMI ≥ 30 kg/m² experienced significantly greater improvements in HbA_{1c} (A1C) levels than those with a BMI < 30 kg/m² (–1.4 vs. –0.4%, $P = 0.032$). In addition, regression analysis showed that BMI, total daily insulin dose, and total, LDL, and HDL cholesterol levels were predictors of improvement in A1C (1). In his letter (2), Orchard raises the intriguing possibility that an estimate of insulin sensitivity (eGDR), which is based on waist-to-hip ratio, hypertension status, and A1C (3), could be

an identifier of type 1 diabetic individuals who might benefit from thiazolidinedione therapy. We calculated eGDR in our subjects and found that in the rosiglitazone-treated subjects, eGDR was significantly related to change in A1C level ($P = 0.003$, $r = 0.575$). No such relationship was found in the placebo-treated subjects. However, a regression analysis incorporating BMI; total daily insulin dose; total, LDL, and HDL cholesterol; and eGDR showed that eGDR was not a significant predictor of improvement in A1C ($P = 0.155$) in the rosiglitazone-treated subjects.

Waist-to-hip ratios were the same in both the rosiglitazone and placebo groups at baseline (0.91 ± 0.06) and at the end of the study (0.93 ± 0.06), which is consistent with the observation that weight gain with thiazolidinediones is mainly peripheral rather than central. Orchard (2) noted that blood pressure but not lipids improved in our rosiglitazone-treated type 1 diabetic subjects. This result was somewhat surprising since we had observed the opposite results in our studies of troglitazone in combination with insulin in type 2 diabetic subjects (4,5). It is important to keep in mind that these studies were not designed to evaluate the effect of thiazolidinedione therapy on blood pressure; all of our subjects were treated with antihypertensive medications in an effort to normalize blood pressure levels. In addition, baseline blood pressure and history of hypertension were not related to change in A1C and were not significant predictors of improvement in A1C level in our rosiglitazone-treated type 1 diabetic subjects. Triglyceride levels also were not related to change in A1C. On the other hand, markers of insulin resistance in the type 1 diabetic subjects, such as BMI, total daily insulin dose, and cholesterol levels, were related to improvement in glycemic control when rosiglitazone treatment was used. Therefore, we do not believe that we can draw any firm conclusions from our data about the relative linkage of blood pressure versus lipid levels to insulin resistance.

SUZANNE M. STROWIG, MSN, RN
PHILIP RASKIN, MD

From the Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas.

Address correspondence to Suzanne M. Strowig, MSN, RN, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX 75390-8858. E-mail: suzanne.strowig@utsouthwestern.edu.

tween the level of UAER (30 mg/g creatinine), suggesting microalbuminuria, and the level of UPER (1–2 g/g creatinine; equal to overt nephropathy). An inconsistent effect of mineral and vitamin supplementation on UAER and UPER was reported, suggesting a chance finding.

Furthermore, mean diastolic blood pressure in the minerals and vitamins group before treatment dropped from 94 (Table 1 in Farvid et al.) to 83 (Table 6) mmHg after exclusion of 2 of the 19 patients; this indicates an error in one of the tables, as it would only be possible if the two excluded patients had a mean diastolic blood pressure of 187 mmHg. The technique for blood pressure measurement was not stated. The conditions for the power calculation were not stated, but according to their previous reports, it was powered to detect changes in HDL cholesterol (2) and blood pressure (3).

It is claimed that the UAER findings are in accordance with the literature (refs. 14–16 in Farvid et al.). However, pharmacological doses of vitamins C and E had no or minimal effect (19%) on UAER (refs. 14,15). In contrast, a 50% reduction in UAER was reported in nine patients, applying pharmacological doses of vitamin C (ref. 16).

In conclusion, the study was not powered for realistic changes in UAER/UPER, insufficient methods for valid characterization of UAER/UPER were applied, and the effect of minerals and vitamins on UAER/UPER was not consistent, clearly suggesting a type 1 error or chance finding.

