OBSERVATIONS

Please, Let My Doctor Be Obese

Associations between the characteristics of general practitioners and their patients with type 2 diabetes

Obesity is an important cardiovascular risk factor in type 2 diabetes (1). Physician characteristics such as age and sex are related to counseling for overweight (2). Other physician characteristics may also be related. Patients indicated greater confidence in nonobese versus obese physicians. Whether this translates into increased success in obesity management is unknown (3). We aimed to study associations between the weight of general practitioners and their type 2 diabetic patients.

A postal survey was performed among 36 general practitioners participating in a shared-care diabetes project in 2000. It contained questions about the general practitioners' age, sex, weight, height, smoking behavior, work experience, practice population size, and opinion regarding how much influence they have on a patient's weight and smoking cessation. The project's target population consisted of type 2 diabetic patients who were exclusively treated in primary care. Patients who were cotreated in secondary care or who were terminally ill or had dementia were excluded. Participating patients ($n = 1,441$) represented 87% of the target population. Data on patient age, sex, diabetes duration, BMI, and smoking were collected by nurses. We performed a regression analysis with the mean BMI of patients as the dependent variable and the above variables as predictors.

The survey response rate was 100%. Most general practitioners were nonsmoking (94%) men (83%) with a mean (±SD) age of 51.1 ± 7.0 years and work experience of 18.1 ± 8.9 years. The general practitioners' mean BMI was 24.4 ± 3.5 kg/m^2 (BMI <25 in 72%). For patients (per general practitioner), mean age was 68.2 ± 2.9 years, diabetes duration 7.2 ± 1.3 years, and BMI 29.3 ± 0.85 kg/m^2; 44 ± 9% were men. The mean BMI of patients showed the strongest correlation with the BMI of general practitioners: −0.40 (partial correlation) and unstandardized coefficient B of −1.05 (95% CI −0.197 to −0.013). The optimal model ($P = 0.07$) had a multiple correlation (R) of 0.56, and explained variance (R^2) was 31% (adjusted 17%).

We found a negative correlation between the BMI of type 2 diabetic patients and their general practitioners. Obese doctors had lean patients. Our study is limited by the cross-sectional design; associations were found, not causal relations.

Hash et al. (3) showed that patients indicated greater confidence in nonobese physicians. However, we found no translation into increased success in obesity management. On the contrary, patients of nonobese general practitioners had a higher BMI compared with patients of obese general practitioners. A discernable negative impact of patient weight on physician behavior was shown earlier (4). Could it be that nonobese general practitioners lack motivation to treat overweight patients? Is it time for general practitioners to search our own hearts?

LIELITH J. UBINK-VELTMAAT, MD[1,2]
ROGER A.J.M. DAMOISEAUX, PHD[3]
ROEL O. RISCHEN, MD[4]
KLAAS H. GROENIER[1]

From the [1]Department of Family Practice, University of Groningen, Groningen, the Netherlands; the [2]Isala Clinics, Weezenlanden, Diabetes Outpatient Clinic, Zwolle, the Netherlands; the [3]General practice 'de Hof van Blom', Hattem, the Netherlands; and the [4]General practice 't Veen, Hattem, the Netherlands.

Address correspondence to Lielith J. Ubink-Veltmaat, MD, Vechtdijk 7, 7721 AG Dalfsen, Netherlands. E-mail: l.j.veltmaat@isala.nl.

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Prognostic Factors of Sudden Sensorineural Hearing Loss in Diabetic Patients

Sudden sensorineural hearing loss (SSNHL) is defined as the sudden onset of unilateral sensorineural hearing loss of ≥30 dB over at least three contiguous audiometric frequencies (1). Diabetes is a risk factor of SSNHL, possibly due to microangiopathy (2). Currently, the clinical studies of SSNHL rarely focus on diabetic patients. The correlations between biochemical data and hearing outcomes in SSNHL are seldom analyzed. We analyzed the characteristics of SSNHL in diabetic patients and tried to elucidate the possible prognostic factors.

Medical charts of diabetic patients admitted for SSNHL from 1984 to 2003 were retrospectively reviewed. A total of 67 patients (38 men and 29 women) with a mean age of 60.1 ± 11.9 years were included. Their mean duration of diabetes was 7.5 ± 7.7 years and mean HbA_{1c} 9.9 ± 2.9%. Measuring by initial and follow-up pure-tone audiometries, improvement in hearing was divided into favorable outcome (FO) (hearing returned to at least the same level as the opposite ear or with improvement ≥30 dB) or poor outcome (PO) (hearing improvement <30 dB) groups.

All of the patients denied previous episodes of SSNHL. After treatment, 23 patients (34.3%) had a favorable hearing outcome, while 44 patients (65.7%) had a poor hearing outcome. The age and sex distributions were not statistically different in the FO and PO groups. Duration of diabetes, medication type, and control levels of diabetes, hypertension, or hyperlipidemia were also not correlated with hearing outcome. Factors such as the type of initial audiogram, the period of SSNHL onset to therapy, and the presenting symptoms (vertigo, tinnitus, aural fullness, etc.) had no significant impact on the hearing prognosis.

SSNHL occurring in the summer had better a hearing outcome than that occurring in the nonsummer seasons (adjusted

for sex and age, odds ratio [OR] for the PO group 0.093 [95% CI 0.02–0.428], $P = 0.002$). The glucocorticoid regimen had a dose-dependent effect on the outcome (χ^2 for trend test 5.4159, $P = 0.020$). Using no steroid treatment as a reference group, the adjusted OR for the PO group was 0.762 (0.231–2.516, $P = 0.656$) and 0.355 (0.157–0.802, $P = 0.013$) for the low- and high-steroid groups (prednisolone 1 mg $\cdot$ kg^{-1} $\cdot$ day^{-1} for at least 7 days), respectively. When we compared the hearing outcomes using binary covariates, such as using or not using steroids, the difference was not significant. Vitamin B treatment had a significantly adverse effect for hearing recovery (adjusted OR for the PO group was 3.676 [1.081–12.5], $P = 0.037$). The adjusted OR for the PO group for every gram per liter increment of serum albumin was 0.659 (0.471–0.922, $P = 0.015$). The increment in serum lactate dehydrogenase was borderline significantly correlated with poor hearing outcome ($P = 0.050$), but the effect was not significant after adjustment for sex and age. In multivariate logistic regression, only the increment in albumin remained independently associated with the hearing outcome.

