OBSERVATIONS

Birthweight and Risk for Diabetes

Four independent studies, three in the U.S. and one in Norway, have recently examined 254,481 persons to find a relationship between each individual's own birth weight and his or her risk of subsequently developing diabetes (1–4). The first two studies used type 2 diabetes as the sought end point; the second two focused on gestational diabetes. The occurrence of diabetes in a pregnant woman is in itself a marker for a heightened risk of subsequently developing frank diabetes, usually type 2. Table 1 shows the relative risk (RR) of subsequently developing diabetes at or below each designated birth weight; data are shown as RR (95% CI). Birth weights that were originally published in Imperial units have been converted to SI units.

While none of these observations can in themselves answer questions of causation, nonetheless the RR ratios found in the four studies are remarkably uniform and highly predictive.

None of these studies has identified a statistically significant increase in risk associated with birth weight greater than expected, but together they establish beyond all reasonable doubt that being small for gestational age at birth increases one's risk of developing diabetes later in life. Moreover, they suggest that the smaller one begins life, the more likely one will be diabetic at its end.

RICHARD X. DAVEY, MD

From the Pathology Division, Western Hospital, Footscray, Victoria, Australia.

Address correspondence to Dr. Richard X. Davey, Pathology Division, Western Hospital, Gordon Street, Footscray, Victoria 3011 Australia. E-mail: richard.davey@wh.org.au.

Table 1—*Birthweight and risk for diabetes in the given person*

Source	*N*	Sex	Form	Birthweight (g) <2,000	<2,240	2,000–2,499	2,240–2,464	<2,500	2,500–2,999	<3,000	2,464–3,136
Nurses' Study (1)	69,526	Female	DM2		1.83 (1.55–2.16)		1.76 (1.49–2.07)				1.23 (1.11–1.37)
Health Profession Follow-Up Study (2)	22,846	Male	DM2				1.75 (1.21–2.54)				
Norway Women's Study (3)	138,714	Female	GDM					1.8 (1.1–3.0)		1.6 (1.1–2.3)	
New York Women's Study (4)	23,395	Female	GDM	2.16 (1.04–4.50)		1.57 (1.03–2.40)			1.35 (1.02–1.80)		

Data are RR (95% CI). DM2, type 2 diabetes; GDM, gestational diabetes mellitus.

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Significance of Cord-Blood Leptin in Newborns of Diabetic Mothers

Human fetal adipocyte produces leptin. At birth, cord-blood leptin concentration closely correlates with the amount of newborn fat mass. It is suggested that the sexual dimorphism observed in adults already exists in utero. The higher leptin levels in newborns of diabetic mothers (1) compared with the offspring of nondiabetic mothers could reflect increased adipose tissue. It has also been postulated that hypoxic conditions during pre-eclamspsia affect cord-blood leptin (2) and that fetal insulin stimulates fetal adipocyte leptin production (3).

We assessed cord-blood levels of leptin and insulin in 56 neonates born to diabetic mothers (preexisting diabetes $n = 15$, gestational diabetes mellitus [GDM] $n = 41$) and in 25 born to control subjects and investigated whether leptin levels are related to ponderal index (PI), sex, pre-eclampsia, or fetal insulinemia. Leptin assays were performed using radioimmunoassay (Diagnostic Systems, Webster, TX). Inter- and intra-assay variations were 5.3 and 3.7%, respectively. The detection limit was 0.10 ng/ml. The PI, used for nutritional assessment of the neonate, was calculated as body weight (g)/[crown-heel length (cm)]$^3 \times 100$.

Leptin was found to correlate with PI ($r = 0.31$, $P = 0.02$). It was significantly higher in newborns of mothers with preexisting diabetes than in newborns of mothers with GDM or control subjects (median 15 ng/ml, range 9–20.2 vs. median 8.3, range 5–11.3 vs. median 9, range 5.3–16, $P = 0.04$). After adjust-

ment for PI, there was a difference in sex ($P = 0.002$) in newborns of diabetic mothers with higher leptin values in females (median 11.2 ng/ml, range 8.1–20.2) than males (median 7.7, range 4–12). No difference was observed between the absence and presence of maternal pre-eclampsia. Reflecting maternal-hyperglycemia influence on fetal growth, offspring of mothers with preexisting diabetes had higher PI and insulin levels than those of mothers with GDM or control subjects (2.89 ± 0.25 vs. 2.69 ± 0.26 vs. 2.68 ± 0.18, $P = 0.01$, median 17.3 μIU/ml, range 7.1–25 vs. median 4.8, range 2.5–8.5 vs. median 2.5, range 2.5–6.2, $P = 0.001$). Insulin levels correlate strongly to leptin levels independently of PI, but only in the GDM group ($P = 0.014$).

Cord-blood leptin reflects the fetal growth in newborns of diabetic mothers. It appears as a valuable marker of fat mass at birth and allows to quantify even the mild "maternal diabetes effect" on the progeny. Nevertheless, sexual dimorphism already exists in utero and sex could affect leptin level independently of fat mass. The maternal diabetes effect on fetal leptin is likely to arise from fetal insulin overproduction, which subsequently contributes to fat deposition.

Sylvie Hieronimus, MD[1]
Stephanie Bastard, MD[1]
Jean-Yves Gillet, MD[2]
Jean Giudicelli, MD[3]
Françoise Brucker-Davis, MD[1]
Frederic Berthier, MD[4]
Emmanuel Van Obberghen, PHD[5]
Patrick Fenichel, PHD[1]

From the [1]Department of Endocrinology, University Hospital of Nice, Nice, France; the [2]Department of Obstetrics and Gynaecology, University Hospital of Nice, Nice, France; the [3]Department of Clinical Biochemistry, University Hospital of Nice, Nice, France; the [4]Department of Biostatistics, University Hospital of Nice, Nice, France; and the [5]INSERM U-145, School of Medicine, Nice, France.

Address correspondence to Dr. Sylvie Hiéronimus, Department of Endocrinology, Archet Hospital BP 3079 06202 Nice Cedex 3, France. E-mail: hieronimus.s@chu-nice.fr.

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Prevalence of Postprandial Hyperglycemia in Adolescents

A population-based study

Population-based studies determining the prevalence of type 2 diabetes in adolescents are sparse. Therefore, we designed a feasibility population-based study to detect postprandial hyperglycemia, an early manifestation of diabetes, in adolescents.

The study population consisted of all students taking a mandatory sophomore health class at a suburban Chicago high school during the 1998–1999 school year. Those who returned parental consent, student assent, and a parental questionnaire entered the study. Within 90–120 min of completing a standardized lunch (~100 g carbohydrate), students had a capillary blood glucose (CBG) exam for acanthosis nigricans (AN), as well as height and weight measurements. Study was approved by the institutional review board and the school board.

Of 553 students, 284 (51%) enrolled and 255 (90%) completed the study. The ethnic profile of our sample (46% Caucasian, 38% African American, and 6% Hispanic) closely paralleled that of the school. The mean age was 15.9 ± 0.5 years; 53% were female; 38% had a first- or second-degree relative with diabetes; 3% had maternal gestational diabetes; and 27% had BMI ≥85th percentile. Mean CBG was 5.1 ± 0.7 mmol/l.

Postprandial CBG was significantly associated with BMI ≥85th percentile ($P < 0.01$) and a first-degree relative with diabetes ($P = 0.001$). However, these two factors only accounted for 6% of the variation in CBG ($R^2 = 0.06$).

Prevalence of AN in African American, Hispanic, and Caucasian students was 51, 25, and 1%, respectively. AN was significantly associated with a first- or second-degree relative with diabetes ($P = 0.004$), ethnicity ($P < 0.001$), and BMI ≥85th percentile ($P < 0.001$).

No postprandial CBG was ≥7.8 mmol/l. The absence of undiagnosed hyperglycemia is consistent with findings of the Third National Health and Nutrition Examination Survey (2) and speaks against population-based studies. Limiting screening to high-risk individuals may better improve efficacy and feasibility.

Recently Sinha et al. (3) reported the prevalence of impaired glucose tolerance in obese Caucasian and African American adolescents to be 16 and 27%, respectively, and undiagnosed diabetes in African American teens to be 8%. The absence of hyperglycemia in our obese subjects (including 6 Caucasian and 17 African American) may be due to ascertainment bias, given small sample size, or because teens with a postprandial CBG <7.8 mmol/l may still have abnormal glucose tolerance.

Interestingly, our results suggest that a normal but higher CBG is associated with adult risk factors for type 2 diabetes. We propose that subtle abnormalities in glucose homeostasis may present in adolescence and then track with the development of overt abnormalities in adulthood.

Wendy J. Brickman, MD[1]
Julie S. Holland, MD[1]
Bernard L. Silverman, MD[2]

From the [1]Department of Pediatrics, Northwestern University, Evanston, Illinois; and the [2]Department of Medical Affairs, Alkermes, Cambridge, Massachusetts.

Address correspondence to Dr. Wendy Brickman, Children's Memorial Hospital, 2300 Children's Plaza mail code no. 54, Chicago, IL 60091. E-mail: w-brickman@northwestern.edu.