PETER ROSSING, MD, DMSC¹

MARK E. COOPER, MD, PHD²

HANS-HENRIK PARVING, MD, DMSC^{1,3}

From the ¹Steno Diabetes Center, Gentofte, Denmark; the ²Baker Medical Research Institute, Danielle Alberti Memorial Centre, Melbourne, Australia; and the ³University of Aarhus, Faculty of Health Science, Aarhus, Denmark.

Address correspondence to Peter Rossing, MD, DMSc, Steno Diabetes Center, Niels Steensens Vej 2, Gentofte DK-2820, Denmark. E-mail: pro@steno.dk.

M.E.C. is a member of a steering committee for Amgen.

© 2006 by the American Diabetes Association.

References

1. Farvid MS, Jalali M, Siassi F, Hosseini M: Comparison of the effects of vitamins and/or mineral supplementation on glomerular and tubular dysfunction in type 2 diabetes. *Diabetes Care* 28:2458–2464, 2005

2. Farvid MS, Siassi F, Jalali M, Hosseini M, Saadat N: The impact of vitamin and/or mineral supplementation on lipid profiles in type 2 diabetes. *Diabetes Res Clin Pract* 65:21–28, 2004
3. Farvid MS, Jalali M, Siassi F, Saadat N, Hosseini M: The impact of vitamins and/or mineral supplementation on blood pressure in type 2 diabetes. *J Am Coll Nutr* 23:272–279, 2004

Comparison of the Effects of Vitamins and/or Mineral Supplementation on Glomerular and Tubular Dysfunction in Type 2 Diabetes

Response to Rossing et al.

We thank Rossing et al. (1) for their interest in our article (2) and agree that one measurement of albumin-to-creatinine ratio in morning spot urine at baseline and after 3 months is a potential limitation to our study. This limitation is described in detail in our discussion section. Although we did not obtain multiple spot urine samples or a 24-h urine collection to assess microalbuminuria, the random microalbumin-to-creatinine ratio has high reported sensitivity and specificity compared with 24-h urine microalbumin testing (3). The ratio of protein or albumin to creatinine in an untimed urine specimen has replaced protein excretion in a 24-h collection as the preferred method for measuring proteinuria. Using a ratio corrects for variations in urinary protein concentration due to hydration and is far more convenient than timed urine collections. The ratio of protein or albumin to creatinine in an untimed urine sample is an accurate estimate of the protein or albumin excretion rate (4). Also, it should be noted that after 3 months of supplementation, significant decreases in our vitamins group and minerals and vitamins group for albumin-to-creatinine ratio were observed from baseline and when compared with the placebo group. There were no significant changes in the other two groups. If the results were related to chance, microalbuminuria would have decreased in the other two groups.

We acknowledge Rossing et al. for

drawing our attention to an error in Table 1. The diastolic blood pressure in the minerals and vitamins group should be amended to 84 ± 11 mmHg. Blood pressure was recorded semiautomatically using a Dinamap recorder (Critilzon, Tampa, FL). Before the study, the calculated sample size was 18 patients in each group, having 80% power to detect the postulated differences in HDL cholesterol, blood pressure, and microalbuminuria with an α error of 5%. But, after the supplementation, the calculated power for albumin-to-creatinine ratio was 0.7.

In conclusion, we do not agree with the concerns of Rossing et al. that our study was inadequately powered for detecting realistic changes in urinary albumin/protein excretion rate, that insufficient methods for valid characterization of urinary albumin/protein excretion rate were applied, and that the effect of minerals and vitamins on urinary albumin/protein excretion rate was inconsistent, which would suggest a type 1 error or a chance finding. In view of this, we believe our conclusions are valid.

MARYAM SADAT FARVID, PHD¹

MAHMOUD JALALI, PHD²

FEREYDOUN SIASSI, PHD²

MOSTAFA HOSSEINI, PHD³

From the ¹Department of Community Nutrition, School of Nutrition and Food Technology, Shaheed Beheshti University of Medical Sciences, Tehran, Iran; the ²Department of Nutrition and Biochemistry, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; and the ³Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

Address correspondence to Maryam Farvid, School of Nutrition and Food Technology, Shaheed Beheshti University of Medical Sciences, Tehran 19395-4741, Iran (Islamic Republic). E-mail: farvidm@yahoo.ca or farvidm@hotmail.com.