In conclusion, our data reveal that onset in summer and higher serum albumin concentrations are favorable prognostic factors of SSNHL in diabetic patients. A vitamin B regimen may lead to a poor hearing outcome. We suggest a high-dose glucocorticoid treatment for SSNHL in diabetic patients. Further prospective studies are needed to confirm the true effects of these prognostic factors.

Shuen-Fu Weng, MD[1]
Yuh-Shyang Chen, MD[2]
Tien-Chen Liu, MD, PHD[2]
Chuan-Jen Hsu, MD, PHD[2]
Fen-Yu Tseng, MD, MPH[1]

From the [1]Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; and the [2]Department of Otolaryngology, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan.

Address correspondence to Dr. Fen-Yu Tseng, MD, MPH, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan. E-mail: fytseng@ha.mc.ntu.edu.tw.

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Gastric Bypass Surgery in Severely Obese Type 1 Diabetic Patients

Obesity is common in type 2 diabetes but is rarely seen in autoimmune type 1 diabetes (1). However, as shown in the Diabetes Control and Complications Trial cohort (2,3), a subset of type 1 diabetic patients are overweight, and it has been suggested that intensive insulin therapy may unmask the central obesity or metabolic syndrome in susceptible individuals.

Gastric bypass is considered a gold standard procedure in the surgical treatment of severe obesity, with >50% of excess weight loss occurring within 2 years after the surgery. The weight reduction is maintained over the following years in a vast majority of patients (4). Numerous reports have been published on the beneficial effects of obesity surgery on glucose control and metabolic disorders in impaired glucose tolerant and type 2 diabetic subjects, with an impressive 70–90% of diabetic patients remaining euglycemic without diabetes medications several years after the surgery (5,6). This significant impact of gastric bypass surgery on glucose control is thought to not only result from significant weight loss but also from the exclusion of hormonally active foregut (7,8). It is worth noting that in recent years, gastric bypass has become an increasingly safe procedure (9).

We performed gastric bypass operations in two young women with autoimmune type 1 diabetes associated with severe obesity. Both patients had been obese for many years and were unsuccessful in their previous multiple attempts at losing weight. Having been informed about the benefits and risks of the surgery, they gave their consent to have bariatric surgery performed.

The first patient was a 23-year-old woman with type 1 diabetes since age 15 years, which was poorly controlled (HbA_{1c} 9.5%) and treated with a basal bolus insulin regimen (daily insulin dose 68 IU). Her body weight was 113.5 kg, height 171 cm, and BMI 38.8 kg/m^2. She was mildly hypertensive and had hypercholesterolemia treated with a low-cholesterol diet. The patient underwent Roux-en-Y gastric bypass surgery, as described before (9), in August 2000. The surgery and postoperative period were uneventful. Six months after the surgery, her body weight was 84.3 kg (BMI 28.8 kg/m^2; 25.7% reduction). After 1 year, it was 77.7 kg (BMI 26.6 kg/m^2; 31.5% reduction). However, 2 years after the surgery, her weight increased to 85.0 kg (BMI 29.1 kg/m^2) and has remained stable ever since. Eventually, the patient lost 28.5 kg, i.e., 25% of her initial body weight. Her glucose control improved markedly (HbA_{1c} 5.7%), with daily insulin dose reduced to 45 IU, and her blood pressure and plasma lipids returned to normal.

The second patient was a 28-year-old woman who was diagnosed with type 1 diabetes when she was 5 years old. She had been obese since childhood, and her body weight, as in the first patient, had been steadily increasing since the diagnosis of diabetes. Upon presentation, her weight was 126 kg, height 165 cm, and BMI 46.3 kg/m^2. She had also been diagnosed with hypertension, hypertriglyceridemia, and, more recently, Sjögren's Syndrome. She was also treated with intensive insulin therapy (120 IU/day); however, her blood glucose control had been extremely poor for >10 years (HbA_{1c} during this period was between 10.4 and 11.8%). Her other medications included enalapril, bisoprolol, and fenofibrate. She had Roux-en-Y gastric bypass successfully performed in November 2002. Her surgery was complicated by bilateral pneumonia. Ten months after the operation, her weight was 84 kg (BMI 30.1 kg/m^2; 33% reduction) and, similar to the previous patient, increased slightly 18 months after the surgery to 89.5 kg (BMI 32.9 kg/m^2; 29% reduction). Her metabolic control has improved substantially (HbA_{1c} 7.3%), and her daily insulin dose is now 70 IU. In addition, she no longer requires any treatment for hypertension or lipid disorders and her blood pressure and plasma triglycerides values are now normal.

Our report is, to the best of our knowledge, the first one describing the effects of obesity surgery in type 1 diabetes. In our opinion, gastric bypass surgery, which is being performed increasingly often (~100,000 operations in the U.S. annually [10]) in obese individuals, also with type 2 diabetes (4–8), is a feasible, safe, and effective method of weight reduction in young type 1 diabetic patients with severe obesity and comorbidities leading to metabolic syndrome (e.g., hypertension, hyperlipidemia) (11). In our patients, surgery-induced weight loss was also associated with a decrease in insulin requirement per kilogram of body weight (0.60 to 0.53 IU/kg in the first patient and from 0.95 to 0.83 IU/kg in the second patient). This observation may suggest the presence of clinically significant insulin resistance in severely obese type 1 diabetic subjects (12), which was subsequently reduced once weight loss occurred. Importantly, neither of the patients had any significant hypoglycemic episodes after the surgery, despite considerable reduction in HbA_{1c} level and apparent increase in insulin sensitivity.

