

Shortened Telomere Length in White Blood Cells of Patients with IDDM

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IDDM is a polygenic and autoimmune disorder in which subsets of white blood cells (WBCs) are engaged in the destruction of β -cells of the pancreas. The mechanisms that account for the abnormal behavior of these cells in IDDM are not fully understood. By measuring the mean length of telomeres of WBCs from patients with IDDM, we tested the concept that telomeres might play a role in IDDM. We examined the lengths of the terminal restriction fragments (TRFs) of DNA of WBCs from 234 white men comprising 54 patients with IDDM, 74 patients with NIDDM, and 106 control subjects. When adjusted for age, the TRF length from WBCs of patients with IDDM was significantly shorter than that of nondiabetic control subjects (mean \pm SE: 8.6 ± 0.1 vs. 9.2 ± 0.1 , $P = 0.002$). No significant difference was observed between the TRF length from WBCs of patients with NIDDM versus nondiabetic subjects. Neither the duration nor the complications of IDDM (i.e., nephropathy and hypertension) had an effect on the TRF length of WBCs from patients with IDDM. The shortened TRF length of WBCs of patients with IDDM likely reflects a marked reduction in the TRF length of subsets of WBCs that play a role in the pathogenesis of IDDM. *Diabetes* 47:482-486, 1998

The biology of telomeres, the ends of chromosomes, has been the focus of numerous investigations. Many of these investigations have attempted to understand the role of telomeres in human cancer (1,2). However, telomere biology may play a role in other disorders. For instance, telomere length in subsets of peripheral lymphocytes might reflect the immune status of patients with human immunodeficiency virus (HIV) infection (3,4). A recent communication has also proposed that telomeres might also play primary or secondary roles in complex genetic disorders, including essential hypertension and atherosclerosis (5). However, the cells that play key roles in these disorders (e.g., renal cells, vascular endothelial cells)

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HIV, human immunodeficiency virus; TRF, terminal restriction fragment; WBC, white blood cell.

are not easily accessible for large-scale clinical investigations. IDDM is also a complex polygenic disorder (6,7), arising from an autoreactivity of subsets of white blood cells (WBCs) (8), and these cells are readily available for research. The present project was therefore undertaken with a view to explore whether telomere biology is altered in WBCs of patients with IDDM.

The hypothesis we tested was that when adjusted for age, the mean length of telomeres, expressed as the mean length of the terminal restriction fragments (TRFs) (9), of WBCs is shorter in patients with IDDM than in nondiabetic subjects. To examine whether chronic hyperglycemia might modify TRF length in WBCs independent of an abnormal WBC function, we also examined DNA from WBCs of patients with NIDDM. At the core of this investigation was the concept that diminished TRF length might represent primary genetic variations in patients with IDDM that promote intrinsic alterations in lymphocyte functions that play a role in the destruction of β -cells in the pancreas. Alternatively, diminished TRF length could reflect a secondary phenomenon resulting from an accelerated telomere attrition because of an increase in the rate of turnover of subsets of lymphocytes, due to the chronic activation of these cells.

RESEARCH DESIGN AND METHODS

Study population. Samples of DNA from WBCs for this study were taken from three panels of DNA established in the Genetics Core Laboratory at the Diabetes and Endocrinology Research Center at the Joslin Diabetes Center in Boston. These panels include DNA samples from IDDM patients, NIDDM patients, and nondiabetic control subjects. Patients were classified as having IDDM if diabetes was diagnosed before age 25 years and was treated with insulin during the first year of diagnosis. Patients were classified as having NIDDM if diabetes was diagnosed at age 26 years or older and was not treated with insulin until at least 1 year after diagnosis. All IDDM and NIDDM patients were under the care of the Joslin Diabetes Center. DNA samples from 54 patients with IDDM, 74 patients with NIDDM, and 106 control subjects were used for this study. All subjects were white men. The unrelated nondiabetic control subjects were individuals who had random blood glucose values below 100 mg/dl. Patients with IDDM or NIDDM were evaluated for the presence of nephropathy by measuring albumin/creatinine ratio in random urine samples (10). All individuals completed a standardized questionnaire regarding demographic information, current health, and drug treatment and provided a venous blood sample for DNA. Blood, drawn into EDTA tubes, was stored at -20°C until DNA extraction (11). The consent form for this study was approved by the Human Subject Committee at the Joslin Diabetes Center.