© 2006 by the American Diabetes Association.

References

1. Rossing P, Cooper ME, Parving H-H: Comparison of the effects of vitamins and/or mineral supplementation on glomerular and tubular dysfunction in type 2 diabetes (Letter). *Diabetes Care* 29:747–748, 2006
2. Farvid MS, Jalali M, Siassi F, Hosseini M: Comparison of the effects of vitamins and/or mineral supplementation on glomerular and tubular dysfunction in type 2 diabetes. *Diabetes Care* 28:2458–2464, 2005
3. Zelmanovitz T, Gross JL, Oliveira JR, Paggi A, Tatsch M, Azevedo MJ: The receiver operating characteristics curve in

the evaluation of a random urine specimen as a screening test for diabetic nephropathy. *Diabetes Care* 20:516–519, 1997

- Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T: Diabetic nephropathy: diagnosis, prevention, and treatment (Review). *Diabetes Care* 28:164–176, 2005

Relationship Between Testosterone Levels, Insulin Sensitivity, and Mitochondrial Function in Men

Response to Pitteloud et al.

We read with interest the excellent study by Pitteloud et al. (1) demonstrating that low serum total testosterone levels are associated with an adverse metabolic profile in aging men and suggesting a novel unifying mechanism for the previously independent observations that low testosterone levels and impaired mitochondrial function promote insulin resistance in these patients. The authors concluded their report by stating that there is a need for evaluation of the potential benefits of androgen supplementation in preventing or treating the metabolic syndrome and/or type 2 diabetes in men.

While we agree with their conclusion, we would like to provide the authors with a cautionary comment regarding the means by which androgen levels should be supplemented in these patients. The most commonly used method to increase androgen levels in aging, hypogonadal men is to administer testosterone supplementation therapy (2). From a urological perspective, a major problem with the use of testosterone supplementation alone in aging men is that the exogenously administered testosterone is metabolized by 5 α -reductase to dihydrotestosterone (DHT). Based on newly emerging data from the National Cancer Institute–sponsored Prostate Cancer Prevention Trial, DHT is a proven risk factor for the development of prostate cancer in aging men (3). Moreover, the use of testosterone supplementation alone in men with low serum testosterone levels has been shown to lead to an elevation in their intraprostatic DHT levels (4).

In light of the potentially serious safety concerns associated with the use of testosterone supplementation alone in aging men, we respectfully suggest that the authors consider using androgen supplementation strategies that avoid the potential problems associated with the 5 α -reduction of testosterone to DHT. A simple, safe, and effective treatment option in this regard may be to coadminister a 5 α -reductase inhibitor as adjunctive therapy with a testosterone supplement. Such an approach would prevent the DHT elevation associated with testosterone supplementation, while still allowing for testosterone to exert its beneficial metabolic and anthropometric effects. We and others have extensively studied the use of 5 α -reductase inhibitors in the treatment of aging men with benign prostatic hyperplasia (5); these drugs are well tolerated and have been shown to markedly suppress the reduction of testosterone to DHT.

STEVEN A. KAPLAN, MD¹
E. DAVID CRAWFORD, MD²

From the ¹Columbia University Medical Center, New York, New York; and the ²University of Colorado Health Sciences Center, Aurora, Colorado.

Address correspondence to Steven A. Kaplan, MD, Department of Urology, Weill Cornell Medical College, F9-West, Box 261, 1300 York Ave., New York, NY 10021. E-mail: kaplans@med.cornell.edu.

S.A.K. is currently affiliated with the Department of Urology, Weill Cornell Medical College, New York, New York.

© 2006 by the American Diabetes Association.