In conclusion, gastric bypass surgery not only leads to a significant and maintained weight loss in type 1 diabetic patients, but also results in remarkable improvement in metabolic control (absolute reduction in HbA_{1c} of 3–4%) and concomitant disorders. Interestingly, the need for constant intensive insulin therapy in these patients had no detrimental influence on weight loss as an effect of obesity surgery. Both patients lost 50–60% of their excessive body weight during the follow-up period, which is also the rate reported in nondiabetic subjects (4,5,7).

LESZEK CZUPRYNIAK, MD, PHD[1]
JANUSZ STRZELCZYK, MD, PHD[2]
KATARZYNA CYPRYK, MD, PHD[3]
MACIEJ PAWLOWSKI, MD[1]
DARIUSZ SZYMANSKI, MD, PHD[2]
ANDRZEJ LEWINSKI, MD, PHD[3]
JERZY LOBA, MD, PHD[1]

From the [1]Department of Diabetology and Metabolic Diseases, Medical University of Lodz, Lodz, Poland; the [2]Department of General and Transplant Surgery, Medical University of Lodz, Lodz, Poland; and the [3]Department of Endocrinology and Isotope Therapy, Polish Mother's Memorial Hospital Research Institute, Medical University of Lodz, Lodz, Poland.

Address correspondence to Leszek Czupryniak, MD, PHD, Department of Diabetology and Metabolic Diseases, Barlicki University Hospital, No. 1, Ul, Kopcinskiego 22, 90-153 Lodz, Poland. E-mail: bigosik@poczta.onet.pl.

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Dysadipocytokinemia in Werner Syndrome and Its Recovery by Treatment With Pioglitazone

Werner syndrome (WS) (Mendelian Inheritance in Man no. 277700) is an autosomal recessive disorder known for progeroid phenotypes including graying and loss of hair, juvenile cataracts, insulin-resistant diabetes, skin atrophy, premature atherosclerosis, and cancer (1). Mutations in *WRN*, a RECQ family DNA/RNA helicase gene, have been identified to cause this disease. The mechanism for insulin resistance in WS remains to be elucidated.

Adipocytes secrete a number of hormones (or adipocytokines), such as tumor necrosis factor-α (TNF-α), leptin, adiponectin, and resistin, thereby regulating insulin sensitivity (2). WS patients typically show the lipoatrophic skinny extremities with an obese trunk (1). The accumulated intra-abdominal visceral fat (3) suggests an altered production of adipocytokines.

To investigate the role of adipocytokines in the pathophysiology of WS, we examined the serum levels of TNF-α and adiponectin in WS. Sera sampled from 24 WS patients (14 men and 10 women; 16 with and 8 without diabetes) proven to be homozygous for *WRN* mutations, and 40 age- and sex-matched normoglycemic healthy volunteers were assayed after informed consent was obtained. Age (43 ± 8.1 vs. 41.6 ± 7.5 years) and BMI (19.4 ± 1.9 vs. 18.8 ± 2.0 kg/m^2) were similar for diabetic and nondiabetic WS patients.

The serum level of TNF-α, a mediator of insulin resistance, was significantly elevated in WS regardless of having diabetes (21.8 ± 8.7 pg/ml, $P < 0.0001$ by Mann-Whitney test) or not having diabetes (14.0 ± 3.2 pg/ml, $P = 0.002$) compared with the healthy control group (6.05 ± 3.0 pg/ml). Adiponectin levels in diabetic WS patients (3.1 ± 2.9 μg/ml) was significantly lower than in nondiabetic WS patients (11.6 ± 9.2 μg/ml, $P = 0.006$) or control subjects (14.4 ± 8.8 μg/ml, $P < 0.0001$). The growing evidence indicates insulin sensitizing as well as antiatherogenic actions of adiponectin and the association of decreased serum adiponectin with insulin resistance, obe-

sity, and type 2 diabetes (2,4). Although WS patients are usually not obese by the definition of BMI, the visceral fat specifically accumulated by an unknown mechanism (3) might cause high TNF-α and low adiponectin levels, characteristics similar to morbid obesity.

We recently reported the successful improvement of glycemic control and insulin sensitivity by pioglitazone in diabetic WS patients (5). Therefore, we next assessed adipocytokines before and after 16 weeks on pioglitazone (15 mg/day) in three diabetic WS patients. The treatment significantly elevated adiponectin levels from 2.57 ± 1.36 to 7.07 ± 2.48 μg/ml ($P = 0.03$ by paired t test). TNF-α and HbA_{1c} levels showed a tendency to decline from 16.1 ± 4.75 to 3.53 ± 0.58 pg/ml ($P = 0.052$) and from 7.7 ± 0.6 to 6.4 ± 0.5% ($P = 0.17$), respectively.

To our knowledge, this is the first study to examine serum adipocytokine levels in WS patients. Reduced insulin sensitivity with increased visceral adiposity is the hallmark of both WS and normal aging. Because pioglitazone achieved improvement of glycemic control as well as correction of adiponectin and TNF-α levels, these cytokines are likely to be at least in part responsible for insulin resistance in WS. Adipocyte function may be a key element linking *WRN* mutation and the metabolic abnormalities observed in WS. It is also of our interest to know whether pioglitazone and other thiazolidinediones can prevent or delay the onset of diabetes in WS by modulating adipocytokines. Our present findings raise a possibility that pioglitazone could extend the lifespan of WS patients by improving metabolism and preventing early cardiovascular death.