Each diabetic patient was characterized with regard to age at the time of blood donation, age at the time of diagnosis of diabetes, presence or absence of hypertension, and presence or absence of micro- or macroalbuminuria. Hypertension was diagnosed if the patient had been told by a physician that he had hypertension and was treated with antihypertensive drugs at the time of examination, or if the sitting blood pressure was greater than or equal to 160 mmHg systolic or 95 mmHg diastolic. Blood pressure measurements were available for only 52 patients with IDDM, 72 patients with NIDDM, and 76 control subjects. The ages of control subjects without available blood pressure records were between 20 and 45 years.

TRF length analysis. DNA samples were numerically coded and sent in a number of batches to the laboratory of the Hypertension Research Center of the University of Medicine & Dentistry of New Jersey. Half of the samples in each batch

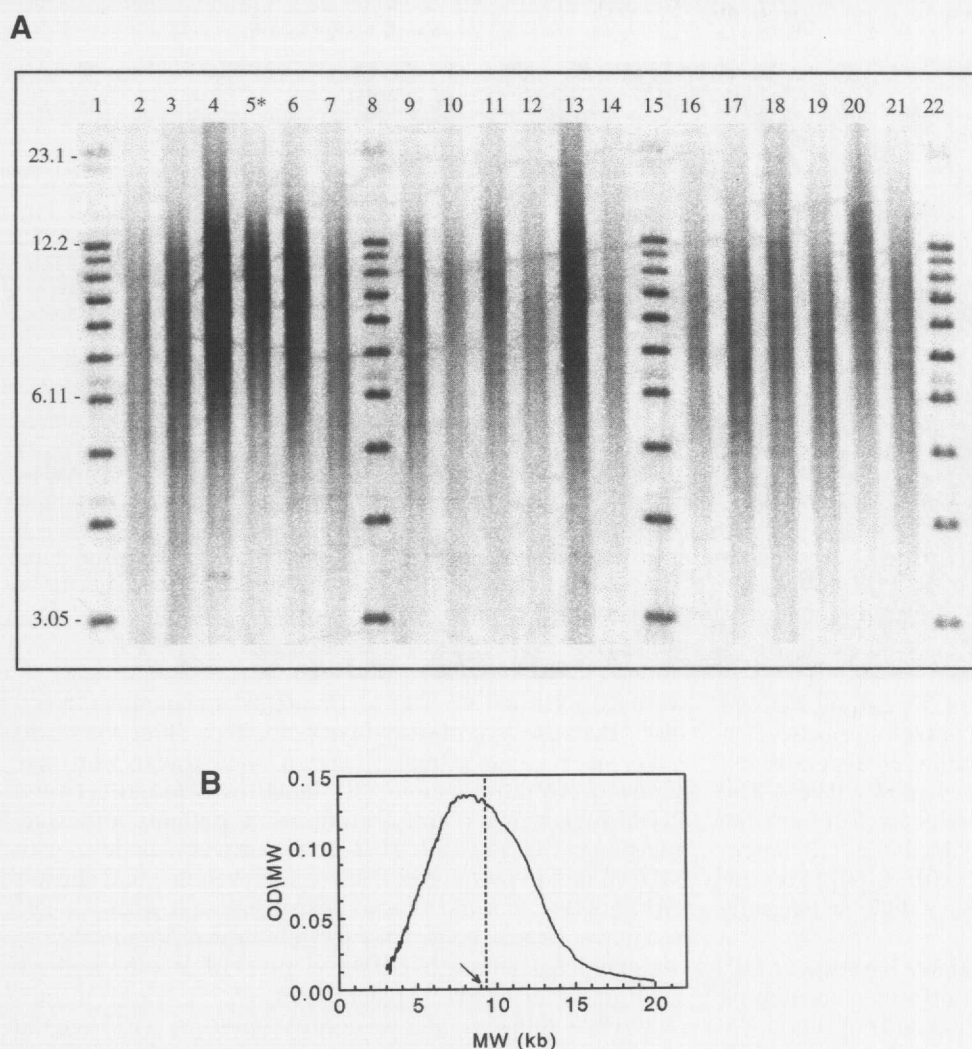


FIG. 1. An autoradiogram showing the length of the TRFs of genomic DNA from WBCs of diabetic patients and control subjects (A) and a densitometrical scan of the TRF length for lane 5 between 3 and 20 kb (B). The mean TRF length was calculated as follows: $TRF = \sum OD_i / \sum (OD_i / MW_i)$, where OD_i is optical density at a given position in the lane and MW_i is molecular weight at that position; this formula (12) accounts for the fact that longer telomeres bind more labeled probes and consequently appear darker on the X-ray film. The mean of the duplicate of each sample was used for data analysis. Lanes 2–7 and 9–11 show TRFs from patients with IDDM, and lanes 12–14 and 16–21 show TRFs from control subjects. Lanes 1, 8, 15, and 22 are molecular weight reference ladders. Samples were referred to the nearest ladder. For instance, the ladder in lane 1 served as a reference for samples in lanes 2, 3, and 4. *The lane that was scanned in the lower panel. Arrow indicates the mean TRF length.