References

- Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson KF, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ: Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. *Diabetes Care* 28:1636–1642, 2005
- Matsumoto AM: Andropause: clinical implications of the decline in serum testosterone levels with aging in men. *J Gerontol* 57A:M76–M99, 2002
- Thompson IM: New insights and developments from the Prostate Cancer Prevention Trial: the promise of SELECT [presentation online], 2005. Available from <http://webcasts.prous.com/aua2005/article.asp?AID=22&CID=YY&CLID=2>. Accessed 26 September 2005
- Page ST, Lin DL, Hess DL, Amory JK, Nelson PS, Matsumoto AM, Bremner WJ: Prostate tissue dihydrotestosterone, but not testosterone, levels are decreased by medical castration in normal middle-aged men (Abstract). In *Proceedings of the 87th Annual Meeting of The Endocrine Society, San Diego, CA, 2005*. Chevy Chase, MD, The Endocrine Society, p. 161–162, 2005

ceedings of the 87th Annual Meeting of The Endocrine Society, San Diego, CA, 2005. Chevy Chase, MD, The Endocrine Society, p. 161–162, 2005

- McConnell JD, Bruskewitz R, Walsh P, Andriole G, Lieber M, Holtgrewe HL, Albertsen P, Roehrborn CG, Nickel JC, Wang DZ, Taylor AM, Waldstreicher J: The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia: Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med* 338:557–563, 1998

Relationship Between Testosterone Levels, Insulin Sensitivity, and Mitochondrial Function in Men

Response to Kaplan and Crawford

I thank Drs. Kaplan and Crawford (1) for their kind remarks on our article (2) on the relationship between testosterone levels and insulin sensitivity in men and for their thoughtful comments on the optimal form of androgen replacement for older men.

While the standard form of androgen replacement for hypogonadal men is testosterone, the authors express concern about its use in older men, given that it results in an increase in levels of dihydrotestosterone (DHT), which, in as-yet-unpublished data, has been identified as a risk factor for prostate cancer (3). On this basis, Drs. Kaplan and Crawford recommend that a regimen comprising coadministration of testosterone with the 5 α -reductase inhibitor finasteride be considered for androgen replacement in older men.

Preliminary evidence suggests that this may indeed be a reasonable strategy. In a carefully conducted three-arm study (testosterone alone, testosterone plus 5 mg/day finasteride, and placebo) of 70 men aged ≥ 65 years with testosterone levels < 350 ng/dl, Tenover and colleagues (4,5) demonstrated that testosterone therapy both alone and in combination with finasteride improved body composition, physical performance, bone mineral density, and total cholesterol. However, concomitant treatment with finasteride ap-

peared to attenuate the negative effect of testosterone on the prostate in that subjects who received the dual regimen had no increase in prostate-specific antigen levels and had a significantly lower increase in prostate volume than those treated with testosterone alone (5). While these data are encouraging, they are based on small patient numbers, and the favorable effects on prostate-specific antigen levels may not necessarily translate to a reduction in prostate cancer risk. In addition, while finasteride was shown to reduce the development of prostate cancer in middle-aged men, the incidence of high-grade prostate tumors and sexual side effects was increased (6).

Therefore, I believe that further research is still needed to identify the androgen regimen that confers optimal benefit to older men without compromising prostate health and overall patient safety.

FRANCES HAYES, MB, FRCPI

From the Reproductive Endocrine Unit, Massachusetts General Hospital, Boston, Massachusetts.

Address correspondence to Frances Hayes, Reproductive Endocrine Unit, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114. E-mail: fhayes@partners.org.

F.H. has been an advisory board member for Auxilium and has received honoraria from Solvay.

© 2006 by the American Diabetes Association.

References

1. Kaplan SA, Crawford ED: Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men (Letter). *Diabetes Care* 29:749, 2006
2. Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson KF, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ: Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. *Diabetes Care* 28:1636–1642, 2005
3. Thompson IM: New insights and developments from the Prostate Cancer Prevention Trial: the promise of SELECT [presentation online], 2005. Available from <http://webcasts.prous.com/aua2005/article.asp?AID=22&CID=YY&CLID=2>. Accessed 26 September 2005
4. Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL: Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab* 90:1502–1510, 2005
5. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL: Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 89:503–510, 2004
6. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA Jr: The influence of finasteride on the development of prostate cancer. *N Engl J Med* 349:215–224, 2003

Hepatitis C Virus Infection: Evidence for an Association With Type 2 Diabetes

Response to Antonelli et al.