KOUTARO YOKOTE, MD[1,2]
KAZUO HARA, MD[3]
SEIJIRO MORI, MD[1,2]
TAKASHI KADOWAKI, MD[3]
YASUSHI SAITO, MD[1,2]
MAKOTO GOTO, MD[4,5]

From the [1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Chiba University Hospital, Chiba City, Japan; the [2]Department of Clinical Cell Biology, Chiba University Graduate School of Medicine, Chiba City, Japan; the [3]Department of Metabolic Diseases, Graduate School of Medicine, University of Tokyo, Tokyo, Japan; the [4]Department of Rheumatology, Tokyo Metropolitan Otsuka Hospital, Tokyo, Japan; and the [5]Institute of Bioengineering, Toin Yokohama University, Yokohama, Japan.

Address correspondence to Koutaro Yokote, MD, Division of Endocrinology and Metabolism, Department of Internal Medicine, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan. E-mail: kyokote-cib@umin.ac.jp.

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Effect of α-Linolenic Acid–Containing Linseed Oil on Coagulation in Type 2 Diabetes

Blood coagulation in diabetes is known to be increased (1,2). Because levels of n-3 and n-6 polyunsaturated fatty acids (PUFAs) influence the parameters of blood coagulation, the aim of this study was to determine the effects of n-3 PUFA supplementation on coagulation and fibrinolytic factors in type 2 diabetic subjects. While it is not clear what the appropriate intake ratio of n-6 to n-3 PUFAs should be for diabetic subjects, it is known that the dietary intake ratio of n-6 to n-3 PUFAs is roughly 4:1 in Japanese subjects (3).

Ten subjects (six women and four men, average age 59.6 years) with type 2 diabetes participated in this study as inpatients. Their average BMI and HbA_{1c} values were 20.9 ± 3.8 kg/m^2 and 10.8 ± 1.1%, respectively. Their daily energy intake during the course of the study was 1,490 ± 166 kcal. After 2 weeks on the control diet, our subjects were placed on a diet in which 5 g linseed oil was added (in salads, miso soup, etc., without heating) in exchange for 5 g cooking oil. The ratio of PUFAs to saturated fatty acids in the subjects' prestudy and study diets were 1.2 and 1.6, respectively, while the ratios of n-6 to n-3 PUFAs in their prestudy and study diets were 3.6 and 1.5, respectively. Blood samples were collected before and 14 days after initiation of the study. Plasmin α2-plasmin inhibitor complex (PPI) level and plasminogen activator inhibitor-1 (PAI-1) activity in plasma was measured using a latex photometric immunoassay, while thrombin antithrombin III complex (TAT) level was measured using an enzyme-linked immunoassay. Differences in these parameters obtained at the start and end of the study were analyzed using a paired t test; values were considered to be significant if the P value was <0.05. Values are expressed as the mean ± SD.

After 2 weeks on a linseed oil–supplemented diet, PPI level, PAI-1 activity, and TAT level fell significantly (0.72 ± 0.19 vs. 0.47 ± 0.14 μg/ml, $P = 0.0009$; 73.3 ± 37.5 vs. 51.6 ± 25.0 ng/ml, $P = 0.02$; and 9.6 ± 9.1 vs. 2.5 ± 1.1 ng/ml, $P = 0.04$; respectively).

Boberg et al. (4) reported that PAI-1 activity was increased in type 2 diabetic subjects after supplementation of their diet with 10 g eicosapentaenoic acid. Kelly et al. (5) reported that a diet containing flaxseed oil (60% α-linolenic acid) did not alter indexes of blood coagulation, i.e., bleeding time, prothrombin time, and partial prothrombin time. Chan et al. (6) showed that altering the dietary n-6–to–n-3 PUFA ratio had no effect on

bleeding time. Our results, on the other hand, showed that a diet-induced reduction in the n-6–to–n-3 PUFA ratio affected parameters of blood coagulation and fibrinolysis. Finally, Freese et al. (7) reported that supplemental α-linolenic acid from vegetable oil and eicosapentaenoic and docosahexaenic acids from a marine source had similar effects on hemostatic factors. In conclusion, our results showed that PPI level, PAI-1 activity, and TAT level were significantly reduced in type 2 diabetic subjects that had their n-6–to–n-3 PUFA ratio lowered by dietary means.

NORIAKI TOHGI, MD

From the Department of Endocrinology and Metabolism, Kurume University School of Medicine, Kurume, Japan.

Address correspondence to Noriaki Tohgi, MD, Midori Hospital 359-1 Yuu-chou Kuga-gun, Yamaguchi 740-1404, Japan. E-mail: tohgi@nanwakai.jp.

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COMMENTS AND RESPONSES

Use of Arterial Transfer Functions for the Derivation of Central Aortic Waveform Characteristics in Subjects With Type 2 Diabetes and Cardiovascular Disease

Response to Hope et al.

We read with interest the recent article by Hope et al. (1) concerning the noninvasive estimation of central aortic pressure waveforms in subjects with type 2 diabetes. We entirely agree with their view that aortic rather than brachial artery pressure is likely to be of greater prognostic value, as are indexes such as aortic augmentation index. We would also agree that the data presented in the article clearly indicate that there was a substantial difference between invasively measured and derived aortic systolic pressure. However, the authors' conclusions seem overstated and may be misinterpreted by nonspecialist readers. The transfer function used by Hope et al. is actually their own and not that which is used in the "commercial devices" that they refer to in their introduction. Indeed, they offer no data to suggest that other transfer functions are unreliable in subjects with diabetes. Therefore, all that Hope et al. can actually conclude is that their own generalized transfer function is unreliable in subjects with diabetes. Thus, other investigators may be better off using "commercial devices" rather than the seemingly discredited transfer function of Hope et al.

IAN B. WILKINSON, DM, MA, MRCP
CARMEL MCENIERY, BSC, PHD

From the Clinical Pharmacology Unit, Addenbrooke's Hospital, Cambridge, U.K.