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Porphyromonas gingivalis Infection Is Associated With Elevated C-Reactive Protein in Nonobese Japanese Type 2 Diabetic Subjects

Coronary heart disease (CHD) is the leading cause of death among patients with type 2 diabetes. Several factors were observed to be associated with an increased risk of major manifestations of CHD. Elevated levels of C-reactive protein (CRP), although often in the healthy reference range, have been associated with increased risk of future CHD (1). We hypothesized that periodontal infection might contribute to the elevated CRP in diabetic populations, since periodontal disease has recently been declared the sixth complication of diabetes (2). Serum IgG antibody levels against several periodontal pathogens, especially against *Porphyromonas gingivalis* (*P. gingivalis*), are elevated in chronic adult periodontitis patients and decline with therapy (3). However, a major problem is that the degree of being overweight or of hyperglycemia per se greatly affects CRP levels in type 2 diabetes. To overcome this difficulty, we recruited nonobese well-controlled unique Japanese type 2 diabetic patients who had no evidence of cardiovascular disease, ischemic stroke, hepatic disorders, or chronic renal failure and investigated the association between IgG titer against *P. gingivalis* and CRP level. A total of 131 patients aged 36–84 years were enrolled in the study. The patients were nonobese (BMI >20.0 and <27.0 kg/m^2) and were well controlled in terms of HbA_{1c} (mean HbA_{1c} 7.2%) and blood pressure (BP) (mean BP 130/76 mmHg). All diabetic subjects were treated either with sulfonylureas or with diet alone. None of them received insulin therapy.

No significant correlation was observed between high sensitive CRP value and known risk factors such as triglycerides ($r = 0.108$, $P = 0.108$; Spearman's correlation coefficiency), LDL cholesterol ($r = 0.155$, $P = 0.155$), hyperglycemia (FBS $r = 0.125$, $P = 0.156$; HbA_{1c} $r = 0.153$, $P = 0.152$), and the degree of obesity (BMI) ($r = 0.161$, $P = 0.161$), except for a very weak correlation with total cholesterol ($r = 0.047$, $P = 0.047$). Yet, significant correlations between high sensitive CRP value and IgG titers against *P. gingivalis* FDC 381 (serotype a) and against SU63 (serotype b) were observed ($r = 0.219$, $P < 0.013$ and $r = 0.233$, $P < 0.008$, respectively). Serum IgG titer to *P. gingivalis*, however, did not correlate with lipid abnormalities.

Thus, it is possible that periodontal infection is an independent contributing factor for future cardiovascular events, as recently proposed by others (4). However, there is another possibility that elevated CRP is simply a result of local periodontal infection. In that case, high sensitive CRP may not be a good marker to predict cardiovascular risk. Therefore, we need to undertake a large epidemiological study investigating the relationship between chronic periodontitis and cardiovascular events in such nonobese well-controlled patient populations.

FUSANORI NISHIMURA, DDS[1]
ATARU TANIGUCHI, MD[2]
YOSHIHIRO IWAMOTO, DDS[1]
YOSHIHIKO SOGA, DDS[1]
MITSUO FUKUSHIMA, MD[3]
SHOICHIRO NAGASAKA, MD[4]
YOSHIKATSU NAKAI, MD[5]
YOJI MURAYAMA, DDS[1]

From the [1]Department of Patho-physiology/Periodontal Science, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan; the [2]Division of Diabetes, Kansai-Denryoku Hospital, Osaka, Japan; the [3]Department of Metabolism and Clinical Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, Japan; the [4]Department of Endocrinology and Metabolism, Jichi Medical School, Tochigi, Japan; and the [5]College of Medical Technology, Kyoto University, Kyoto, Japan.

Address correspondence to Fusanori Nishimura, Department of Pathophysiology/Periodontal Science, Okayama University Graduate School of Medicine and Dentistry, 2-5-1 Shikata-cho, Okayama 700-8525, Japan. E-mail: fusanori@md.okayama-u.ac.jp.

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Effect of Sildenafil on Diabetic Gastropathy

Diabetic gastropathy (DG) is the most serious neuromuscular dysfunction of the stomach that may affect diabetic patients. DG is a syndrome of delayed gastric emptying correlated to alterations of gastric tone, contractility, and myoelectrical activity. Gastric dysrhythmias, antral hypomotility, antral dilation, antroduodenal incoordination, and pylorospasm variously relate to DG.

DG pathogenesis is multifactorial: autonomic neuropathy, microangiopathy, and the degenerative impairment of gastric neuromuscular structure are possible mechanisms of gastric dysfunction. Also, the acute increase in blood glucose might reversibly delay gastric emptying (1,2). Gastric dysrhythmias correlate with a disturbance of gastric electrical slow waves (ESWs). ESW rhythm, which is generated by interstitial cells of Cajal, coordinates gastric peristalsis (3,4). Cajal cells, distributed in specific locations within the enteric tunica muscolaris, serve as electrical pacemakers and mediators of neuromuscolar transmission (5).

These cells have close relationships with neurons of myenteric plexus and are specifically responsive to nitric oxide (NO) neurotransmission through the activation of their intracellular cyclic guanosin monophosphate (cGMP), the second messenger of the nitrergic pathway (5,6). Injury or reversible impairment of gastric nitrergic neurons or of Cajal cells may al-

Table 1—*Gastric emptying scintigraphy data from two patients affected by diabetic gastroparesis before and after sildenafil and placebo administration*

	Patient A			Patient B		
	Lag phase (min)	Half time (min)	RA %120	Lag phase (min)	Half time (min)	RA %120
Normal values	<30	88 ± 16	35 ± 10	<30	88 ± 16	35 ± 10
Basal study	45	94	43	90	213	80
Sildenafil	30	67	27	30	68	25
Placebo	30	97	31	30	548	75

Data are means ± SD. RA %120, residual activity at 120 min in percent.

ter nerve-muscle communications. In this sense, reduced NO-dependent neurotransmission might be crucial in the loss of coordinated mechanical smooth muscle response in diabetic patients. Sildenafil, a drug that inhibits phosphodiesterase type 5 (PD-5)-mediated cGMP breakdown, might increase cGMP of Cajal cells when the signal linked to NO is low. It is conceivable that in DG, sildenafil could improve gastric emptying by reversing the loss of nitrergic neurotransmission, as already demonstrated in animal models (7).

We recently observed two patients with DG and evaluated a new therapeutic approach to gastric emptying using sildenafil. Two type 1 diabetic females, aged 45 and 40 years and not pregnant, were hospitalized for acute diabetic gastroparesis with early satiety and postprandial fullness, recurrent nausea, vomiting, and heartburn. A complete laboratory workup evidenced normal complete blood cell count, blood urea nitrogen, creatinine, sodium, and potassium. According to the criteria outlined by Ewing and Clarke, a total score >6 was found as index of autonomic nerve damage (8). A complete gastrointestinal radiographic and endoscopic study ruled out peptic disease or mechanical obstructions. Common prokinetic drugs did not relieve symptoms. After informed consent, both patients were evaluated by gastric scintigraphy to assess a possible therapeutic effect of sildenafil. The gastric emptying scintigraphy was perfomed three times: on the first day, without drugs, to obtain a baseline study and on the second and third days 30 min after the oral administration of two different drugs, sildenafil (50 mg tablets) or placebo (vitamin A), according to a randomization to evaluate the different effects of the drugs on gastric emptying. After an overnight fast, each subject consumed, in 5 min, a solid meal that consisted of a sandwich with two ^{99m}Tc MAA-scrambled eggs (74 MBq) and a glass of water (9). The gastric emptying parameters examined were lag phase, which is defined as when activity first exits the stomach (10), half time in minutes, and residual activity at 120 min in percent. The improvement of gastring emptying parameters was only observed after sildenafil administration (Table 1).

Our data seem to confirm the involvement of nitrergic gastric neurotransmission in DG. It would be interesting to further evaluate PD-5 inhibitors as a new therapeutic approach to diabetic gastroparesis.

ALESSANDRO BIANCO, MD[1]
DARIO PITOCCO, MD[1]
VENANZIO VALENZA, MD[2]
SALVATORE CAPUTO, MD[1]
ANT GRIECO, MD[1]
LUCA MIELE, MD[1]
ALDO VIRGILIO GRECO, MD[1]
GIOVANNI GHIRLANDA, MD[1]

From [1]Medicina Interna, Università Cattolica, Rome, Italy; and [2]Medicina Nucleare, Università Cattolica, Rome, Italy.

Address correspondence to Giovanni Ghirlanda, Servizio di Diabetologia Università, Cattolica del Sacro, Cuore, Largo A. Gemelli 00168, Roma, Italy. E-mail: gghirlanda@rm.unicatt.it.

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Insulin Glargine in Continuous Enteric Tube Feeding

In comparison with the traditional long-acting insulins, i.e., NPH and Ultralente (1–3), insulin glargine, a novel insulin analogue has been documented to decrease the number of hypoglycemic episodes while achieving an adequate glycemic control. The decline in hypoglycemic events, especially nocturnal, is attributed to the ability of insulin glargine to attain a steady-state plasma insulin concentration without a peak for ~24 h on a subcutaneous (SC) administration of a single dose (4). Therefore, insulin glargine may achieve an effect similar to that obtained by continuous intravenous (IV) or SC infusion of regular insulin in subjects requiring continuous enteral or parenteral alimentation. However, documentation of the use of glargine in similar circumstances is lacking. In this article, we studied a subject in whom insulin glargine monotherapy attained and maintained desirable glycemic control while receiving continuous enteral feeding.

