OBSERVATIONS

Peripheral Arterial Compliance Differs Between Races

Comparison among Asian, Afro-Caribbeans, and white Caucasians with type 2 diabetes

Patients with type 2 diabetes have two to three times the risk of dying prematurely from cardiovascular disease than their nondiabetic counterparts (1). Many studies have shown that arterial compliance is reduced in type 2 diabetes and that arterial stiffness increases with deteriorating glucose tolerance status, even before the onset of type 2 diabetes (2–4). In a previous brief report, we studied Afro-Caribbean and white Caucasian subjects with diabetes and found a decrease in peripheral arterial compliance in the Afro-Caribbean subjects (5). We also reported an accelerated rate of aging in the elastic arteries of diabetic patients reaching a plateau by the age of 50–60 years (6). The present article examines the control versus diabetic differences in two races, white Caucasians and Afro-Caribbeans, and includes data on Asians from the Indian subcontinent with diabetes.

Fifty-seven patients with a diagnosis of type 2 diabetes for at least 1 year (21 white Caucasian, 20 Afro-Caribbean, and 16 Asian) aged 44–80 years (mean ± SD 61 ± 7.4) and 48 healthy control subjects (30 white Caucasian and 18 Afro-Caribbean) aged 34–86 years (65.5 ± 11.6) took part in this cross-sectional study.

Pulse wave velocity of the carotid-femoral (PWV_{cf}) was measured noninvasively in a thoraco-abdominal segment and in an upper-limb muscular artery (PWV of the carotid-radial [PWV_{cr}]) using the Complior (Colson, Pantin, France) system. PWV from the aorta to the finger (PWV_{fin}) was measured using the Finapress (Ohmeda, Madison, WI) and custom-written software (J.D.C.). Central aortic compliance (CAC) was also assessed from simultaneous measurements of ascending aortic blood flow and surrogate estimates of aortic root pressure using a method described by Liu et al. (7) and previously reported by Cameron et al. (8).

Analysis of the clinical characteristics of the participants for the diabetic and control groups and by ethnicity showed that for the diabetic group, only BMI was significantly different between the races ($P < 0.05$), with the white patient group having the highest mean value (29.9 kg/m^2). For the control population, only age was significantly different ($P = 0.01$), with Caucasians being on average 8 years older than Afro-Caribbeans.

Race was found to be a major determinant of PWV_{cr} in type 2 diabetic subjects, with Afro-Caribbeans having the highest mean value (12.10 ± 1.4 m/s) of the three ethnic origins ($P = 0.03$) compared with Caucasians (11.12 ± 1.3 m/s) and Asians (10.95 ± 1.3 m/s). The racial differences were independent of blood pressure. No differences were found between the races for PWV_{cf}, PWV_{fin}, or CAC. Analysis in the control population showed no differences in arterial compliance between the Afro-Caribbeans and Caucasians.

We have shown that there is a racial preponderance of stiffening of the peripheral arteries in diabetic subjects, with subjects of Afro-Caribbean origin having significantly higher mean indexes for PWV_{cr} compared with those of white and Asian origin. Diabetes led to a decrease in the compliance of the aorto-iliac-femoral segment of the arterial system (PWV_{cf}). The muscular arteries of diabetic subjects of Afro-Caribbean origin tended to have a reduced compliance. This difference could reflect the increased complications observed in Afro-Caribbeans with type 2 diabetes.

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Extrapancreatic Autoimmunity in Patients With Latent Autoimmune Diabetes of Adults

Type 1 diabetes often occurs in association with other autoimmune diseases (thyroid disease [1–3], Addison's disease [2], celiac disease [1,3], autoimmune gastropathy [4], and others), with autoimmune thyroiditis being

the most common (1–3). To determine whether these autoimmune diseases are also more frequent in patients with latent autoimmune diabetes of adults (LADA), we compared the prevalence of anti–21 α-hydroxylase (21OHAb), anti–thyroid peroxidase (TPOAb), anti–parietal gastric cell antibodies, and rheumatoid factor in a group of patients with LADA versus patients with type 2 diabetes.

Fifty-four patients with LADA (>35 years of age at diagnosis who did not require insulin for at least 1 year after diagnosis and with positive GAD antibody [GADA]) (5) were included in the study (group A). Group B consisted of 54 individuals with type 2 diabetes (negative GADA) with the same characteristics (31 men and 23 women in the two groups, mean age 42 ± 5.8 and 43.2 ± 4.9 years, respectively). The interval between the diagnosis of diabetes and antibody measurement was <2 years (14 ± 3 and 13 ± 5 months, respectively). GADAs were determined by radioimmunoassay, with a level ≤1 unit/ml considered negative. TPOAbs were measured by a chemiluminescent assay, with a negative value <15 units/ml. Anti–parietal gastric cell antibodies were assayed by indirect immunofluorescence and 21OHAb by radioimmunoassay-iodine, with a level ≤1 unit/ml considered negative. Rheumatoid factor was measured by nefelometry (reference value <35 units/ml). Differences between the two groups were tested by Fisher's exact test. A *P* value <0.05 was considered statistically significant.