Address correspondence to Dr. Ian B. Wilkinson, Addenbrooke's Hospital, Hills Road, CB2 2QQ Cambridge, U.K. E-mail: ibw20@cam.ac.uk.

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Use of Arterial Transfer Functions for the Derivation of Central Aortic Waveform Characteristics in Subjects With Type 2 Diabetes and Cardiovascular Disease

Response to Hope et al.

In a recent editorial, Mather and Lewanczuk (1) describe the potential value of a generalized transfer function to synthesize the ascending aortic pressure wave from the radial pressure waveform, as recorded indirectly by applanation tonometry. The Food and Drug Administration (FDA) had previously accepted validity under different conditions of a generalized transfer function used in a commercial device: "The SphygmoCor SCOR-Px can calculate the calibrated ascending aortic pressure waveform using the radial artery pressure waveform recorded noninvasively from a radial artery tonometer and a brachial cuff measurement" (2). On the basis of an accompanying article by Hope et al. (3) in *Diabetes Care*, editorialists expressed concern regarding whether such an approach was applicable in diabetic subjects.

There are serious flaws in the report of Hope et al. (3) Their transfer function is different from that accepted by the FDA (2) and had been determined from use of conventional fluid-filled manometer systems of an unknown frequency response. From their original dataset (4), they had opined that different transfer functions were necessary to characterize the vascu-

lar properties of men and women and, subsequently from the same dataset (5), that their transfer function was unreliable for calculating the aortic augmentation index and other features of the synthesized aortic pressure wave. In their article, Hope et al. developed a "diabetes-specific" transfer function and showed that this could accurately generate the aortic from the radial pressure waveform. The problem with such an approach is that the same data used to validate were also used to generate the transfer function.

Other investigators (6) have found the approach used by Hope et al. to be problematic, but these issues are not taken into consideration. Other problems are also apparent. The "representative" (sic) synthesized aortic and measured aortic pressure values in their Fig. 1*B* show no evidence of the substantial (8 mmHg) diastolic pressure offset noted in Table 2. The method used for calibration (assuming mean and diastolic pressure are equal [4,7]) cannot give a diastolic pressure offset of 8 mmHg. In the system approved by the FDA, the difference was <1 mmHg (8). There are serious inconsistencies with other data published by the same authors (9); the time to inflection (144–163 ms) (their Table 2) is far higher than that described for the carotid artery (mean 81 ms), while the aortic augmentation index is much lower (13.1–21.3%) rather than higher than in the carotid (34 ± 13%).

Hope et al. (3) concluded that the use of their nondiabetic transfer function was inaccurate in generating aortic systolic and diastolic pressures in diabetic subjects. However, when the nondiabetic transfer function was used to calculate pulse pressure, as in the system approved by the FDA (2) (without the unexplained diastolic pressure offset), it was actually more accurate in diabetic (mean error 2 mmHg) than in nondiabetic (mean error 6 mmHg in Table 2) subjects.

These points cast doubt over previous publications from this group (4–6). Their transfer function differs markedly from that described by others (6) and those accepted by the FDA at frequencies above 3 Hz, which determines features of the pressure waveforms such as the aortic augmentation index (7).

The validity of the FDA-approved system is supported by studies of changes in heart rate and rhythm (8) and in arterial pressure during Valsalva maneuver (7) and with vasodilator challenge (8). It is also endorsed by modeling studies that have simulated changes in vascular properties in diabetic subjects (10). We believe that editorialists and readers of *Diabetes Care* can be reassured that no "diabetes-specific" (3) or "gender-specific" (4) transfer function is required to generate aortic pressure from the radial pressure waveform. An appropriately validated and approved generalized transfer function, however, is required.

Alberto P. Avolio, PHD[1]
John R. Cockcroft, BSC, MB[2]
Michael F. O'Rourke, MD, DSC[3]

From the [1]Graduate School of Biomedical Engineering, University of New South Wales, Sydney, Australia; the [2]Wales Heart Research Unit, College of Medicine, University Hospital, University of Wales, Cardiff, U.K.; and the [3]St. Vincent's Clinic, University of New South Wales, Sydney, Australia.

Address correspondence to Dr. Michael F. O'Rourke, Suite 810, St. Vincent's Clinic, 438 Victoria St., Darlinghurst, New South Wales 2010, Australia. E-mail: m.orourke@unsw.edu.au.

A.P.A. has received honoraria from, is a consultant for, and is a member of the advisory panel of Atcor Medical. M.F.O. is a founder and director of Atcor Medical and has received consulting fees from Atcor Medical, Philips, Pfizer, Lilly, and Servier.

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Use of Arterial Transfer Functions for the Derivation of Central Aortic Waveform Characteristics in Subjects With Type 2 Diabetes and Cardiovascular Disease

Response to Wilkinson and McEniery and Avolio, Cockcroft, and O'Rourke

We refer to the letters of Wilkinson and McEniery (1) and Avolio, Cockcroft, and O'Rourke (2). In our article, we make it abundantly clear that all results, including the transfer function utilized, were generated from data obtained in our laboratory (3). As the above correspondents note, we have previously reported at length in peer-reviewed literature how this is implemented by our group (4–9).

There is no published data to support the contention that any transfer function performs adequately in subjects with diabe-

tes (10–13). This issue has not been addressed in the literature by enthusiasts of the technique, yet it is of crucial importance if the technique is to be used in clinical practice.

Wilkinson and McEniery (1) make the entirely unsupported suggestion that, on the basis of our results, "investigators may be better off using 'commercial devices.'" We note that both groups of correspondents are prolific users of a particular commercial device and therefore presumably consider themselves "better off" (14–24). We would caution them and others against this leap of faith. While they may not consider our data to support the use of arterial transfer functions in general, there are no data from any source suggesting that any transfer function is able to perform better or that our data might not reflect the maximum achievable accuracy of a "generalized" arterial transfer function. We therefore strongly urge all potential users, especially the "nonspecialist readers" of such concern to Wilkinson and McEniery, to carefully evaluate the proven accuracy and validity of such techniques in the specific population and application of their interest (25).