Antonelli et al. (1) classified diabetes associated with hepatitis C virus (HCV) infection as type 2. However, these patients show slightly different phenotype than typical type 2 diabetic subjects. Of interest, in our study, HCV diabetic patients presented similar intermediate clinical phenotype with significantly lower BMI (26.5 ± 4.8 vs. 30.9 ± 6.3 kg/m²), systolic (133.9 ± 14.0 vs. 142.9 ± 25.6 mmHg) and diastolic (84.4 ± 10.2 vs. 88.1 ± 16.0 mmHg) blood pressure, LDL cholesterol (1.9 ± 0.5 vs. 2.7 ± 0.8 mmol/l), and triglycerides (1.4 ± 0.8 vs. 2.6 ± 1.9 mmol/l). Furthermore, these patients showed lower C-reactive protein concentration (1.53 ± 1.23 vs. 3.54 ± 2.53 mg/l).

There is a groundswell of data now to link HCV infection with diabetes. However, serious doubt concerning the true character of diabetes in HCV patients must be emphasized. An autoimmune basis of the HCV-diabetes link is unlikely because no increased prevalence of β -cell autoimmune markers in HCV patients has been found (2). Nonetheless, there is a report of type 1 diabetes 1 year after blood transfusion-related HCV infection (3). Additionally, diabetic HCV patients with mixed cryoglobulinemia are more likely to carry non-organ-specific autoantibodies (4). Interestingly, there is evidence to support the hypothesis that HCV directly damages β -cells or disturbs their function, which ultimately leads to diabetes (5). Finally, there is no question that HCV, by itself, can induce insulin resis-

tance, disturbing the insulin signaling pathway by the function of HCV core protein (6). Moreover, a crucial association between diabetes and the stage of fibrosis in HCV patients, independent of obesity and steatosis, on liver biopsy has also been demonstrated (6).

Diabetes in HCV patients has a unique and complex pathogenesis. Although both insulin resistance and β -cell dysfunction are responsible for the diabetes-HCV association, the specific nature of that link casts doubt on diagnosis of type 2 diabetes in these patients.

MARCIN SKOWROŃSKI, MD¹
 DOROTA ZOZULIŃSKA, PHD¹
 JACEK JUSZCZYK, PHD²
 BOGNA WIERUSZ-WYSOCKA, PHD¹

From the ¹Department of Internal Medicine and Diabetology, Poznań University of Medical Sciences, Poznań, Poland; and the ²Department of Infectious Diseases, Poznań University of Medical Sciences, Poznań, Poland.

Address correspondence to Dorota Zozulińska, Department of Internal Medicine and Diabetology, Ul. Mickiewicza 2, 60-834 Poznań, Poland. E-mail: zozula@box43.pl.

© 2006 by the American Diabetes Association.

References

1. Antonelli A, Ferri C, Fallahi P, Pampana A, Ferrari SM, Goglia F, Ferrannini E: Hepatitis C virus infection: evidence for an association with type 2 diabetes (Brief Report). *Diabetes Care* 28:2548–2550, 2005
2. Piquer S, Hernández C, Enriquez J, Ross A, Esteban JI, Genescà J, Bonifacio E, Puig-Domingo M, Simó R: Islet cell and thyroid antibody prevalence in patients with hepatitis C virus infection: effect of treatment with interferon. *J Lab Clin Med* 137:38–42, 2001
3. Chen LK, Chou YC, Tsai ST, Hwang SJ, Lee SD: Hepatitis C virus infection-related type 1 diabetes mellitus. *Diabet Med* 22:340–343, 2005
4. Antonelli A, Ferri C, Fallahi P, Sebastiani M, Nesti C, Barani L, Barale R, Ferrannini E: Type 2 diabetes in hepatitis C-related mixed cryoglobulinaemia patients. *Rheumatology* 43:238–240, 2004
5. Masini M, Campani D, Boggi U, Menicagli M, Funel N, Pollera M, Lupi R, Del Guerra S, Bugliani M, Torri S, Del Prato S, Mosca F, Filipponi F, Marchetti P: Hepatitis C virus infection and human pancreatic β -cell dysfunction (Brief Report). *Diabetes Care* 28:940–941, 2005
6. Knobler H, Schattner A: TNF- α , chronic hepatitis C and diabetes: a novel triad. *Q J Med* 98:1–6, 2005

Hepatitis C Virus Infection: Evidence for an Association With Type 2 Diabetes

Response to Skowroński et al.