R.A., a 60-year-old white man with type 2 diabetes of 2 years' duration, underwent radical surgery and was receiving radiation therapy for management of a squammous cell carcinoma of the oral cavity. Postoperatively, he manifested recurrent aspiration on several attempts at oral feeding and therefore was being administered continuous enteral tube feeding. His HbA_{1c} before surgery was 7.5% with capillary blood glucose recordings between 180 and 250 mg/dl (10–14 mmol/l). It was determined that the subject would require enteral nutritional support for a prolonged period of time, even after discharge from the hospital within a week after surgery. Therefore, due to ease of administration, SC insulin glargine was initiated with 24 units at 9:00 P.M. instead of continuous IV or SC infusion administration. The dose of insulin glargine was gradually increased by 2–4 units at intervals of 3 days (even at home via telephone counseling) to attain blood sugars between 100 and 140 mg/dl (5.6–7.8 mmol/l) determined at 6-h intervals. Within 3 weeks, the optimal glycemic control, between 80 and 140 mg/dl, as reflected by most home blood glucose readings, was achieved with 45 units insulin glargine. There was not a single hypoglycemic event during the period. The same insulin dose continued for the next 3 months while monitoring blood glucose levels. The maintenance of optimal glycemic control was further confirmed by an HbA_{1c} concentration of 6.1% at 6 months.

This case study illustrates that SC administration of insulin glargine is able to attain and maintain desirable glycemic control in subjects who require continuous enteral (or parenteral) alimentation without inducement of hypoglycemia. This beneficial effect could be attributed to its unique profile of achieving steady, peakless insulin concentrations. Therefore, it could replace IV or SC continuous infusion of regular insulin during hospitalization, especially on the general ward, and at home because of its ease of administration and convenience.

DARCY PUTZ, MD
UDAYA M. KABADI, MD

From the Division of Endocrinology, University of Iowa, Roy J. and Lucille A. Carver College of Medicine, Iowa City, Iowa.

Address correspondence to Udaya M. Kabadi, Professor of Medicine, Division of Endocrinology, University of Iowa Hospitals and Clinics, 6W27 VAMC, 601 U.S. Highway 6, Iowa City, IA 52246. E-mail: udaya-kabadi@uiowa.edu.

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Diabetes and ST Elevation Myocardial Infarction

How successful is intravenous thrombolysis for the diabetic heart?

Early resolution of ST-segment elevation is associated with enhanced clinical outcome following ST elevation myocardial infarction (STEMI). According to previous studies, the incidence of successful reperfusion following STEMI treated with thrombolytic regimen is similar for type 2 diabetic subjects and nondiabetic subjects as assessed by "snapshot" electrocardiographic or angiographic criteria (1). Nevertheless, type 2 diabetic subjects thrombolysed because of STEMI still seem to fare worse, manifesting impaired left ventricular function or long-term prognosis (2).

The aim of this prospective study was to test the hypothesis that type 2 diabetic subjects may have a protracted ST-segment recovery, even while achieving reperfusion criteria, compared with nondiabetic subjects. Therefore, continuous ST-segment monitoring was used, as it is considered to be more reflective not only of infarct-related artery patency status, but of actual tissue reperfusion (3).

The study cohort included 137 patients with STEMI: 105 nondiabetic subjects and 32 type 2 diabetic subjects (age 58.9 ± 10.3 vs. 67.5 ± 7.1 years, respectively; $P < 0.001$) without history of prior myocardial infarction or coronary artery bypass surgery. Each patient received either streptokinase or tissue-type plasminogen activator (t-PA) in ≤6 h from index pain and was connected to the Eagle 4000 Monitor immediately after admission. All patients integrated to this study attained the criterion of steady ≥50% ST-segment recovery within 90 min after thrombolysis initiation. Significant differences in the two groups were not found concerning time elapsed from index pain to initiation of thrombolytic procedure, location of STEMI, or thrombolytic agents used.

The time required for ≥50% ST-segment steady resolution was significantly greater in type 2 diabetic subjects than in nondiabetic subjects (68.8 ± 15 vs. 45.8 ± 17.9; $P < 0.001$). Moreover, the former had higher subsequent peak creatin kinase myocardial type B isoenzyme release than the latter ($P < 0.001$). According to multivariate linear regression analysis, type 2 diabetic subjects were independently and positively related to the time for ≥50% ST-segment recovery ($P < 0.001$).

In accordance to the original hypothesis, the present study showed that type 2 diabetic subjects required almost 50% more time to achieve satisfactory ST-segment elevation recovery. The diminished benefit from thrombolysis may be attributed to several diabetes-induced disorders from diffuse coronary artery disease, metabolic derangements, complexity of the culprit atheromatic plaque, microangiopathy including endothelial dysfunction, and diminished flow reserve, to impaired glucose utilization and accumulation of fatty acid intermediates (4). The results of the present study imply that the retardation in achievement of satisfactory reperfusion in the myocardial cells, as assessed by ST-segment elevation resolution, may at least partially account for the subsequent detrimental effect on

diabetic hearts when suffering STEMI. If these findings are validated with larger studies, a more aggressive therapeutic approach might prove suitable for type 2 diabetic subjects with STEMI.

MICHAEL N. ZAIRIS, MD
STAMATIS S. MAKRYGIANNIS, MD
OLGA A. PAPADAKI, MD
ANASTASSIOS G. LYRAS, MD
JOHN P. KOUZANIDIS, MD
OLGA S. AMPARTZIDOU, MD
STELIOS M. HANDANIS, MD
SPYROS M. ARGYRAKIS, MD
STEFANOS G. FOUSSAS, MD, FESC, FACC

From the Department of Cardiology, Tzanio Hospital, Piraeus, Greece.

Address correspondence to Dr. Michael N. Zairis, Alkiviadou Str 273, Piraeus, Greece. E-mail: zairis@hellasnet.gr.

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A New Index of Insulin Sensitivity Obtained From the Oral Glucose Tolerance Test Applicable to Advanced Type 2 Diabetes

Matthews et al. (1) demonstrated that the homeostasis model assessment of insulin resistance (HOMA-IR) is closely correlated with the insulin sensitivity index assessed by euglycemic clamp in only a few patients with type 2 diabetes. Emoto et al. (2) and Bonora et al. (3) also reported that HOMA-IR provided a good correlation in the clamp studies in a relatively greater number of diabetic subjects. However, it has been recognized among some investigators that the HOMA-IR shows relatively low value when the insulin secretion decreases in patients with advanced type 2 diabetes, because the HOMA-IR is a product of fasting glucose and insulin levels. On the other hand, several investigators have recently proposed methods to assess insulin sensitivity using an oral glucose tolerance test (OGTT). Stumvoll et al. (4) disclosed that the OGTT can assess insulin sensitivity in nondiabetic subjects. Even in type 2 diabetes, an index proposed by Matsuda and DeFronzo (5) was correlated to clamp-derived insulin sensitivity. Although these parameters from the OGTT decrease with worsening of glucose tolerance, the values inversely increase once the total insulin secretion declined. They have not been fully validated in Japanese subjects, especially in various grades of type 2 diabetes. In this study, we proposed a new index from the results of the OGTT and compared them with the *M*-value obtained from the clamp method.

We studied 113 Japanese subjects (72 men and 41 women; aged 35–79 years, mean 58.9 years; BMI 16.2–32.0 kg/m^2, mean 24.1 kg/m^2) with varying degrees of glucose tolerance. The subjects underwent a euglycemic clamp study and a 75-g OGTT. Subjects were divided into five groups: *1*) normal glucose tolerance (NGT), $n = 42$; *2*) impaired glucose tolerance (IGT), $n = 26$; *3*) type 2 diabetes with normal fasting plasma glucose (FPG <110 mg/dl) (DM-NFG), $n = 13$; *4*) type 2 diabetes with impaired fasting plasma glucose (FPG 110–125 mg/dl) (DM-IFG), $n = 18$; and *5*) type 2 diabetes with diabetic fasting plasma glucose (FPG ≥ 126 mg/dl) (DM-DFG), $n = 14$. None of the patients were treated with insulin or oral antidiabetic drugs. Insulin sensitivity was measured by the euglycemic-hyperinsulinemic glucose clamp technique using an artificial pancreas (Model STG-22; Nikkiso, Tokyo) and expressed as the *M*-value. A standard 75-g OGTT was performed; plasma samples for glucose and insulin were obtained at 0, 30, 60, 90, 120, and 180 min after the glucose load. Insulin sensitivity was assessed as the insulin sensitivity index (ISI) calculated using the OGTT values by three previously proposed formulas. The first index, proposed by Matsuda and DeFronzo (5), was calculated as follows:

$$\text{ISI-M} = 100{,}000 / \sqrt{([\text{0-min PG} \times \text{0-min IRI}] \times [\text{mean PG} \times \text{mean IRI}])} \quad (1)$$

The second index, proposed by Stumvoll et al. (4), was calculated as follows:

$$\text{ISI-S} = 0.226 - 0.0032 \times \text{BMI} - 0.0000645 \times \text{120-min IRI} - 0.00375 \times \text{90-min PG} \quad (2)$$

The third index, proposed by Gutt et al. (6), was calculated as follows:

$$\text{ISI-G} = m/(\text{0-min PG} + \text{120-min PG}) \times 0.5/\log(\text{0-min IRI} + \text{120-min IRI} \times 0.5) \quad (3)$$

where m is the glucose uptake rate in peripheral tissues, calculated as m = (75,000 mg + [0-min PG − 120-min PG] × 0.19 × body weight)/120 min. This study was performed in accordance with the Helsinki Declaration, and written informed consent was obtained from each participant.