The frequency of 21OHAb did not differ between the two groups (5.5% in group A vs. 0% in group B, $P = 0.24$). None of the three 21OHAb-positive patients presented clinical or laboratory evidence of primary adrenal insufficiency (determination of potassium, ACTH, cortisol, aldosterone, and plasma renin activity). There was also no difference in anti–parietal gastric cell antibodies (9.2 vs. 3.7%, $P = 0.43$), and none of the patients presented cobalamin deficiency (vitamin B_{12} <200 pg/ml). Rheumatoid factor was similar in the groups (7.4% in LADA vs. 1.8% in type 2 diabetes, $P = 0.21$), and all patients were clinically asymptomatic (rheumatoid arthritis). The prevalence of TPOAb was significantly higher in group A (24 vs. 5.5%, $P = 0.006$). In addition, a difference in the concentration of TPOAb was also detected (82 vs. 28 IU/ml, $P = 0.003$). Primary hypothyroidism (thyroid-stimulating hormone >5 IU/ml) was observed in 25% of the patients with TPOAb (3 of 13 patients in group A and 1 of 3 patients in group B).

Increased frequency of autoimmune disease–associated antibodies is observed in patients with type 1 diabetes (1–4). Similarly, we demonstrated that patients with LADA also show a higher prevalence of TPOAb when compared with type 2 diabetic individuals. The lack of a significant difference in 21OHAb, anti–parietal gastric cell antibodies, and rheumatoid factor might be attributed to the size of the sample. In agreement with our results, other studies have also reported a higher prevalence of autoantibodies in patients with LADA than in type 2 diabetic individuals, namely TPOAb (6–11), antigliadin and -endomysial antibodies (6), 21OHAb (7,9), and anti–parietal cell antibodies (11).

We conclude that patients with LADA show a higher frequency of autoimmune thyroiditis and should be routinely investigated for this condition.

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Possible Beneficial Effect of Telmisartan on Glycemic Control in Diabetic Subjects

In a recent issue of *Diabetes Care*, Pershadsingh and Kurtz (1) reported an interesting case subject with impaired glucose tolerance, whose insulin resistance and triglycerides improved on the angiotensin II type 1 receptor blocker telmisartan. Telmisartan has a unique agonist activity of the peroxisome proliferator–activated receptor γ (PPARγ) in vitro (2). It reduces glucose, insulin, and triglyceride levels in rats fed a high-fat, high-carbohydrate diet (2). These results suggest that telmisartan may have a beneficial effect on glycemic control in type 2 diabetes.

We investigated the effect of telmisartan or candesartan on glycemic control in 38 Japanese patients with type 2 diabetes and hypertension (22 men and 16 women, mean age 67.0 ± 9.11 years [means ± SD]). Two different doses of telmisartan (20 and 40 mg/day) were given in 20 subjects ($n = 9$ and $n = 11$, respectively), and candesartan (8 mg/day) was given in 18 subjects. HbA_{1c} levels were measured before and 3 months after administration. In the 40-mg telmisartan group, HbA_{1c} was significantly decreased after 3 months (from 8.12 ± 0.97 to 7.43 ± 0.79%, $P < 0.05$, paired t test), whereas no significant change in HbA_{1c} was found in the 20-mg telmisartan group or the control group (7.49 ± 0.70 to 7.45 ± 0.75% and 7.40 ± 1.38 to 7.32 ± 1.28%, respectively).

Since this study was limited by the fact that it was not a randomized study and that it included only a small number of patients, the effect of confounding factors could not be excluded. Therapy was changed during the observation period in some cases (insulin doses were increased up to 2 units in one case or decreased up to 2 units in three cases, whereas no change was made in oral medications), but no apparent correlation could be found between the changes in insulin dose and those in glycemic control. Despite these limitations, this preliminary result is in line with the hypothesis that telmisartan has an insulin-sensitizing effect through PPARγ activation (1). However, our result is not compatible with another report (3) on type 2 diabetes, in which no change in HbA_{1c} was observed after administration of 40 mg telmisartan. The baseline HbA_{1c} level was low in that report (6.45%) compared with our study. In our study, there were considerable variations in HbA_{1c} changes after telmisartan, similar to those after thiazolidnedione ligands of PPARγ, and the patients with lower HbA_{1c} showed a smaller decrease after telmisartan than those with a higher HbA_{1c}. A randomized control study with a larger number of subjects may be justified to test whether telmisartan may improve glycemic control in type 2 diabetes.