We agree with Skowroński et al. (1) that the type of diabetes manifested by patients with HCV chronic infection (HCV⁺) may not be classical type 2 diabetes, and the phenotypic characterization of our patients shows just that. The labeling of HCV⁺ patients as type 2 diabetes is purely conventional and possibly inaccurate: the lines separating type 1 diabetes, from latent autoimmune diabetes in adults and from type 2 diabetes, are fading away as new pathogenetic information is obtained (2).

HCV chronic infection may be responsible for a constellation of extrahepatic immune-mediated manifestations (3). HCV lymphotropism may trigger lymphocyte expansion followed by the production of different autoantibodies (3). For example, we have previously reported (4) on 229 HCV-related mixed cryoglobulinemia (MC-HCV⁺) patients without cirrhosis. We found that 1) the prevalence of type 2 diabetes was significantly higher in MC-HCV⁺ patients without cirrhosis than in control subjects (14.4 vs. 6.9%), 2) MC-HCV⁺ patients with type 2 diabetes were leaner than type 2 diabetic control subjects (24.2 vs. 30.4 kg/m²) and showed significantly lower LDL cholesterol and systolic and diastolic blood pressure, and 3) MC-HCV⁺ patients with type 2 diabetes had non-organ-specific autoantibodies more frequently (34 vs. 18%) than nondiabetic MC-HCV⁺ patients. Thus, in HCV chronic infection, the clinical phenotype of diabetes has been found to be similar across three studies (1,4,5) and different from classical type 2 diabetes. An immune-mediated mechanism for MC-HCV⁺-associated diabetes has been postulated (4), and a similar pathogenesis might be involved in the diabetes of HCV⁺ patients. This hypothesis is strengthened by the finding that autoimmune phenomena in type 2 diabetic patients are more common than previously thought (6). Since the prevalence of classic β -cell autoimmune markers in HCV⁺

patients has not been found to be increased (1), other immune phenomena might be involved, and viral damage to the β -cells may occur by a direct mechanism (7).

ALESSANDRO ANTONELLI, MD¹
 CLODOVEO FERRI, MD²
 POUPAK FALLAHI, MD¹
 SILVIA MARTINA FERRARI¹
 FERNANDO GOGLIA, PHD³
 ELE FERRANNINI, MD¹

From the ¹Metabolism Unit, Department of Internal Medicine and CNR Institute of Clinical Physiology, University of Pisa, Pisa, Italy; the ²Rheumatology Unit, Department of Internal Medicine, University of Modena, Modena, Italy; and the ³Department of Biological and Environmental Sciences, University of Sannio, Benevento, Italy.

Address correspondence to Alessandro Antonelli, MD, Department of Internal Medicine, University of Pisa, School of Medicine, Via Roma, 67, I-56100, Pisa, Italy. E-mail: a.antonelli@med.unipi.it.

© 2006 by the American Diabetes Association.

References

1. Skowroński M, Zozulińska D, Juszczak J, Wierusz-Wysocka B: Hepatitis C virus infection: evidence for an association with type 2 diabetes (Letter). *Diabetes Care* 29: 750–751, 2006
2. Gale EAM: Latent autoimmune diabetes in adults: a guide for the perplexed. *Diabetologia* 48:2195–2199, 2005
3. Ferri C, Mascia MT: Cryoglobulinemic vasculitis. *Curr Opin Rheumatol* 18:54–63, 2006
4. Antonelli A, Ferri C, Fallahi P, Sebastiani M, Nesti C, Barani L, Barale R, Ferrannini E: Type 2 diabetes in hepatitis C-related mixed cryoglobulinaemia patients. *Rheumatology* 43:238–240, 2004
5. Antonelli A, Ferri C, Fallahi P, Pampana A, Ferrari SM, Goglia F, Ferrannini E: Hepatitis C virus infection: evidence for an association with type 2 diabetes (Brief Report). *Diabetes Care* 28:2548–2550, 2005
6. Antonelli A, Tuomi T, Nannipieri M, Fallahi P, Nesti C, Okamoto H, Groop L, Ferrannini E: Autoimmunity to CD38 and GAD in type II and type I diabetes: CD38 and HLA genotypes and clinical phenotypes. *Diabetologia* 45:1298–1306, 2002
7. Masini M, Campani D, Boggi U, Menicagli M, Funel N, Pollera M, Lupi R, Del Guerra S, Bugliani M, Torri S, Del Prato S, Mosca F, Filipponi F, Marchetti P: Hepatitis C virus infection and human pancreatic β -cell dysfunction (Brief Report). *Diabetes Care* 28:940–941, 2005