In the present study, the *M*-value decreased linearly with worsening of glucose tolerance (NGT, 7.71 ± 1.86 mg · kg^{-1} · min^{-1}; IGT, 5.15 ± 1.55 mg · kg^{-1} · min^{-1}; DM-NFG, 3.22 ± 0.80 mg · kg^{-1} · min^{-1}; DM-IFG, 2.73 ± 0.73 mg · kg^{-1} · min^{-1}; and DM-DFG, 2.51 ± 0.63 mg · kg^{-1} · min^{-1}; $r = -0.804$, $P < 0.0001$, by Spearman's correlation test). To search a new index of insulin sensitivity, stepwise multiple regression analysis was performed with the *M*-value as the dependent variable and glucose and insulin concentrations during the OGTT as the independent variables. The multiple regression analysis yielded the following equation ($R^2 = 0.581$, $P < 0.0001$):

$$\text{ISI-K} = 13.192 - 0.712 \times \text{0-min PG} - 0.341 \times \text{120-min PG} + 0.002 \times \text{30-min IRI} - 0.003 \times \text{90-min IRI} \quad (4)$$

The *M*-value was best correlated with the ISI-K ($r = 0.762$, $P < 0.0001$), followed by the ISI-G ($r = 0.692$, $P < 0.001$), the ISI-S ($r = 0.559$, $P < 0.001$), the ISI-M

Table—*Insulin secretion and insulin sensitivity in various degrees of glucose tolerance*

	NGT	IGT	DM-NFG	DM-IFG	DM-DFG	*P**
AUC (insulin)	744 ± 359	927 ± 508†	916 ± 527‡	769 ± 479	579 ± 356§‖	0.0307
HOMA-IR	1.62 ± 0.95	1.96 ± 1.23†	1.97 ± 1.27‡	2.52 ± 1.48§‖	2.26 ± 1.36†	0.1101
ISI-M	6.91 ± 3.38	5.43 ± 2.92†	5.75 ± 4.42‡	4.82 ± 2.81†	5.25 ± 2.75‡	0.5032
ISI-S	0.108 ± 0.017	0.082 ± 0.025†	0.064 ± 0.022†§	0.071 ± 0.022†§	0.072 ± 0.022†§	0.1283
ISI-G	83.2 ± 21.6	53.0 ± 12.3†	35.7 ± 8.4†§	37.1 ± 9.8†§	37.8 ± 12.1†¶	0.2856
ISI-K	7.04 ± 0.77	5.51 ± 0.88†	4.06 ± 0.93†§	3.42 ± 0.92†§¶	2.37 ± 1.51†§‖#	<0.0001

Data are mean ± SD. *P is the significant correlation among the three diabetic groups (DM-NFG, DM-IFG, and DM-DFG) by Spearman's correlation test. †$P < 0.01$, ‡$P < 0.05$ vs. NGT; §$P < 0.01$ vs. IGT; ‖$P < 0.01$, ¶$P < 0.05$ vs. DM-NFG; #$P < 0.05$ vs. DM-IFG. ISI-G, insulin sensitivity index proposed by Gutt et al.; ISI-K, insulin sensitivity index proposed by Kanauchi; ISI-M, insulin sensitivity index proposed by Matsuda et al.; ISI-S, insulin sensitivity index proposed by Stumvoll et al.

($r = 0.214$, $P = 0.023$), and HOMA-IR ($r = -0.257$, $P = 0.006$). Furthermore, we adapted the ISI-K to a large number of subjects with various degrees of glucose intolerance. A series of 551 subjects underwent a 75-g OGTT and were divided into five groups: *1*) NGT, $n = 238$; *2*) IGT, $n = 211$; *3*) DM-NFG, $n = 40$; *4*) DM-IFG, $n = 34$; and *5*) DM-DFG, $n = 28$. The present study showed that the area under the curve (insulin) decreased linearly with a progression of diabetes (from DM-NFG to DM-IFG to DM-DFG), whereas HOMA-IR showed an inverted U-shape relationship (Table). It is possible that the apparent lower HOMA-IR in subjects with advanced type 2 diabetes might be explained by the β-cell failure and insulin deficiency. The ISI-M also showed a U-shape relationship, and both the ISI-S and ISI-G increased linearly with a progression of diabetes, but only the ISI-K significantly decreased (Table). In Japanese subjects, the total insulin secretion during OGTT increased until the FPG level reached 110 mg/dl, but decreased after the inflection point (7). It has been recognized that the compensatory function of the pancreatic β-cell in Japanese subjects is lower than that observed in Caucasian subjects. Ethnic differences may be a factor that determines the role of decreased insulin secretion (8). In conclusion, this equation (ISI-K) may be applicable to even type 2 diabetic Japanese subjects, who are often hypoinsulinemic.

MASAO KANAUCHI, MD, PHD

From the First Department of Internal Medicine, Nara Medical University, Kashihara, Nara, Japan.

Address correspondence to Dr. Masao Kanauchi, First Department of Internal Medicine, Nara Medical University, 840, Shijo-cho, Kashihara, Nara 634-0813, Japan. E-mail: kanauchi@nmu-gw.naramed-u.ac.jp.

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Use of an Oxidized Regenerated Cellulose and Collagen Composite for Healing of Chronic Diabetic Foot Ulcers

A report of two cases

Ulcers of lower extremities are often resistant to therapy in diabetic patients. It has recently been reported that the activity of proteases is crucial in wound repair (1), but excessive protease activity can damage granulation tissue, delaying healing. It is noteworthy that protease activity is elevated in fluid from chronic, nonhealing wounds (1).

A recently described protease inactivator matrix (Promogram; Johnson & Johnson, Skipton, U.K.), composed of oxidized regenerated cellulose and collagen, has been shown to reduce elastase, plasmin, and metalloproteinase activity in chronic wound fluids of diabetic patients, stimulating wound repair process (1,2). Both of the components of this matrix, oxidized cellulose (3) and collagen (4), have been reported to accelerate the healing of diabetic foot ulcers.

We assessed the effects of this matrix in two diabetic patients with chronic foot ulcers. G.C., a 76-year-old man with a BMI of 34.9 kg/m^2, type 2 diabetes of 26-year duration, and a previous myocardial infarction, was treated with metformin 2,550 mg/day. HbA_{1c} was 7.5% (upper limit of normal 6.2%). The patient was also affected by hypertension (treated with enalapril and amlodipine) and untreated hypertriglicerydemia and hypercholesterolemia. The patient showed microalbuminuria, with normal creatinine levels, chronic neuropathy with increased vibratory perception threshold bilaterally, peripheral vascular disease (Winsor Index [ankle/arm blood pressure ratio] = 0.75 bilaterally) and a neuroischemic ulcer (3 cm × 4 cm; Wagner grade I) in the plantar region of the right foot. No dry necrolytic tissue was present, and granulation tissue was clearly detectable. Cultural examination of wound fluid did not identify any microorganism, and X-ray was negative for osteomyelitis. Despite standard wound care (surgery curettage and advanced medications) for 24 weeks, the lower-limb lesion did not show any relevant improvement. The matrix was applied twice a week, after the application of polyuretanic foam and hydrobenda. Improvement was noticeable after 3 weeks, with increase of granulation tissue and reduction of wound area. Healing was complete within 5 weeks from the beginning of treatment.

G.I., a 68-year-old woman, was affected by type 2 diabetes with a duration of disease 22 years; her BMI was 25.6 kg/m^2. G.I. was treated with insulin (50 units/day in four administrations), with an HbA_{1c} of 8.0%. She showed signs of neuropathy, with increased vibratory perception thresholds, and peripheral vascular disease (Winsor Index [ankle/arm blood pressure ratio] = 0.70 bilaterally). The patient also reported suboptimally controlled hypertension, chronic renal failure, chronic heart failure, and diabetic retinopathy. She showed an ulcer of the plantar region of the left foot (5 cm × 6 cm) with extensive necrosis, which was surgically removed. Staphylococcus α-hemolytic, *Candida* nonalbicans, and unidentified anaerobial bacteria were isolated from the lesion. For this reason, general treatment with teicoplanin, imipenem, and fluconazole was undertaken, and the infection eradicated within 3 weeks. An X-ray examination of the right foot did not show any sign of osteomyelitis. Despite standard wound care for 40 weeks, the lesion did not heal, although granulation tissue was present. Treatment with oxidized regenerated cellulose and collagen matrix twice a week, after the application of polyuretanic foam and hydrobenda, resulted in a complete healing within 12 weeks.

These two cases suggest that patients suffering from chronic wounds with delayed healing could benefit from this novel treatment, although randomized controlled trials specifically directed at diabetic patients with nonhealing foot ulcers of long duration are needed.

MATTEO MONAMI, MD
EDOARDO MANNUCCI, MD
MASOTTI GIULIO, MD

From the Department of Critical Care Medicine and Surgery, Unit of Gerontology and Geriatrics, University of Florence, Florence, Italy.

Address correspondence to Matteo Monami, Department of Critical Care Medicine and Surgery, Unit of Gerontology and Geriatrics, University of Florence and Azienda Ospedaliera Careggi, Via delle Oblate 4, 50139 Florence, Italy. E-mail: mmonami@libero.it.

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Assessing the Impact of Diabetes Screening on Quality of Life or Quality of Health?

Semantics are important

Edelman et al. (1) do not, as their title indicates, measure the "impact of screening on quality of life," but rather they measure the effect of screening on health status. Their premise is that it is unclear whether being diagnosed with diabetes might have a potentially detrimental "labeling" effect or whether treatment of previously unrecognized symptoms might improve health-related quality of life (HRQoL). Many important studies, including the U.K. Prospective Diabetes Study (UKPDS) (2), have mistakenly assumed that health status, HRQoL, and quality of life (QoL) are interchangeable terms. However, confusing terminology leads to misinterpreted data and misleading conclusions and titles.