were from diabetic subjects and the other half from nondiabetic control subjects of a similar age. After completion of all TRF measurements in all samples, the numbers were decoded for data analysis. Samples of 5 μ g were studied in duplicate. The samples were digested overnight with restriction enzymes *Hinf*I (10 U) and *Rsa* I (10 U) (Boehringer Mannheim, Indianapolis, IN). The DNA was precipitated and washed before dissolving in Tris-EDTA buffer. Eighteen DNA samples from different individuals and four DNA ladders (1-kb DNA Ladder plus γ DNA/*Hind*III fragments [Gibco Life Technologies, Gaithersburg, MD]) were resolved in a 0.5% agarose gel (20 cm \times 20 cm) at 50V (GNA-200 Pharmacia Biotech, Piscataway, NJ). Duplicates from the same samples were resolved on different gels. After 16 h, the gels were denatured for 30 min in 0.5 M NaOH/1.5 M NaCl and neutralized for 30 min in 0.5 M Tris, pH 8/1.5 M NaCl. The DNA was transferred for 1 h to a nylon membrane positively charged (Boehringer Mannheim) using a vacuum blotter (Appligene, ONCOR, Gaithersburg, MD). The membranes were then hybridized at 42°C with the telomeric probe [digoxigenin 3'-end labeled 5'-(CCCTAA)₃] overnight in 50% formamide, 5 \times SSC, 0.1% Sarkosyl, 0.02% SDS, and 2% blocking reagent (Boehringer Mannheim). The membranes were washed at room temperature, three times in 2 \times SSC, 0.1% SDS, each for 15 min, and once in 2 \times SSC for 15 min. The digoxigenin-labeled probe was detected by the digoxigenin luminescent detection procedure (Boehringer Mannheim) and exposed on X-ray film. The mean TRF length was measured as described in the legend to Fig. 1.

Statistical analysis. The primary objective of analyses was to compare the TRF lengths of WBCs of patients with IDDM and NIDDM to TRF lengths of nondiabetic control subjects. In four subjects, TRF length was only known to be less than 5 kb. For analytic purposes, we imputed the value 4.99 kb to these TRF lengths; substitution of the lowest measured length, 4.71 kb, gave essentially identical results. We used 1) χ^2 and Fisher's exact tests to compare the subsets of diabetic patients with hypertension and with albuminuria; 2) ANOVA with Tukey's multiple comparison method to compare mean ages at blood donation, BMI, and systolic and diastolic blood pressure; and 3) Student's *t* tests or Wilcoxon's rank-sum tests to compare age at diagnosis of diabetes, age at initia-

tion of insulin treatment, duration of diabetes, and duration of insulin treatment in IDDM and NIDDM patients. We used linear regressions to analyze TRF length as a function of age at examination and included age at blood donation as a covariate in general linear models (analysis of covariance) to compare mean TRF lengths after adjustment for age. Means are expressed \pm SD; linear regression slopes and least square estimates are expressed \pm SE of the estimate. The analyses were conducted with SAS statistical software. The criterion for statistical significance was $P < 0.05$ in two-tailed or global comparisons.

RESULTS

Table 1 shows the characteristics of the 234 subjects at the time of blood donation. Differences in age at blood donation reflect the age-based definitions of IDDM and NIDDM and the recruitment of adult control subjects of all ages. IDDM patients range in age from 17 to 48 years; NIDDM patients from 34 to 75 years; and control subjects from 20 to 87 years. Ten IDDM patients had microalbuminuria and 11 had macroalbuminuria. Twenty-two patients with NIDDM had microalbuminuria and 15 had macroalbuminuria. Four nondiabetic subjects had microalbuminuria. IDDM and NIDDM patients differed in age at diagnosis, age at first insulin treatment, duration of diabetes, and duration of insulin treatment as a consequence of the diagnostic class definition.