Metformin and Heart Failure: Innocent Until Proven Guilty

Response to Inzucchi

The editorial by Inzucchi (1) in the October 2005 issue of *Diabetes Care* on the effects of metformin in type 2 diabetic patients with heart failure deals in a masterly manner with the choice of the most suitable treatment of this condition. Since both diabetic heart failure and mechanism of metformin action are not completely understood, it is difficult, in the author's opinion, to find a convincing explanation of the benefit from the use of this drug. However, as the contracting heart gets most of its energy from nonesterified fatty acids (FFAs), and even does so more in the insulin-resistant state of diabetes, the author correctly states that a drug that enhances the uptake of the more metabolically efficient glucose instead of FFA may improve the function of the failing heart.

What the author is not aware of is that the mechanism of shift from one substrate to another has just been demonstrated for metformin and the other biguanides. In fact, dose-dependent inhibition of long-chain fatty acid oxidation in red muscle restores the glucose oxidation when depressed by concurrent oxidation of palmitic acid; hence, the proposed definition of biguanides as drugs of the Randle's cycle (2,3).

Fischer et al. (4) describe increased content of glucose transporters GLUT1 and GLUT4 produced by metformin in heart cells.

Essop and Opie (5) stress the concept that high blood FFAs, especially in the presence of a hyperadrenergic state, can damage the ischemic myocardium and that agents that inhibit myocardial FFA oxidation should improve the work efficiency of the failing heart.

In conclusion, in my opinion there is good evidence that the beneficial effect of metformin in heart failure in type 2 diabetic patients rests on the same underlying mechanism shared by other well-known effects of the drug, i.e., increased utilization of glucose by red muscle and hindered gluconeogenesis in liver, as consequences of depressed fatty acid oxidation (2,3).

SERGIO MUNTONI, MD, PHD

From the Center for Metabolic Diseases and Atherosclerosis of Cagliari, The ME.DI.CO. Association, Cagliari, Italy.

Address correspondence to Sergio Muntoni, MD, PhD, 29 Viale Merello, 09123 Cagliari, Italy. E-mail: sergiomuntoni@hotmail.com.

© 2006 by the American Diabetes Association.

References

1. Inzucchi SE: Metformin and heart failure: innocent until proven guilty (Editorial). *Diabetes Care* 28:2585–2587, 2005
2. Muntoni S: Inhibition of fatty acid oxidation by biguanides: implications for metabolic physiopathology. *Adv Lipid Res* 12: 311–377, 1974
3. Muntoni S: Metformin and fatty acids. *Diabetes Care* 22:179–180, 1999
4. Fischer Y, Thomas J, Rosen P, Kammermeier H: Action of metformin on glucose transporter GLUT1 and GLUT4 in heart muscle cells from healthy and diabetic rats. *Endocrinology* 136:412–420, 1995
5. Essop MF, Opie LH: Metabolic therapy for heart failure. *Eur Heart J* 25:1765–1769, 2004

Metabolic Syndrome or “Central Obesity Syndrome”?

I read with interest the recent two articles on metabolic syndrome published in *Diabetes Care*, one by Ford (1) on the prevalence of metabolic syndrome defined by the International Diabetes Federation (IDF) among adults in the U.S. and the other by Kahn et al. (2) that critically appraised the definitions of metabolic syndrome.

