

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).

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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 lipotrophic 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/m²) 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 μ g/ml) was significantly lower than in nondiabetic WS patients (11.6 ± 9.2 μ g/ml, $P = 0.006$) or control subjects (14.4 ± 8.8 μ g/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 $\mu\text{g/ml}$ ($P = 0.03$ 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 $6.4 \pm 0.5\%$ ($P = 0.17$), 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.

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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/m² and $10.8 \pm 1.1\%$, respectively. Their daily energy intake during the course of the study was $1,490 \pm 166$ 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 α 2-plasmin inhibitor complex (PPI) level and plasminogen activator inhibitor-1 (PAI-1) activity in plasma was measured using a latex photometric immunoassay, while thrombin anti-thrombin 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 \pm 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 $\mu\text{g/ml}$, $P = 0.0009$; 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 docosahexaenoic 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.

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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.

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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-

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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.

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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 con-

cerned. While a cure for type 1 diabetes has not yet been achieved, comprehensive, multidisciplinary treatment strategies have led 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.

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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 toler-

ance 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).

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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.

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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.

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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.

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