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The Concurrent Validity of the Chinese Version of the Diabetes Empowerment Scale

In 2003 , we developed and psychometrically tested the Chinese version of the Diabetes Empowerment Scale with 20 items (C-DES-20) (1) in 207 patients. It was cross-culturally adapted from the Diabetes Empowerment Scale, which was previously established in the U.S. (2–4) to measure the psychosocial self-efficacy of people with diabetes. The C-DES-20 ($\alpha = 0.86$) contains five subscales: overcoming barriers (four items; $\alpha = 0.89$), determining suitable methods (five items; $\alpha = 0.79$), achieving goals (four items; $\alpha = 0.78$), obtaining support (four items; $\alpha = 0.78$), and coping (four items; $\alpha = 0.76$). The test-retest reliability of the C-DES-20 was good (intraclass correlations = 0.75, 95% CI 0.43–0.91). There was criterion validity between the C-DES-20 and HbA_{1c} ($r = -0.17$, $P = 0.03$).

To further determine the validity of the C-DES-20, we asked an additional 102 community-dwelling individuals with type 2 diabetes to administer the scale using structured interviews, along with a previously validated Chinese version of the General Self-Efficacy scale (C-GSE10), which contains 10 items (5,6). A sample item is "I can always manage to solve difficult problems if I try hard enough." The Cronbach's α of this scale for the current sample was 0.93.

Subjects were recruited using convenience sampling from a patient-led nongovernment organization that provided peer support services. The subjects ranged from 38 to 81 years of age, and the mean (±SD) age was 58 ± 12 years. Half of the sample was female. The majority of subjects had a primary to secondary level of education, and 17% were illiterate. Thirty-nine percent were employed. The mean length of time since diagnosis was 9 ±7 years. The Pearson correlation coefficient of the two scales, C-DES-20 and C-GSE-10, was 0.63 ($P = 0.001$). The positive correlation remained $r = 0.48$ ($P = 0.001$), after controlling for age, education level, and adequacy of self-

management knowledge, indicating concurrent validity.

These findings add another piece of evidence to support that the C-DES-20 is a valid and reliable measure. Considering its brevity and easy administration, the C-DES-20 offers a useful instrument of the psychosocial self-efficacy of Hong Kong residents with diabetes. Further study with different Chinese populations will be required to confirm the factor structure of the scale.

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Randomized Trial of a Color-Coded Slide Rule in Children With Diabetes

Self-management is important, but difficult, in children with diabetes. A color-coded slide rule containing a color scheme representing a treatment algorithm might help diabetic children with self-management (1). Moving the slide rule to the right moment of the day reveals a color that corresponds to the glucose value. The slide rule will describe the correct action to be undertaken. These actions include taking extra insulin but can also include consuming more carbohydrates, as well as ketone monitoring, blood glucose checking, or consulting a diabetes expert. The amount of insulin taken is individualized to the patient by using a written insert paper with the actual amount recorded.

To determine the effect of a color-coded slide rule, we performed a randomized multi-center trial in three Dutch hospitals. Children with diabetes from ages 1 to 16 years were randomly assigned to the intervention group, where they immediately started to use the slide rule for a period of 6 months, or to the control group, in which they began using the slide rule after 3 months for a period of 3 months. The outcome measures were changes in HbA_{1c}, blood glucose levels, knowledge about glucose values, and quality of life. Informed consent was obtained from the patients and/or their families before entry into the study, which was approved by the medical ethical committees of the three participating hospitals.

A total of 79 children (mean age 11.1 years, mean duration of diabetes 4.9 years) were enrolled in our study. The intervention group had similar outcomes compared with the control group on all outcome measures. However, in the group with a high baseline HbA_{1c} ($\geq$7.7%), there was a significant difference in the decrease in HbA_{1c}. HbA_{1c} decreased 0.4 $\pm$ 0.2% in the intervention group and increased 0.1 $\pm$ 0.3% in the control group ($P = 0.049$). No negative side effects were found, i.e., the amount of hypoglycemic episodes was not affected during use. Patients liked using the slide rule and referred to it as a good tool in the day-to-day care of their diabetes.

Metabolic control is linked to a patient's level of knowledge and their application of this knowledge. Increased knowledge about diabetes and blood glucose levels has been related to better metabolic control (2), although this is not always the case (3,4). We conclude that a color-coded slide rule is safe and that patients liked using it. We also conclude that children with a higher baseline HbA_{1c} might benefit from the slide rule by obtaining better metabolic control. Use of the slide rule did not affect patients' knowledge of the interpretation of blood glucose levels or their quality of life.