Ford reported a higher prevalence estimate of the metabolic syndrome than the estimate based on the National Cholesterol Education Program (NCEP) definition (unadjusted prevalence 39.0 ± 1.1 vs. $34.5 \pm 0.9\%$, respectively) in U.S. adults (1). The lower IDF criteria as compared with NCEP criteria for defining central obesity (men ≥ 94 vs. >102 cm and women ≥ 80 vs. >88 cm) appeared to account for much of this difference (3,4). The NCEP criteria suggest selecting three of five parameters, whereas IDF criteria have one fixed component (central obesity) and then select two of the other four parameters (3,4). With high-school mathematics, we can calculate the number of possible combinations in selecting X of Y items by the following equation: $Y! / [(X!)(Y - X)!]$, where Y! reads as Y fac-

torial = $Y \times (Y - 1) \times (Y - 2) \dots \times 3 \times 2 \times 1$. The number of combinations in selecting three parameters out of five (the NCEP criteria) = $5! / (3! \times 2!) = (5 \times 4 \times 3 \times 2 \times 1) / (3 \times 2 \times 1 \times 2 \times 1) = 10$, whereas IDF criteria has $4! / (2! \times 2!) = 6$ combinations. The prevalence of metabolic syndrome will depend on the percentage of individual combinations. In other words, if all five parameters of NCEP or IDF criteria are the same, the IDF criteria will always diagnose less (instead of more) subjects with metabolic syndrome as compared with NCEP criteria.

Following this mathematical exercise, we can also see that the prevalence of the metabolic syndrome defined by IDF criteria is highly dependent on and will be always less than the prevalence of central obesity of that particular population, since central obesity is regarded by IDF as a prerequisite and those centrally obese subjects having two additional parameters will be defined as having metabolic syndrome (5). Kahn et al. (2) have commented that the metabolic syndrome has been imprecisely defined with a lack of certainty regarding its pathogenesis. Whereas the IDF criteria have identified central obesity as the only essential component of metabolic syndrome, Kahn et al. reminded us that the attempt to define the metabolic syndrome as the result of a single (or even major) unifying pathophysiological process, e.g., insulin resistance, is problematic.

The ultimate importance of metabolic syndrome is that it helps identify individuals at high risk of cardiovascular disease (CVD) (maybe type 2 diabetes as well) (3,6,7). While central obesity is a strong CVD risk factor, it is unlikely to be the only pathogenetic cause for metabolic syndrome (i.e., high CVD risk). The new IDF criteria for metabolic syndrome has evolved to identifying a selected or complicated subgroup of subjects with visceral obesity who are centrally obese and have already developed at least two complications such as hypertension or dyslipidemia (3). In that case, it is more appropriate to call the new IDF criteria for metabolic syndrome the “central obesity syndrome.”

But then what about metabolic syndrome? Metabolic syndrome should be a concept instead of a strict definition. Subjects with more than one well-established CVD risk factor are at increased risk for developing CVD. Other CVD risk factors tend to cluster in this group of patients as

well. If we all agree that the metabolic syndrome is implying a cluster of CVD risk factors, then it can be labeled to all individuals with two, three, or more well-established CVD risk factors such as hypertension, dysglycemia, dyslipidemia (not only high triglyceride and low HDL cholesterol but also high total cholesterol), obesity (both general and central), strong family history of CVD, ageing, and so on. It should be a “loose” but serious term, just like “high CVD risk.”

GARY T.C. KO, MD, FRCPI

From the Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, Tai Po, Hong Kong.

Address correspondence to Gary T.C. Ko, Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, 11 Chuen On Road, Tai Po, NT, Hong Kong. E-mail: gtc_ko@yahoo.com.hk.

© 2006 by the American Diabetes Association.

References

1. Ford ES: Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care* 28:2745–2749, 2005
2. Kahn R, Buse J, Ferrannini E, Stern M: The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 28:2289–2304, 2005
3. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group: The metabolic syndrome: a new worldwide definition. *Lancet* 366:1059–1062, 2005
4. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
5. Ko GTC, Cockram CS, Chow CC, Yeung V, Chan WB, So WY, Chan NN, Chan JCN: Metabolic syndrome by the International Diabetes Federation definition in Hong Kong Chinese. *Diabetes Res Clin Pract* [Epub ahead of print]
6. Eckel RH, Grundy SM, Zimmet PZ: The metabolic syndrome. *Lancet* 365:1415–1428, 2005
7. Ford ES: Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care* 28:1769–1778, 2005