Avolio, Cockcroft, and O'Rourke (2) opine that "an appropriately validated and approved generalized transfer function, however, is required." The implication in this opinion, with which we agree, is that no such entity exists. Whether our results are indicative of the fundamental accuracy of a generalized arterial transfer function can only be disputed when appropriate and comparable data are available concerning other proposed transfer function techniques, commercially available or not. Unfortunately, such data can only be provided by those with access to and specific knowledge of the individual implementation, and we would strongly request that those groups, which presumably include the current correspondents, provide such data. Users could then move away from the "black-box" approach with some confidence regarding the likely accuracy for their application, whether it be simple central pulse pressure or more sophisticated waveform analysis. Until such data are available, we cannot share Avolio, Cockcroft, and O'Rourke's optimistic belief (no evidence supplied) that "editorialists and readers of *Diabetes Care* can be reassured that no 'diabetes-specific' or 'gender-specific' transfer function, however, is required."

As might be predicted, enthusiasts of the technique do not like our findings. However, the mature scientific response is to disprove a hypothesis rather than assign discredit (2). We therefore suggest that such enthusiasts provide robust data in support of oft-stated beliefs; in the absence of credible data we argue against an "ignorance is bliss" approach.

SARAH A. HOPE, MBCHB[1]
DAVID B. TAY, BE, PHD[2]
IAN T. MEREDITH, MBBS, PHD[1]
JAMES D. CAMERON, MBBS, MD[1]

From the [1]Cardiovascular Research Centre, Monash Medical Centre, Monash University, Melbourne, Australia; and [2]Department of Electronic Engineering, La Trobe University, Melbourne, Australia.

Address correspondence to Sarah A. Hope, MBChB, Cardiovascular Research Centre, Monash Medical Centre, 246 Clayton Rd., Clayton, Victoria 3168, Australia. E-mail: sarah.hope@med.monash.edu.au.

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Use of Arterial Transfer Functions for the Derivation of Central Aortic Waveform Characteristics in Subjects With Type 2 Diabetes and Cardiovascular Disease

Response to Avolio, Cockcroft, and O'Rourke

Avolio, Cockcroft, and O'Rourke (1) raise some valid concerns regarding the approach taken by Hope et al. (2) in generating and validating an arterial transfer function in subjects with diabetes. The rigorous evaluation and validation process, which undoubtedly supported the Food and Drug Administration approval of the SphygmoCor SCOR-Px device, could be used as a model for parallel evaluations in specific populations of interest. Despite these authors' assurances of universal applicability, however, given the profound effects of diabetes on all dimensions of the vascular tree, it does seem reasonable to specifically test whether generalized transfer functions are valid in subjects with diabetes. The manuscript by Hope et al. was of value in that it raises questions about the validity of this tool in this setting. We are in full agreement with Avolio, Cockcroft, and O'Rourke that appropriate validation of the generalized transfer function in subjects with diabetes is required before the use of this tool in research or clinical applications can be advocated.

KIEREN MATHER, MD, FRCPC[1]
RICHARD LEWANCZUK, MD, PHD, FRCPC[2]

From the [1]Division of Endocrinology & Metabolism, Indiana University School of Medicine, Indianapolis, Indiana; and the [2]Division of Endocrinology & Metabolism, University of Alberta, Alberta, Canada.

Address correspondence to Kieren Mather, MD, FRCPC, Indiana University School of Medicine, Division of Endocrinology & Metabolism, 975 West Walnut St., IB424, Indianapolis, IN 46202. E-mail: kmather@iupui.edu.

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Insulin Detemir Offers Improved Glycemic Control Compared With NPH Insulin in People With Type 1 Diabetes

Response to Home et al.

The article by Home et al. (1) in the May issue of *Diabetes Care* prompted us to respond and comment on the current practice of reporting on clinical trials when insulin analogs are concerned. While a cure for type 1 diabetes has not yet been achieved, comprehensive, multidisciplinary treatment strategies have lead the way to offer patients and their families a near-normal life and affected children a near-normal life expectancy. Multiple injections, insulin pump therapy, and frequent blood glucose measurements have provided the basis for better quality of life and good metabolic control in people with type 1 diabetes. However, the value of insulin analogs is still in question (2). There is no doubt that industry has invested vast resources to develop new insulin types for safety and efficacy reasons. However, at present, there is no doubt that insulin analogs are more expensive, and in view of the rising tide of financial problems in healthcare systems globally, this in itself can potentially pose an additional threat to the free availability and affordability of insulin treatments for patients with type 1 diabetes worldwide. The Diabetes Control and Complications Trial (DCCT) research group showed the importance of strict metabolic control for the delay and/or prevention of diabetes complications (3,4). The indiscriminate use of terms such as "conventional" and "intensified" insulin treatment has been abandoned, and "simplified" therapies should not be recommended (4). Pre- or even postprandial administration of rapid-acting insulin analogs, especially in very young children, has been reported by some authors (5) to be safe and even advantageous. Multiple injection regimens allow greater freedom in daily routines and are therefore clearly the standard of insulin-replacement therapy. However, reports on the advantages of insulin analog therapy have very often been published only in abstract form and as supplements to company-organized meetings (1).