Throughout their article, Edelman et al. recognize the 36-Item Short-Form Health Survey (SF-36) (3) as a health status measure. However, the assumption that health status is synonymous with HRQoL flaws their interpretation. This culminates in their ill-advised conclusion that "early HRQoL changes might not have to be considered in the complex calculations that underlie the decision to undertake or not undertake mass screening for diabetes." From the data presented, it is only evident that changes in perceived health status might not have to be considered.

Bradley (4) has provided a useful commentary on the "importance of differentiating health status from quality of life." Impaired health or well-being may lead to, or be experienced at the same time as impaired quality of life—but not necessarily. Furthermore, excellent health does not infer excellent quality of life. Ware and Sherbourne (3) describe the SF-36 as a health survey but many others treat it, erroneously, as a measure of quality of life.

It is widely acknowledged that the psychological impact of screening for diabetes can vary among individuals, reassuring some and increasing anxiety in

others, although initial distress often wanes over time (5). A more accurate interpretation of the data by Edelman et al. indicates that physical health (measured by the Physical Component Scale) was not affected by undiagnosed diabetes at baseline or by diagnosed diabetes 1 year later. This is unsurprising given that, as the authors acknowledge, complications (which have not been developed yet) and comorbidity are primary determinants of SF-36 scores. However, the controversy regarding screening lies in its impact on mental health, which, in this study, was not affected by undiagnosed diabetes at baseline or by diagnosed diabetes 1 year later. Analysis of the subscales contributing to the Mental Component Scale might provide further insight. "Vitality" might be improved as a result of treating previously undiagnosed symptoms, but improvements might be hidden by deterioration in other subscales, e.g., "mental health."

Edelman et al. present an interesting article about the effects of diabetes screening on health status and discuss several limitations of their study. However, the major criticism of the article concerns their misinterpretation of the data due to the use of misconstrued terminology. Their misleading use of terminology suggests that they have measured the impact of screening on quality of life; in actuality, however, they have only measured the impact of screening on quality of health.

JANE SPEIGHT, MSC

From Health Psychology Research, the Department of Psychology, Royal Holloway, University of London Correspondence, Egham, Surrey, U.K.

Address correspondence to Jane Speight, MSc, Health Psychology Research, Department of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, U.K. E-mail: j.speight@rhul.ac.uk.

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A Case of Fulminant Type 1 Diabetes With Graves' Disease

Type 1 diabetes is now classified as classic autoimmune (type 1A) and idiopathic (type 1B) diabetes. Fulminant type 1 diabetes was recently characterized as a novel subtype of type 1B diabetes. This disease was characterized as rapid onset, having an absence of diabetes-related autoantibodies, and having the presence of lymphocyte infiltration in exocrine pancreatic tissue without insulitis (1–3). Although fulminant type 1 diabetes has been clinically recognized, its etiology still remains obscure. In this article, we report a case of fulminant type 1 diabetes developed during pregnancy with manifested Graves' disease, which was developed 1 year after onset of diabetes.

A 28-year-old female was admitted to the hospital with diabetic ketoacidosis. She was 27 weeks pregnant and presented no symptom of preceding infection. After admission, she became comatose. Her arterial pH was 6.988 and she had marked elevation of ketone bodies. Her plasma glucose was 43.8 mmol/l; however, her HbA_{1c} was 4.8%. Serum C-peptide was under the detection limit (<0.03 ng/ml), and urinary C-peptide was 0.86 μg/day. There was no response to a glucagon C-peptide stimulation test. Autoantibodies to the cytoplasm of islet, GAD, insulin, and tyrosine phosphate-like protein (IA-2) were all negative. Her serum amylase was 267 IU/l. Both her serum lipase and elastase 1 levels were elevated 55 IU/l and 1,200 ng/dl, respectively. These findings were consistent with symptoms of fulminant type 1 diabetes. Her fetus died, and artificial abortion was performed. The fetus had no superficial abnormality. The subject had HLA-DRB1*0101/*0901, DQB1-*0612/*0306, A2/A24 (9), B7/B61 (40), and Cw7. She was in a euthyroid state, and autoantibodies to the thyroid were negative at that time.

After 1 year she presented overt thyrotoxic symptoms such as hyperhydrosis, palpitation, finger tremor, and poor glycemic control. Her thyroid hormones were elevated, and the thyroid-stimulating hormone receptor antibody was positive. She was diagnosed with Graves' disease and administered propylthiouracil. Her glycemic control was fair with continuous subcutaneous insulin infusion. Diabetes-related autoantibodies were still negative, and her intrinsic insulin secretion was scant. Like a previous short report (4), our case had immunogenetic characteristics of an autoimmune disease except for endocrine pancreas. We often observed classic type 1A diabetes associated with autoimmune thyroid disease. This case was unique in that diabetes developed during pregnancy and was complicated with autoimmune disease. This case may help clarify the etiology of this disease entity.

YOSHITAKA MIURA, MD
ATSUSHI SUZUKI, MD
IKUKO SATO, MD
YOKO KATO, MD
YUTAKA OISO, MD

From the First Department of Internal Medicine, Nagoya University School of Medicine, Nagoya, Japan.

Address correspondence to Yoshitaka Miura, First Department of Internal Medicine, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550 Japan, E-mail: ymiura64@med.nagoya-u.ac.jp.

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Diabetic Muscle Infarction

Myocardial infarct equivalent

Diabetic muscle infarction (DMI) is a serious complication seen in patients with long-standing diabetes. Evidence is accumulating since the first description of this entity in 1965 (1). Increasing awareness has led to prompt recognition of this previously underdiagnosed condition. Typically, acute presentation with atraumatic painful swelling, notably of the quadriceps or thigh muscles, is found in diabetic subjects with established vasculopathy including retinopathy and nephropathy. Laboratory investigations generally show high erythrocyte sedimentation rate, normal white cell count, and normal or mild elevation of creatine phosphokinase. Magnetic resonance imaging (MRI) findings are invariably characterized by increased signal intensity of the diffusely enlarged muscle groups on T2-weighted sequences, inversion-recovery, and gadolinium-enhanced images (2–4). The disease is generally believed to be self-limiting, although recurrence can occur in half of the cases (4,5).

We have previously reported two cases of diabetic muscle infarction in our dialysis population (6). Over the last 2 years, we encountered six patients who had confirmed diabetic muscle infarction. Half of them were males. The vast majority of subjects were in their forties, with a mean age of 43.5 ± 6.5 years. All cases had established complications of diabetic nephropathy and retinopathy. Of the six patients, five had reached end-stage renal disease, with average duration of dialysis for 17 months. Only one had angiographic evidence or symptoms suggestive of coronary artery disease. When we examined the survival outcome in temporal relationship to the onset of diabetic muscle infarct, there appeared to be an early hazard of death of all causes related to this particular complication. Of the original six patients, three had succumbed after a median follow-up of 10 months (range 2–20 months). No fatality was directly related to diabetic muscle infarct. One death was related to cardiac ischemia and the other two were attributed to infection. The estimated 1-year survival for the cohort was 55%, as compared with 58% in patients with ischemic heart disease and 75% for those without history of coronary heart disease or diabetic muscle infarct among our dialyzed diabetic populations. The low survival figure of the muscle infarct group is surprisingly comparable to the overall mortality of 59% at 1 year after acute myocardial infarction among (diabetic and nondiabetic) patients on long-term dialysis (7).

Interestingly, our findings coincide with another series of six patients with diabetic muscle infarct, in which five subjects died after being followed-up for at least 4 years (8). The abysmal prognosis or survival outcomes of patients with diabetic muscle complications were also similar to that of the diabetic population after an acute myocardial infarction episode. In general, the chance of diabetic patients being alive 1 year after myocardial infarct was 47% (9).

In other words, skeletal muscle infarction in a diabetic population has similar prognosis as compared with myocardial infarct. It should be pointed out that, although the two conditions have similar prognosis, they are probably mediated by different vascular events. The former is related to major coronary arterial occlusive disease while diabetic skeletal muscle infarction is believed to involve microvasculature and ischemia reperfusion injury (5,6,8). Nevertheless, both disease processes signify considerable vascular disease and systemic inflammation. Elevation of erythrocyte sedimentation rate in many cases of diabetic muscle infarction does support the presence of an inflammatory reaction (4), although it remains unclear whether this is a primary event or a consequence of muscle infarction and necrosis.

From our preliminary findings and others (8), we have shown that DMI is a catastrophic event associated with dismal long-term survival. Current data support a link with inflammation, but the association between DMI and poor long-term survival has yet to be elucidated. Alternatively, DMI indicates a very late stage of terminal diabetic complication. This may represent a new paradigm for prognostic stratification of diabetic patients based on the presence of microangiopathy. It remains unknown whether therapeutic measures that are effective in improving the prognosis of patients after acute myocardial infarction, aspirin for example, would be equally useful in diabetic muscle infarction.

Kai Ming Chow, mrcp[1]
Cheuk ChunSzeto, mrcp, md[1]
Teresa Yuk-hwa Wong, mrcp[1]
Franky Kay-tai Leung, mrcp[2]
Au Cheuk, mrcp[3]
Philip Kam-tao Li, frcp, facp[1]

From the [1]Department of Medicine & Therapeutics, Prince of Wales Hospital, the Chinese University of Hong Kong, Shatin, Hong Kong, SAR, China; the [2]Department of Medicine & Geriatrics, Tuen Mun Hospital, Tuen Mun, Hong Kong, SAR, China; and the [3]Department of Medicine & Geriatrics, Princess Margaret Hospital, Hong Kong, SAR, China.