Figure 2 depicts the relationship between TRF length and age at blood donation. The figure illustrates that the range of age is not comparable among the three groups. In particular,

TABLE 1
Characteristics at time of examination by diabetic class

Characteristic	IDDM	NIDDM	Control
<i>n</i>	54	74	106
Age (years)	30.4 ± 7.7	59.5 ± 8.0	51.5 ± 18.1
BMI (kg/m ²)	24.6 ± 3.9	29.4 ± 4.9	28.5 ± 4.9
Systolic blood pressure (mmHg)	129.9 ± 15.3	137.8 ± 19.7	131.8 ± 17.2
Diastolic blood pressure (mmHg)	73.1 ± 9.9	79.7 ± 8.5	81.4 ± 9.6
Age at diagnosis (years)	12.5 ± 7.1	44.7 ± 8.2	—
Age at first insulin treatment (years)	12.5 ± 7.1	53.4 ± 7.9	—
Duration of diabetes (years)	17.9 ± 9.3	14.8 ± 8.2	—
Duration of insulin treatment (years)	17.9 ± 9.3	7.1 ± 5.0	—

Data are means ± SD. For age, $P < 0.001$ by analysis of variance (ANOVA). All pairwise differences are significant by Tukey's method. For BMI, $P < 0.001$ by ANOVA. IDDM mean is lower than NIDDM or control group mean by Tukey's method. Means are based on 52 IDDM, 74 NIDDM, and 80 control subjects. For systolic blood pressure, $P = 0.04$ by ANOVA. IDDM mean is lower than NIDDM by Tukey's method. Systolic and diastolic blood pressure means are based on 52 IDDM, 72 NIDDM, and 76 control subjects. For diastolic blood pressure, $P < 0.001$ by ANOVA. IDDM mean is lower than NIDDM or control group mean by Tukey's method. For age at diagnosis and at first insulin treatment, $P < 0.001$ by t test for difference in means. Means for age at first insulin treatment and duration of treatment are based on 47 insulin-treated NIDDM patients. For duration of diabetes, $P = 0.05$ by t test for difference in means. For duration of insulin treatment, $P < 0.001$ by rank-sum test. Durations are greater among IDDM patients.

all IDDM patients are under the age of 50, and all NIDDM patients are older than 30. Among control subjects, TRF length declines significantly with age; the linear regression estimate of slope was -0.027 ± 0.005 kb/year ($P < 0.001$). The decline in TRF length among IDDM patients was of the same magnitude, -0.030 ± 0.015 kb/year. The decline in TRF length with age among NIDDM patients was -0.018 ± 0.014 kb/year. The slopes for decline in TRF length did not differ significantly among the three groups.

To test the hypothesis that IDDM patients have lower TRF lengths than nondiabetic subjects, we performed an analysis of covariance with adjustment for age at blood collection. We restricted this analysis to control subjects under the age of 50, the upper end of the IDDM age range, so that age adjustment would provide an estimate of mean TRF in the middle of the IDDM age range and would not be influenced by control data beyond the observed IDDM age range. TRF lengths were significantly lower among IDDM patients, by a difference of 0.6 kb (8.6 vs. 9.2 kb, $P = 0.002$; Table 2). A comparison of TRF lengths in NIDDM patients and control subjects was restricted to subjects between the ages of 30 and 75, the approximate range for NIDDM patients. Age-adjusted means were 8.1 kb for NIDDM patients and 8.3 kb for control subjects (difference not significant).

We investigated the relationship between time since diagnosis of diabetes, time on insulin therapy, hypertensive status, and micro- or macroalbuminuria. These age-related correlates of diabetes are potential confounders of the relationship between diabetes and TRF length. Within the classes of IDDM and NIDDM patients, neither time since diagnosis nor duration of insulin therapy was correlated with TRF length. Partial correlation coefficients that adjusted for age at examination also showed no significant association between TRF length and duration of diabetes or insulin treatment: correlation coefficients ranged from -0.21 to 0.13 . Presence of albuminuria was not related to TRF length among IDDM patients or NIDDM patients.