In their original article, Home et al. included an example of another misleading way of reporting on insulin analog treatment and its alleged advantages; their investigations were setup mainly to study safety and suitability issues. In the title, and in some key passages of the article, it is suggested that the insulin analog was superior in terms of achieving glycemic control and reducing hypoglycemic episodes when compared with NPH insulin. The data from their article, however, do not support this over-optimistic view and clearly show that HbA_{1c} levels for each of

the detemir groups were not different from those of the NPH group. In addition, and probably most importantly, the reduction of hypoglycemic episodes so enthusiastically reported was seen exclusively for "minor events," specifically during the night, while "major" hypoglycemic events were not reduced or eventually even greater in their $IDet_{morn + bed}$ group when compared with their NPH group. While we do not suggest that Home et al. have failed to carry out a useful and carefully executed study, we very much regret to see that the interpretation of their data is far from careful and not at all balanced. Since co-authors have industry affiliations and their interpretations may naturally reflect company interests. However, such reports as the article by Home et al. influence clinical decision making in daily practice and are based on individual beliefs and personal interests rather than on solid data when it comes to conclusions and decision making. A much more responsible attitude and more careful interpretation of data is clearly warranted and should guide clinical scientists when interpreting their data and writing articles for reputable peer-reviewed journals. As such, wording and biased phrasing in scientific papers is often more powerful than the actual data and scientific work. The scientific community should therefore behave responsibly when writing the results from clinical trials in order to not tarnish its reputation and most importantly to not lead the public and ultimately the patient to untimely and probably incorrect conclusions.

WIELAND KIESS, MD
KLEMENS RAILE, MD
ANGELA GALLER, MD
THOMAS KAPELLEN, MD

From the Hospital for Children and Adolescents, Medical Faculty, University of Leipzig, Leipzig, Germany.

Address correspondence to Prof. Dr. Wieland Kiess, Hospital for Children and Adolescents, University of Leipzig, Oststr. 21-25, D-04317 Leipzig, Germany. E-mail: kiw@medizin.uni-leipzig.de.

The authors of the original article did not wish to respond to this letter.

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Global Prevalence of Diabetes: Estimates for the Year 2000 and Projections for 2030

Response to Wild et al.

Global diabetes prevalence estimates for adults in 2000, which were derived from population-based data using oral glucose tolerance tests, were recently reported by Wild et al. (1). Because there are few OGTT-based data in the European region, estimates from a regional study carried out in the Netherlands were applied to 13 other countries, including Germany (2). For Germany, a prevalence of 4.1% was estimated, which corresponds to 2.6 million people with diabetes in 2000 (1).

In the German National Health Interview and Examination Survey in 1998, prevalence of known diabetes (self-reported) was assessed in a representative sample (aged 18–79 years) (3). Furthermore, from 1999 to 2001, glucose tolerance tests were carried out in the population-based KORA Survey 2000 (Augsburg, Germany) among 1,353 subjects aged 55–74 years (4). Both provided higher age- and sex-specific prevalence estimates than the Dutch study (2). Thus, ~5% of the adult German population had known diabetes in 1998. In addition, at least in the age-group >55 years, one-half of the total cases were undiagnosed (4). The total diabetes prevalence (diagnosed and undetected cases) in the 55- to 74-year age-group was 16.6% in the KORA Survey (4). As the one-for-one ratio for known/undiagnosed case subjects is valid for all age-groups, the total diabetes prevalence in the adult German population in 2000 was ~10%, corresponding to 6.3 million people. Germany should be listed among the 10 countries with the highest estimated number of people with diabetes in the world (1).

Thus, there is a greater diversity of diabetes prevalence in European countries than suggested by Wild et al. There are also differences in known risk factors for type 2 diabetes at the population level in European countries, e.g., the prevalence of obesity in Germany (20%) was almost twofold higher than in the Netherlands (5). Furthermore, the percentage of persons who did not partake in physical activity during their leisure time was higher in Germany (22.6%) than in the Netherlands (14.4%) and other European countries, which may partly explain the wide variation of diabetes prevalence (6).

WOLFGANG RATHMANN, MD, MSPH
GUIDO GIANI, PHD

From the Department of Biometrics and Epidemiology, German Diabetes Research Institute, Heinrich Heine University, Düsseldorf, Germany.

Address correspondence to Dr. Wolfgang Rathmann, MD, MSPH, German Diabetes Research Institute, Auf'm Hennekamp 65, D-40225 Düsseldorf, Germany. E-mail: rathmann@ddfi.uni-duesseldorf.de.

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Global Prevalence of Diabetes: Estimates for the Year 2000 and Projections for 2030

Response to Rathman and Giani

Rathmann and Giani (1) point out that there is a greater diversity of diabetes prevalence in Europe than suggested by our recent article (2) on the global prevalence of diabetes. We agree with this point. Unfortunately, the data from their study (3) in Augsburg, Germany, had not been published when the data for our article were assembled in 2002. As described in the article, we plan to update the estimates of diabetes prevalence and will include the Augsburg data in the next revision.

The global burden of disease study (4) only included studies describing the prevalence of diabetes defined using oral glucose tolerance tests. Prevalence studies based on self-reported diabetes were excluded because, as Rathmann and Giani found, ~50% of diabetes in European populations is undiagnosed. (This proportion varies with age, sex, and ethnicity).

We had similar concerns as Rathmann and Giani about applying diabetes prevalence rates from the Netherlands to other European countries, given the higher levels of physical activity and lower prevalence of obesity in the Netherlands compared with many other countries. For example, total diabetes prevalence, as derived from the study in the Netherlands, was lower in middle-aged people even when compared with self-reported diabetes prevalence from the Health Survey for England (5). A recent article (6) on the prevalence of known diabetes in eight European countries was published using data from sentinel general practices. The results suggest that the estimated prevalence of 2.7% for both diagnosed and undiagnosed diabetes for both sexes at all ages presented in our article for the Netherlands may be an underestimate, as the estimate for diagnosed diabetes for the Netherlands was ~2.6%. In Belgium, the prevalence of diagnosed diabetes at all ages was higher at ~3.3% than the estimate of 3.1% for both diagnosed and undiagnosed diabetes given in the global prevalence article.