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COMMENTS AND RESPONSES

Guidelines for Computer Modeling of Diabetes and Its Complications

Response to American Diabetes Association Consensus Panel

The ADA consensus panel guidelines for computer modeling (1) may create a misleading and unduly optimistic view of modeling for general readers. Repeated use of the terms "accurate" and "reliable" suggests that models are capable of generating precise predictions of long-term clinical outcomes and costs. Sadly, models do no more than encompass our current understanding (and ignorance) of a disease, its treatment , and its natural history. Despite powerful computers and sophisticated software, no model generates new data—it merely combines existing findings within a framework of human assumptions and generalizations. The modern era of diabetes modeling is only 7 years old (2) and, despite strenuous efforts in four Mount Hood challenges (3), shows no evidence of achieving convergent accuracy.

Readers should not be misled into concluding that "validation" confers "validity" on a model's results. Internal validation is a very low standard, only requiring a model to reproduce the data originally used in its calibration. Even successful replication of an independent result (external validation) may only be a "lucky hit" and cannot guarantee that model predictions for longer timescales, different patient groups, or other clinical settings are any more accurate or reliable than long-range weather forecasts.

The discussion of uncertainty in the guidelines emphasizes parameter variability and thereby masks the main cause of imprecision. A model's Achilles' heel lies in the assumptions and design choices governing how numerical values are generated. Experience shows that small differences in functional forms, when extrapolated, often lead to widely differing predictions, yet these qualitative uncertainties are rarely discussed.

Despite these cautions, researchers in medicine, epidemiology, economics, and operations research have made important progress in developing various types of diabetes models for different purposes, including individual patient management, public health policy, service planning, and economic evaluation. However, diabetes presents the modeling community with its greatest test, encompassing probably the widest range of serious comorbid interacting conditions of any chronic disease. Many modeling problems (practical and methodological) remain unresolved for even the "simple" conditions, such as terminal cancer. Although the progress in diabetes modeling is encouraging, it should not be overstated, and those outside the modeling community should not be misled into believing that model predictions constitute accurate and reliable evidence similar to a clinical trial. A model is a tool to help decision makers explore various aspects of their dilemma, not an objective mechanism to relieve them of responsibility for weighing the evidence. Greater clarity in how models and results are reported is more helpful here than general prescriptive pronouncements.

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Guidelines for Computer Modeling of Diabetes and Its Complications

Response to Bagust and McEwan

As Bagust and McEwan (1) indicate, diabetes models are being used for a variety of purposes, such as patient management, public health policy, and economic evaluation. Potential "end-users" of the results from modeling studies turn to this technology largely because evidence from empirical studies is lacking and cannot be easily or quickly obtained .

As our consensus statement points out, if the results from modeling studies are to be believed, the end-user must have confidence that the model itself "accurately and reliably" represents the real world, in which the subsequent modeling study will take place. That is, do the components of the model (equations/formulas) truly capture what we know about the real world? A user will have confidence that this critical assumption is true when it has been shown that the model reproduces the studies used to construct the equations (i.e., internal validation) and that the model can replicate the results of studies that were not used to build the model (i.e., external validation).

Without having such validations, users should be very skeptical of the results of a modeling study. Indeed, users would be better off knowing that a model has been extensively validated even before collaborating on or commissioning a project.

Bagust and McEwan offer no alternative approach to engender believability, likely because there is none. Downplaying the enormous value of model validation may mislead users into thinking that all models are the same, when they are far from it.

In addition, Bagust and McEwan contend that models are incapable of generating accurate predictions of long-term clinical outcomes and costs. In fact, the very purpose of external validation is to prove that a model is capable of doing just that, as well as to improve the believabil-

ity of the model's results when there are no real-life data for comparison. Readers should keep in mind that even the results of well-controlled randomized trials do not precisely depict reality, but they are the best models we have. "Real" patients often do not meet all inclusion and exclusion criteria, or in practice receive all of the health care given in a trial, or visit doctors with the same enthusiasm and commitment as trial participants.

The ultimate purpose of the Guidelines (2) is to encourage clinicians and policy makers to more readily incorporate the results of a model in decision making. If hundreds of thousands of people every day stake their lives on the accuracy and reliability of validated mathematical models (e.g., by flying on an airplane), surely clinicians and policy makers can depend on models as a "level of evidence" well above many others (e.g., expert opinion). But to do so first requires modelers to demonstrate the accuracy and reliability of their approach. The Guidelines help lay the framework toward achieving that confidence.

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