Hypertensive patients with IDDM had shorter TRF lengths than did normotensive patients with IDDM: respective means

were 8.0 ± 1.1 and 8.8 ± 0.7 kb ($P = 0.004$, unequal-variance t test). Because hypertensive patients were older than normotensive patients in this population, comparisons were age-adjusted. No difference in TRF length was found between IDDM hypertensive and normotensive patients after age-adjustment (8.5 vs. 8.8 kb, $P = 0.4$). Hypertensive patients with NIDDM and hypertensive control subjects also had shorter TRF lengths than did normotensive patients with NIDDM and normotensive control subjects, but the differences were not significant: among NIDDM patients, TRF lengths were 8.0 ± 1.0 in hypertensive subjects versus 8.1 ± 0.9 kb in normotensive subjects; among control subjects, TRF lengths were 8.1 ± 0.9 in hypertensive subjects versus 8.4 ± 1.0 kb in normotensive subjects.

DISCUSSION

Telomeres comprise TTAGGG tandem repeats (1). The mean length of telomeres (expressed as the TRF length) of somatic cells is progressively shortened as a function of the donor's age (9,12–14). In vitro, the TRF length is a predictor of the overall replicative potential of cells (9,15), because with continuous replication, cultured cells manifest progressively shorter telomeres and become senescent when telomere length reaches a critical length (reviewed in 1). The attrition in the length of telomeres in vivo and in vitro is attributed to the "end replication problem," which arises from the incomplete replication of the ends of linear chromosomes with each cell division (16,17). One way to counteract telomeric attrition is through the activation of the enzyme telomerase, a ribonucleoprotein complex that uses its RNA component as a template to add TTAGGG repeats onto the ends of chromosomes (reviewed in 1,18). Although recent studies have demonstrated that normal hematopoietic cells (19–21), as well as other somatic cells (22,23) with a high turnover rate, might have some telomerase activity in vivo, the rudimentary activity of the enzyme is insufficient to counterbalance the progressive attrition in the length of TRFs. TRF length has therefore been considered an indicator of the replicative history of cells not only in vitro but also in vivo. It is noteworthy

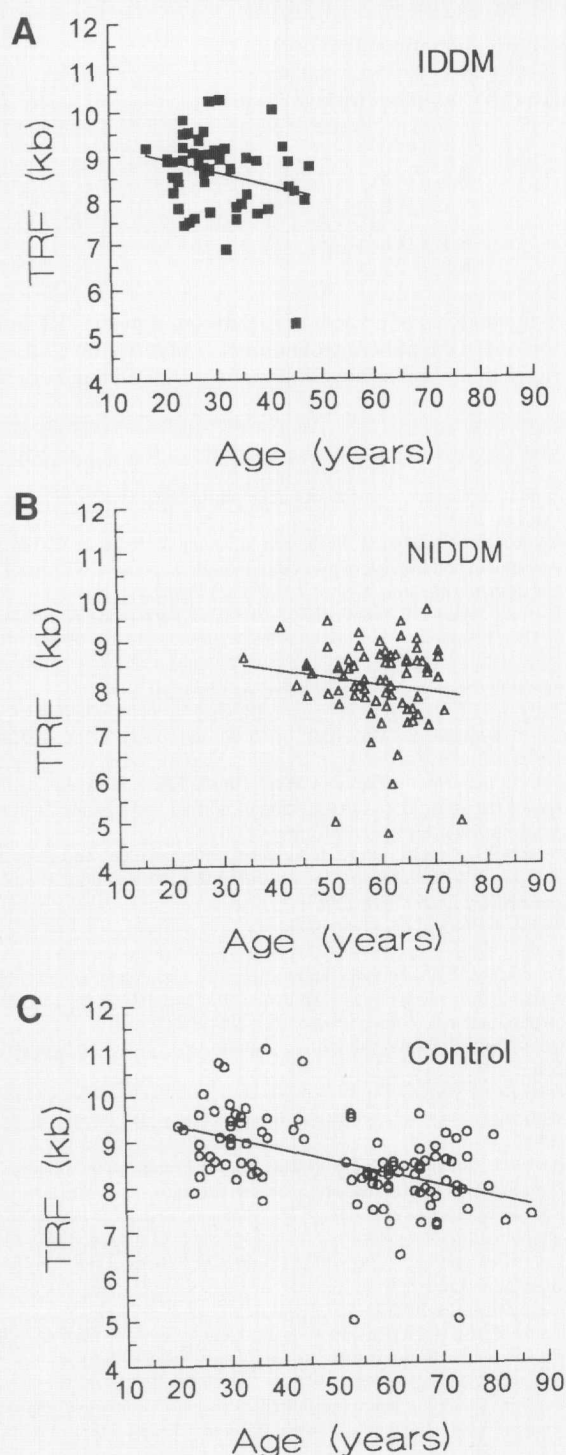


FIG. 2. Length of TRFs from WBCs as a function of the ages of the donors. TRF length from patients with IDDM (A), patients with NIDDM (B), and nondiabetic control subjects (C) are presented. Linear regressions are shown for each panel.

span (9,13–15). This is due to the wide scatter in TRF length among individuals of the same age and the slow, age-dependent attrition rate of TRFs. To a great extent, the scatter of TRF length represents genetic determinants, because the TRF length is highly heritable (13). Thus, at any age, the TRF length reflects not only the replicative history of cells, but also genetic factors.