The estimates of diabetes prevalence presented in the global burden article (2) are likely to represent conservative estimates for most regions as a consequence of the inclusion criteria and the need to extrapolate the limited available data, which may not reflect current patterns of diabetes prevalence. Even these conservative estimates have major public health implications. We hope that their publication will provide an incentive for better data collection on diabetes prevalence around the world, ideally as part of diabetes prevention programs.

SARAH H. WILD, MBBCHIR, PHD[1]
GOJKA ROGLIC, MD[2]
ANDERS GREEN, MD, PHD, DRMEDSCI[3]
RICHARD SICREE, MBBS, MPH[4]
HILARY KING, MD, DSC[2]

From the [1]Department of Public Health Sciences, University of Edinburgh, Edinburgh, Scotland; the [2]Department of Non-Communicable Diseases, World Health Organization, Geneva, Switzerland; the [3]Department of Epidemiology and Social Medicine, University of Aarhus, Aarhus, Denmark; and the [4]International Diabetes Institute, Caulfield, Australia.

Address correspondence to Dr. Sarah Wild, MBBCHIR, PhD, Department of Public Health Sciences, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG, Scotland. E-mail: sarah.wild@ed.ac.uk.

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Biological Variation in HbA_{1c} Predicts Risk of Retinopathy and Nephropathy in Type 1 Diabetes

Response to McCarter et al.

We read the article by McCarter et al. (1) with interest. Technically, all nonanalytical variation, irrespective of its source, is biological variation. Thus, mean blood glucose (MBG)-associated changes are included in biological variation. It must also be stressed that all population regression equations have confidence limits that need to be taken into account when comparing values from individuals to the population study mean.

However, such points do not take away from the message of McCarter et al. (1) that non-MBG–related biological variation may be an important prognostic indicator. The real question is how health care professionals are to identify this variation in routine clinical practice. MBG has many problems such as a large variation, which is common when many indepen-

dent analytes are measured (2), bias due to calibration issues (3), or the time taken for separation (4). Most importantly, it is rarely used in routine clinical practice. In addition, HbA_{1c} also has its problems (5). Accordingly, the calculation of the hemoglobin glycation index is problematic in routine clinical practice. Furthermore, calculated indexes will suffer from the propagation of error, contributing to misclassification and inaccurate prediction of complications (6).

We previously recommended the use of a rolling mean to reduce the effect of analytical and biological variation (7). The associated SD in stable patients would reflect the total variation for HbA_{1c}. Since the majority of the total variation is nonanalytical, use of the SD would easily identify those patients in routine clinical practice with large non-MBG–related biological variation. As well as being easier to perform in routine clinical practice, it would also be a more valid way of identifying within-patient HbA_{1c} variability. In addition, the use of a rolling mean and its associated SD makes the detection of critical changes in HbA_{1c} levels easier and more objective (5). Accordingly, we recommend the use of a rolling mean and its associated SD for the investigation of non-MBG–related biological variation.

PATRICK J. TWOMEY, MD, MRCPATH[1]
ADIE VILJOEN[2]
TIMOTHY M. REYNOLDS[3]
ANTHONY S. WIERZBICKI[4]

From the [1]Department of Clinical Biochemistry, The Ipswich Hospital, Ipswich, U.K.; the [2]Department of Clinical Biochemistry, Addenbrookes Hospital, Cambridge, U.K.; the [3]Department of Clinical Chemistry, Queen's Hospital, Burton-on-Trent, U.K.; and the [4]Department of Chemical Pathology, Guy's and St. Thomas' Hospital, London, U.K.

Address correspondence to Patrick J. Twomey, MD, MRCPath, The Ipswich Hospital, Department of Clinical Biochemistry, Heath Road, Ipswich, Suffolk IP4 5PD, U.K. E-mail: pattwomey@doctors.org.uk.

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Biological Variation in HbA_{1c} Predicts Risk of Retinopathy and Nephropathy in Type 1 Diabetes

Response to Twomey et al.

We appreciate the comments of Twomey et.al. (1) in regard to our recent article (2) about biological variation in HbA_{1c} and its relationship to microvascular complications. They point out potential obstacles to the general use of the hemoglobin glycation index (HGI) by clinical practitioners. The best approach to calculating the HGI of individual patients from populations besides the Diabetes Control and Complications Trial (2) and our original patient data (3) still needs to be established for the clinician.

We point out, however, that a moving average of an individual patient's HbA_{1c} will not provide the same information as the HGI. Our analyses indicate that HbA_{1c} carries two important components of clinically relevant information: *1*) an estimate of the patient's preceding mean blood glucose (MBG) and *2*) patient-specific factors besides MBG that influence glycation of hemoglobin. Both of these components are independently associated with the risk of development of microvascular complications (2). Currently, clinical therapy is only directed at altering the first component. Calculation of the HGI allows us to separate the two components of risk from the patient's HbA_{1c} measurements. In this fashion, individual patients who have consistently high or low hemoglobin glycation status can be identified. However, calculating a patient's HGI requires knowledge of the patient's preceding MBG, the population relationship between HbA_{1c} and MBG, and the patient's HbA_{1c}.

We foresee the future development of databases that will assist clinicians in calculating an HGI necessary to assess the hemoglobin glycation status of their patients. These computational sources will need to be referenced to population data that are specific for the methods of determining both the MBG and HbA_{1c} used for that particular patient.

STUART A. CHALEW, MD[1]
ROBERT J. MCCARTER, SCD[2]
JAMES M. HEMPE, PHD[3]

From the [1]Department of Endocrinology, Children's Hospital, New Orleans, Louisiana; the [2]Department of Bioinforatics and Statistics, Children's National Medical Center, Washington, D.C.; and the [3]Department of Pediatrics, Louisiana State University Health Sciences Center, New Orleans, Louisiana.

Address correspondence to Stuart A. Chalew, MD, Children's Hospital, Department of Endocrinology, 200 Henry Clay Ave., New Orleans, LA 70118. E-mail: schale@lsuhsc.edu.

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