Address correspondence to Dr. C.C. Szeto, Department of Medicine and Therapeutics, the Chinese University of Hong, Kong, Prince of Wales Hospital, Shatin, Hong Kong. E-mail: ccszeto@cuhk.edu.hk.

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Pancreas Transplantation for Type 2 Diabetes at U.S. Transplant Centers

Pancreas transplantation, the most effective method of normalizing glucose control in type 1 diabetes, is not commonly used in type 2 diabetes, although patient and graft survival rates are equivalent (1). We conducted a mail survey of American transplant programs on 15 September 2000 characterizing the approach to pancreas transplantation in type 2 diabetic end-stage renal disease (ESRD) patients.

A total of 44 (30.3%) centers responded. The mean center-specific cumulative volume was 70 ± 227 cases (0–1,300), with a total of 6,014 procedures. The collective experience of 872 cases in 1999 represents 71% of the 1,237 American pancreas transplants reported to the United Network for Organ Sharing.

Diabetes is classified at more programs (86% [38/44]) than renal transplantation (63.6% [28/44]). Of pancreas recipients in 1999, 1.8% (16/872) had type 2 diabetes; they were intentionally selected (87.5% [14/16]).

Age, associated with declining tissue strength and healing potential, and obesity, linked with increased anesthetic problems and wound failure, are key features of type 2 diabetes. The median age of 64 years for incident ESRD patients compels transplant consideration, even when life expectancy is shorter than that of an allograft. Advanced age absolutely precludes renal transplantation at only 3 of 44 (6.8%) centers and relatively at 28 of 44 (63.6%). For pancreas candidates, 14 of 44 (31.8%) centers view advanced age as an absolute contraindication and 35 of 44 (79.5%) as one that is relative. A few centers proffer either procedure to patients of virtually any age, but at all ages, there is a consistently lower acceptance rate for pancreas versus renal candidates. A 65-year-old candidate would be placed on the pancreas waiting list at only 14% (6/44) of centers, and even a 55-year-old candidate would be declined at 27% (12/44). Nine of 44 (22.7%) centers considered obesity an absolute contraindication to renal transplantation compared with 8 of 44 (18.2%) for pancreas transplantation, and a total of 32 of 44 (72.7%) centers considered obesity a relative contraindication for kidney transplantation compared with 39 of 44 (88.6%) for pancreas transplantation.

Pancreas transplantation is not immediately life saving. Few donors are available, and the use of less-than-ideal allografts is generally deferred. Candidate selection is similarly restrained. Currently representing 78% of incident diabetic ESRD patients in the U.S., type 2 diabetic patients are older (median age 65 vs. 54 years), less likely to undergo even renal transplantation (2% vs. 9%), and more likely to die (23% vs. 18%) than those with type 1 diabetes (2). Selection policies for pancreas transplantation corroborate a conservative approach that excludes most type 2 diabetic patients. This judicious strategy likely accounts for the small but encouraging results reported and seems unlikely to change without augmentation of the supply of good-quality cadaver donors.

Amy L. Friedman, MD[1]
Eli A. Friedman, MD[2]

From the [1]Department of Surgery, Section of Organ Transplantation and Immunology, Yale University School of Medicine, New Haven, Connecticut; and the [2]Department of Internal Medicine, Division of Nephrology, State University of New York Health Science Center at Brooklyn, Brooklyn, New York.

Address correspondence to Amy L. Friedman, MD, Department of Surgery, Yale University School of Medicine, FMB 112, 333 Cedar St., New Haven, CT 06520. E-mail: amy.friedman@yale.edu.

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HbA_{1c} and Glycemic Profile, Basal- and Post-Treatment With Miglitol, in an Area With a Mediterranean Diet

HbA_{1c} is the main indicator in the metabolic control of diabetic patients. It it has been used as a guide in therapeutic intervention studies on type 1 diabetic patients, as in the Diabetes Control and Complications Trial (1), and type 2 diabetic patients, as in the U.K. Prospective Diabetes Study (2). These studies have shown that an HbA_{1c} decrease is followed by a reduction in the appearance of microvascular and neuropathic complications. The relative impact of fasting glycemia and the glycemic levels at other times of the day on the HbA_{1c} value is therefore of considerable interest when trying to increase control at the times of the day when this impact is at its highest level. Fasting glycemia has traditionally been considered the main HbA_{1c} marker (3–6). Recently, however, the validity of this has been questioned (7),and it has even been suggested that the main marker is the postprandial glycemic level (8). On the other hand, postprandial glycemia has been described as being more related to the development of macroangiopathy than fasting glycemia (9,10), which increases interest in its relative contribution to the HbA_{1c} value.

We carried out an observational, prospective, open, nonrandomized, multicenter study comprised of 3,354 recently diagnosed (at least 3 months) patients with type 2 diabetes. Our aim was to identify the impact of glycemia (fasting and at other times of the day) on the HbA_{1c} values in a Spanish type 2 diabetic population, with typical Mediterranean nutritional habits, who were being treated with different types of oral antidiabetic drugs, before and after treatment with miglitol, a drug that basically controls postprandial glucose absorption. All patients were treated with diet and either oral antidiabetic drugs (74%) or insulin (19%), and were considered to be noncontrolled according to the European Diabetes Policy Group criteria. Patients were excluded if they were <40 years of age, pregnant or breast-feeding, or had

type 1 diabetes or diabetes secondary to pancreatopathy, a BMI <25 kg/m^2 with clinical decompensation (fasting glycemia >250 mg/dl or ketosis), serum creatinine >150 mmol/l, gastrointestinal disease, and comprehension difficulties that could prevent collaboration.

In each case, we recorded the anthropometric data and basal HbA_{1c} (high-performance liquid chromatography) together with a capillary glycemia profile at four times (fasting glycemia at 8 h, preprandial glycemia at 14 h, postprandial glycemia at 15 h, and late postprandial glycemia at 19 h) on or around the same day as the HbA_{1c} reading, for which Glucocard/Glucocard Memory was administered. The patients were specifically asked not to make significant changes to their diet, physical activity, or pharmacological treatment on the day the analyses were taken. Treatment with miglitol was then started, as follows: 1st week 50 mg/day, 2nd week 100 mg/day in two doses, 3rd week 150 mg/day in three doses, and finally a maintenance dose of 300 mg/day in three doses. Analyses of the same characteristics were taken after 12 months of treatment. Linear and multiple regression analyses were applied to the data to examine the relation between the glycemic profile parameters and the HbA_{1c} at each time. The multiple regression analysis provided the standardized partial regression coefficients of each variable for comparative purposes. A receiver-operating characteristic curve analysis provided the sensitivity, specificity, and positive predictive value of the glycemic profile values for predicting deficient control of the HbA_{1c}.

In the basal assessment, preprandial glycemia showed significantly lower values than fasting glycemia (166.7 ± 47 vs. 172.6 ± 39.4 SD, $P < 0.001$), whereas early postprandial glycemic values were significantly higher (209.3 ± 53.1 vs. 172.6 ± 39.4 SD, $P < 0.001$). Glycemia 5 h after the meal showed no statistically significant difference from fasting glycemia. After 12 months of follow-up, preprandial glycemia showed similar values than fasting glycemia (133. ± 35.9 vs. 136.6 ± 30.4 SD, NS), whereas early postprandial glycemic values were significantly higher (165.8 ± 38.1 vs. 136.6 ± 30.4 SD, $P < 0.001$). When compared with the basal assessement, both early and late postprandial glycemic levels were significantly reduced at 12 months (209.3 ± 53.1 vs. 165.8 ± 38.1 SD, $P < 0.001$) and (171.4 ± 47.2 vs. 139.8 ± 31.7 SD, $P < 0.001$).

Throughout the study, the four parameters of the glycemic profile showed a similar, statistically significant, correlation with the HbA_{1c} (fasting $r = 0.39$, preprandial $r = 0.37$, early postprandial $r = 0.34$, late postprandial $r = 0.33$; $P < 0.001$). The multiple standardized regression coefficients of the glycemic profile with the HbA_{1c} throughout the study show that fasting glucose was the best HbA_{1c} marker (standarized regression coefficient 0.21, $P < 0.001$).

The HbA_{1c} value at each time was estimated from the multiple linear regression of the capillary glycemia. Predicted HbA_{1c} values were classified as good control (<7.5%) and bad control (>7.5%), and they were compared with the real HbA_{1c} analytical values. The sensitivity and specificity analyses again identified fasting glycemia as the best HbA_{1c} predictor either at baseline or after 12 months (sensitivity 71%, specificity 61%, positive predictive value 61%). The specificity improved with the treatment. This was basically due to the fact that more patients were controlled as the study progressed.

According to the results of our study obtained from a large number of patients, we can conclude that the most extreme glycemic profile values have the least impact on HbA_{1c} levels, and that fasting glycemia has the most impact. This is probably because it is included in the period that contains more glycemic values equal to the average, and consequently has a greater impact on the global glycemic profile. However, the above does not prevent the association of postprandial glycemic spikes, which could be risk factors for the development of macroangiopathy (10).

