

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.

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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.

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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.

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 Iftar (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-Iftar 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.

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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.

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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-

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.

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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

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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.

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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.

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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.

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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.

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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