EDUARDO FAURE, MD[1]
LUIS FELIPE PALLARDO, MD[2]
JORDI MESA, MD[3]
MANEL PUIG-DOMINGO, MD[4]
RICARDO GARCÍA-MAYOR, MD[5]
PEDRO BENITO, MD[6]
RAMÓN RAVELLA, MD[7]
MAITE ARTÉS, MSC[8]
JUAN S. LÓPEZ, MSC[8]
FOR THE MIDIA STUDY GROUP

From the [1]Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain; the [2]Hospital Universitario La Paz, Madrid, Spain; the [3]Hospital Universitario Vall d'Hebrón, Barcelona, Spain; the [4]Hospital de Mataró, Mataró, Spain; the [5]Hospital Xeral-Cies, Vigo, Spain; the [6]Hospital Universitario Reina Sofia, Córdoba, Spain; the [7]Department of Medicine, Sanofi-Synthelabo, Barcelona, Spain; and the [8]Pharma Consult Services, Pharma Research, Barcelona, Spain.

Address correspondence to Salvador López, Pharma Consult Services, S.A., Trav. de Gracia, 17-21, 1º 5ª, 08021 Barcelona, Spain. E-mail: vicky.vidal@pharma.

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Glycotoxins: A Missing Link in the "Relationship of Dietary Fat and Meat Intake in Relation to Risk of Type 2 Diabetes in Men"

We have read with great interest the article entitled "Dietary Fat and Meat Intake in Relation to Risk of Type 2 Diabetes in Men," by Van Dam et al. (1), which suggests a relationship between increased consumption of animal fat and red and processed meats and higher risk of type 2 diabetes in men.

We propose that the recently recognized toxic derivatives of advanced glycation and lipoxidation abundant in diets may explain the associations observed. Advanced glycation end products (AGEs) and lipoxidation end products (ALEs) are well-known glucose-derived factors contributing to diabetes-related complications (2). In addition to endogenous glucose, diet constitutes an important exogenous source of reactive precursor and terminal AGE and ALE, including a-β-dicarbonyl–containing derivatives. Common methods of food processing include heating, sterilizing, or ionizing, all of which tend to accelerate the nonenzymatic addition of nonreducing sugars to free NH_2-groups of proteins and lipids, a chemical process known as the Maillard reaction (3). This process, also known as "browning" of foods, is largely responsible for the color and flavor of cooked foods that most people are drawn to.

Recent estimates of AGE levels in ~200 commonly consumed foods, based on immunoreactivity assays for specific AGEs (4G9; Alteon, Northvale, NJ) (4), found AGE and ALE content of these foods to be relative not only to food composition, but also to mode of cooking, temperature, and duration of exposure to heat. In particular, the presence of fats, which are major generators of free radicals that can enhance oxidative processes, including butter and margarine, attributes to high AGE and ALE levels. Thus, the highest AGE levels were observed in animal products high in protein and fat, such as meats and cheeses. Furthermore, high AGE levels were observed in (industrially) preprocessed foods from animal products like frankfurters, bacon, and powdered egg whites, compared with the unprocessed forms. Across all categories, exposure to higher temperature raised the AGE and ALE content (for equal food weights). The temperature level appeared to be more critical than the duration. Also, microwaving increased AGE content more rapidly compared with conventional cooking methods (5).

Studies in humans and animals have confirmed the significant intestinal absorption of consumed meal AGEs and their subsequent tissue retention (6,7). Restriction of food AGE intake in animals offered a marked protection against significant pathology observed in animal models of diabetic atherosclerosis, nephropathy, wound healing, and postinjury restenosis (femoral artery) (8–11). Recently, a marked improvement of various features of insulin resistance was demonstrated in *db/db* mice fed a diet low in AGEs (lower glucose and insulin responses to glucose challenge and improved lipid profiles) (12). Preliminary data from a 6-week study in patients with type 1 or type 2 diabetes, randomized to a high- or low-AGE diet, showed a significant reduction in the low-AGE diet group of circulating markers of inflammation, typical of diabetes vascular disease (13).

Based on the above data, we propose that dietary glycoxidation products may constitute an important link between the increased consumption of animal fat and meats and the subsequent development of type 2 diabetes.

MELPOMENI PEPPA, MD
TERESIA GOLDBERG, RD
WEIJING CAI, MD
ELLIOT RAYFIELD, MD
HELEN VLASSARA, MD

From the Division of Experimental Diabetes and Aging, Department of Geriatrics, Mount Sinai School of Medicine, New York, New York.

Address correspondence to Melpomeni Peppa, Mount Sinai School of Medicine, Box 1640, New York, NY 10029. E-mail: moly.peppa@mssm.edu.

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Tenascin-C Levels in the Vitreous of Patients With Proliferative Diabetic Retinopathy

Tenascin-C is a large hexameric extracellular matrix glycoprotein that modulates cellular growth and adhesion. Tenascin-C is associated with angiogenesis (1,2) and has been detected in the epiretinal membranes of patients with proliferative diabetic retinopathy (PDR) (3). There are no reports, however, on the vitreous concentration of tenascin-C. In this study, we investigated the vitreous of patients with PDR for the presence of tenascin-C.

We assayed tenascin-C levels in vitreous samples from 108 consecutive patients with either PDR (58 patients) or macular hole or idiopathic epimacular membrane (nondiabetic control subjects, 50 patients) who underwent pars plana vitrectomy. In all cases, patients who had a recent vitreous hemorrhage were not included. The stage of PDR was classified as active (33 patients) if there were new preretinal capillaries and as quiescent (25 patients) if the vasoproliferation consisted of only large vessels within the membrane (4,5). Informed consent was obtained from each patient. The undiluted vitreous samples were collected during the pars plana vitrectomy before intraocular infusion. Enzyme-linked immunosorbent assay was used to determine vitreous tenascin-C concentrations as previously described (6). The total protein concentration of the vitreous samples was measured using a commercial assay (Pierce Chemical, Rockford, IL). The Mann-Whitney *U* test was used to compare vitreous concentrations of protein and tenascin-C.

There was no significant difference in intravitreous protein levels (median range) between patients with PDR (3.35 mg/ml, range 0.91–9.12) and control subjects (2.41 mg/ml, 0.92–9.31) ($P = 0.1287$). Tenascin-C levels in PDR (761.0 ng/ml, 12.0–1330.0) were significantly higher than in the control subjects (18.7 ng/ml, 9.9–713.0) ($P < 0.0001$). Moreover, the differences remained highly significant ($P < 0.0001$) when the ratio of tenascin-C to protein was considered (PDR 237.9, 2.1–926.5; control subjects 8.2, 1.6–136.3) (5,7).

Intravitreous tenascin-C concentrations in active PDR patients were significantly higher than those in quiescent PDR patients in absolute terms (777.0 ng/ml, 729.0–1330.0 vs. 761.0 ng/ml, 12.0–1030.0; $P = 0.0334$). The differences remained significant when the ratio of tenascin-C to protein was considered (308.9, 85.0–926.5 vs. 168.0, 2.1–671.7; $P = 0.0074$).

Neovascularization is the most important event in PDR. Tenascin-C is involved in the sprouting of endothelial cells, which is a necessary step in angiogenesis (1). Jallo et al. (2) reported that tenascin-C is associated with vessel formation in brain tumors. Tenascin-C mRNA expression significantly increases in diabetic retinopathy retina compared with normal retina (8) and has been detected in the epiretinal membranes of PDR (3). Our results are consistent with these previous reports, implicating tenascin-C in the pathophysiology of PDR.

In conclusion, vitreous levels of tenascin-C increase in PDR patients and tenascin-C levels are elevated in the active PDR stage. These results indicate that tenascin-C might be involved in the pathogenesis of PDR.

YOSHINORI MITAMURA, MD[1,2]
SHINOBU TAKEUCHI, MD[1]
KENJI OHTSUKA, MD[2]
AKIRA MATSUDA, MD[3]
NORIKO HIRAIWA, MS[4]
MORIAKI KUSAKABE, DVM, PHD[5]

From the [1]Department of Ophthalmology, Toho University Sakura Hospital, Sakura, Chiba, Japan; the [2]Department of Ophthalmology, School of Medicine, Sapporo Medical University, Sapporo, Japan; the [3]Department of Ophthalmology, Hokkaido University School of Medicine, Sapporo, Japan; the [4]Experimental Animal Division, Bio Resource Center, RIKEN, Tsukuba, Japan; and the [5]ANB Tsukuba Institute, Aloka, Ibaraki, Japan.

Address correspondence to Yoshinori Mitamura, Department of Ophthalmology, School of Medicine, Sapporo Medical University, S-1, W-16, Chuo-ku, Sapporo 060-8543, Japan. E-mail: ymita@sapmed.ac.jp.

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COMMENTS AND RESPONSES

Response to Lamotte et al.

In the February 2002 issue of *Diabetes Care*, Lamotte et al. (1) present a provocative study of the cost-effectiveness of orlistat in obese type 2 diabetic pa-

tients. We suspect, however, that the authors have greatly overestimated the cost-effectiveness of this drug, due primarily to inappropriate parameter estimates.

First, the authors estimated the impact of reductions in HbA_{1c} on the risks of macrovascular complications and death based on a finding from the Diabetes Control and Complications Trial (DCCT)—a 40% decrease in the risk of complications for every 10% reduction in HbA_{1c} (2,3). The DCCT, however, included only type 1 diabetic patients, and this particular finding applied to microvascular complications only. Nevertheless, Lamotte et al. used this estimate—along with data from the U.K. Prospective Diabetes Study (UKPDS)—to project the risks of microvascular and macrovascular complications, as well as death, among type 2 diabetic patients (4). The authors estimated that a 0.46% absolute decrease in HbA_{1c}, the assumed reduction with orlistat therapy (versus placebo), would reduce the annual risk of mortality by 27%, myocardial infarction (MI) by 29%, and stroke by 31% (5).

In our opinion, a better source with which to estimate these relationships is the UKPDS study of the association between glycemia and the complications of type 2 diabetes (6). In this study, a 1% absolute reduction in HbA_{1c} was associated with 14% risk reductions in mortality and MI and a 12% reduction in stroke. Based on these data, estimated risk reductions with orlistat therapy (assuming a 0.46% absolute decrease in HbA_{1c}) would have been substantially lower; 7% for mortality and MI, and 6% for stroke.

Second, they estimated the relationship between LDL cholesterol level and coronary events among type 2 diabetic patients using data from the Helsinki Heart Study (HHS), which was not adequately powered to accurately estimate treatment effects within subgroups (7,8). In this study, a 21.9-mg/dl reduction in LDL cholesterol was associated with a nominal 68% reduction in MI and cardiac death.

More reliable estimates can be found, we believe, in subgroup analyses from secondary prevention studies. In the Coronary Atherosclerosis and Recurrent Events (CARE) study, a mean 37-mg/dl decrease in LDL cholesterol was associated with a significant 25% reduction in coronary events (9). In the Scandinavian Simvastatin Survival Study (4S), an ~75-mg/dl reduction in LDL cholesterol was associated with a significant 57% reduction in major coronary events (10). These estimates are substantially lower than the HHS estimate (a reduction in coronary events of <1% per 1 mg/dl decrease in LDL cholesterol, versus 3% in the HHS), even though they occurred in the context of secondary prevention.

In summary, while it is impossible for us to calculate with certainty the effect that questionable parameter estimates had on their results, we believe it is quite likely that if the authors had used more appropriate data sources, their study would have yielded substantially higher cost-effectiveness ratios (i.e., they would have found orlistat to be substantially less cost-effective).

JOHN EDELSBERG, MD, MPH
DEREK WEYCKER, PHD
GERRY OSTER, PHD

From Policy Analysis Inc. (PAI), Brookline, Massachusetts.

Address correspondence to Gerry Oster, Policy Analysis Inc. (PAI), Four Davis Ct., Brookline, MA 02445. E-mail: goster@pai2.com.

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Response to Öncül

Insulin sensitivity in patients with chronic hepatitis C virus infection

We read with great interest the recent letter from Öncül et al. (1) reporting the correlation of serum leptin levels with insulin sensitivity in patients with chronic hepatitis C virus (HCV) infection. Their findings showed that fasting serum insulin levels and serum leptin levels were significantly elevated in patients with chronic HCV infection compared with control subjects and that fasting serum leptin and insulin levels and homeostasis model assessment–estimated insulin sensitivity were correlated in the whole group. Öncül et al. concluded that HCV infection may serve as an additional risk factor for the

development of type 2 diabetes due to insulin resistance and hyperleptinemia.

Certainly, insulin resistance plays an important role for the development of type 2 diabetes in patients with chronic HCV infection because levels of fasting serum C-peptide were significantly more elevated in non–insulin-treated diabetic patients with ($n = 18$) than in those without ($n = 72$) HCV infection (0.73 ± 0.27 vs. 0.57 ± 0.27 nmol/l; $P = 0.0321$) who were matched by BMI. The authors should show the correlation of serum leptin levels with insulin sensitivity not in the whole group but only in patients with chronic HCV infection, and should exclude the effect of BMI to demonstrate the correlation of serum leptin levels with insulin sensitivity in patients with chronic HCV infection. Conversely, elevated levels of serum leptin and insulin resistance might be correlated regardless of HCV infection (2). Contrary to the conclusion by Öncül et al., that HCV infection may serve as an additional risk factor for the development of type 2 diabetes due to insulin resistance and hyperleptinemia, there are some reports that leptin reverses insulin resistance (3,4). Elevated levels of serum leptin in patients with chronic HCV infection were compatible with previous data (5), although the reason was not fully determined. The mechanism of insulin resistance in patients with chronic HCV infection may be due to decreased liver carbohydrate metabolism and hypersecretion of insulin-resistant cytokines, such as interleukin-6 (6) and tumor necrosis factor (7), which have been shown to be elevated in patients with chronic HCV infection, most likely as a result of HCV-induced inflammation (8,9).

Michiaki Fukui, md
Yoshihiro Kitagawa, md
Naoto Nakamura, md
Toshikazu Yoshikawa, md

From the First Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan.

Address correspondence to Michiaki Fukui, First Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602-8566, Japan. E-mail: sayarinapm@hotmail.com

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Response to Fukui et al.

In response to the letter by Fukui et al. (1) in this issue of *Diabetes Care*, we first must comment on the possible interaction between leptin and insulin, independent of body fatness. Leptin is mainly an adipocyte-secreted protein. Leptin, the obese (*ob*) gene product, is an adipose tissue hormone that has been closely linked to the amount of body-fat stores. Most of the research following the discovery of leptin was focused on the role it plays in body weight regulation, aiming to illuminate the pathophysiology of human obesity. However, more data are emerging that show that leptin is not only important in the regulation of food intake and energy balance, but that it also has a function in metabolism, as well as in normal sexual maturation and reproduction. Leptin may thus be considered a new endocrine mediator, besides its obvious role in body weight regulation. A possible interaction between leptin and insulin was first suggested by the strong correlations between fasting serum leptin and insulin levels observed in human studies, independent of body fatness (2). Convincing evidence has shown that insulin can regulate leptin expression. This is most evident from studies with isolated adipocytes, which all showed that in vitro insulin clearly stimulates the mRNA expression and secretion of leptin in cultured rat and human adipocytes. Leptin probably acts at different intracellular levels, from transcription to membrane permeability, to inhibit insulin synthesis as well as secretion. Leptin can impair insulin production, and some data indicate that leptin could also play a role in the development of peripheral insulin resistance (3).

In our study, 44 consecutive eligible patients with chronic hepatitis C virus (HCV) infection were studied. The study group had a BMI of 22.6 ± 1.3 kg/m^2 and were aged 27.3 ± 6.8 years. The control group was matched for age, sex, and BMI. All study patients were evaluated to rule out other causes of chronic liver disease such as hepatitis B virus (HBV) infection, alcohol abuse, autoimmune hepatitis, and primary biliary cirrhosis. There was no evidence of decompensated liver disease. No patient received any antiviral, immunomodulatory, or immunosuppressive therapy. Patients with any other causes of peripheral insulin resistance were excluded. Therefore it is impossible to determine whether the correlation between fasting serum leptin and insulin levels/HOMA-estimated insulin sensitivity in the whole group depends on the effect of BMI and any other causes of peripheral insulin resistance.

In the letter by Fukui et al., it was mentioned that leptin reverses insulin resistance (1,4). We think that this reversal is the result of leptin in physiological levels because previous studies showed that the high serum leptin levels cause desensitization of the receptor and thus defective leptin receptor signaling in β-cells,

which leads to chronic hyperinsulinemia and may thus contribute to the pathogenesis of diabetes (3).

Fukui et al. also mentioned that the mechanism of insulin resistance in patients with chronic HCV infection may be due to HCV-induced inflammation. Yet, it is impossible to say that the only mechanism of insulin resistance in these patients was HCV-induced inflammation and that leptin played no role. Leptin receptors are present on human hepatocytes, and leptin was shown to modulate several insulin-induced activities in these cells. Leptin antagonizes insulin signaling by decreasing insulin-induced tyrosine phosphorylation of insulin receptor substrate-1. It increases PEPCK and decreases glucokinase expression, leading to increased gluconeogenesis and decreased glycogenolysis. The hepatic effects of high leptin levels may thus contribute to hepatic insulin resistance (5). Leptin also plays an important role in liver fat storage. Steatosis is a common finding in chronic HCV infections. Overaccumulation of lipids in nonadipose tissues may lead to lipotoxic complications such as diabetes (6). Previous studies reported that the serum leptin levels were significantly higher in patients with steatohepatitis, and elevated serum leptin levels may promote hepatic steatosis and steatohepatitis (7).

There are also several pathogenetical mechanisms to explain the insulin resistance in patients with chronic HCV infection. Bonora et al. (8) reported that the peripheral hyperinsulinemia observed in subjects with chronic hepatic disease was due to diminshed insulin removal by the diseased liver rather than pancreatic hypersecretion. Bonora et al. also reported that both hyperinsulinemia and high concentrations of counterregulatory substances might play a role in the pathogenesis of insulin resistance in subjects suffering from chronic liver disease (9). So, we cannot say that the only mechanism of insulin resistance in such patients was hypersecretion of insulin-resistant cytokines and decreased liver carbohydrate metabolism. For these reasons, we believe that high serum leptin levels are an important etiological factor of insulin resistance in patients with chronic HCV infection.

ORAL ÖNCÜL, MD[1]
CIHAN TOP, MD[2]
SABAN CAVUSLU, MD[1]

From the [1]Department of Infectious Disease, Gülhane Military Medical Academy, Haydarpasa Training Hospital, Istanbul, Turkey; and the [2]Department of Internal Medicine, Gülhane Military Medical Academy, Haydarpasa Training Hospital, Istanbul, Turkey.

Address correspondence to Oral Öncül, MD, Department of Infectious Disease, Gülhane Military Medical Academy, Haydarpasa Training Hospital, 81327 Uskudar, Istanbul, Turkey. E-mail: gataheh@hotmail.com.

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