Because of their rapid and sustained proliferation, malignant cells and immortalized cell lines must overcome telomere attrition, which results from cell division. These cells frequently stabilize their TRF length in concert with activation of telomerase (reviewed in 1 and 18). Accordingly, multiple studies have examined telomere biology and pathobiology in the context of cancer research. However, a number of studies have also shown that altered telomere length is associated with genetic as well as acquired disorders other than cancer, including Hutchinson-Gilford progeria (9), Down syndrome (1,3), and HIV infections (3,4). Infection with HIV is associated with diminished TRF length in subsets of T-cells (3,4), suggesting altered turnover rates of these cells during the course of the disease. It was therefore proposed that the accelerated telomere attrition in HIV infection might contribute to replicative senescence and thus the exhaustion of the immune system that is observed in this disease.

For several reasons, telomeres in WBCs might play a role in the pathophysiology of IDDM. Substantial evidence exists that although diverse in its etiology, IDDM is mediated via immunologic processes, reflected in inflammatory infiltrates of the pancreas and in altered profiles of circulating WBCs, primarily subsets of T-cells that express CD4 and CD8 surface markers (7,8). Such circumstances must be associated with altered turnover rates of these cells and therefore different rates of attrition in the length of their telomeres. An accelerated rate of telomere attrition in lymphocytes in this setting would be of great importance because it could lead to premature replicative senescence and an aberrant behavior due to immune exhaustion. Alternatively, if short telomeres are inherited in patients with IDDM, then telomeres might play a primary role in promoting IDDM by mechanisms that are unclear at present.

The findings of the present work are relevant on two major accounts. First, they establish an association between shortened TRF length in WBCs and IDDM. Second, they suggest that the shortened TRF length is not a simple function of hyperglycemia, because it was not related to the duration of IDDM and because the TRF length of WBCs from patients with NIDDM was not statistically different than that from nondiabetic subjects. In addition, hypertension and micro- and macroalbuminuria, which in IDDM are indicators of nephropathy and predictors of cardiovascular complications, did not correlate with the TRF length of WBCs. Thus, shortened TRF length in IDDM does not appear to reflect the duration and severity of IDDM. Rather, it may be a feature that is intrinsic to WBCs of patients with IDDM. Such a conclusion must, however, await reevaluation by prospective, longitudinal monitoring of telomeric attrition in patients with IDDM. Because IDDM is an indolent process, years might elapse between the onset of insulinitis and the clinical manifestation of the disorder. Therefore, it is still possible that an accelerated rate of telomeric attrition might occur before the overt manifestations of hyperglycemia and insulin dependency. In this context, reduced TRF length in DNA obtained from WBCs might reflect a modest

thy, however, that in a heterogeneous human population, the demonstration of a significant age-dependent attrition rate in TRF length is possible only when the age distribution is very wide; some studies have shown this phenomenon among individuals whose age range extends through an average life

TABLE 2
TRF lengths of IDDM and NIDDM patients compared with TRF lengths of nondiabetic subjects

	<i>n</i>	TRF length (kb), adjusted for age (years)	<i>P</i> value
Comparison groups			
IDDM	54	8.6 ± 0.1	0.002
Control	42	9.2 ± 0.1	
NIDDM	74	8.1 ± 0.1	0.1
Control	80	8.3 ± 0.1	

Data are means ± SE. *For comparison of age-adjusted mean TRF length by analysis of covariance. Estimated mean TRF length for IDDM versus control group is at age 30.7; ages included in the comparison of IDDM and control subjects ranged from 17 to 49. Estimated mean TRF length for NIDDM versus control groups is at age 58.1; ages included in the comparison of NIDDM and control subjects ranged from 30 to 75.

shortening of telomere length of all WBCs or more likely a pronounced shortening of subsets of WBCs, e.g., CD4⁺ and/or CD8⁺ T-cells. Considering that the length of TRFs in WBCs in the general population (13) and some altered expressions of subsets of T-cells in IDDM (24) are heritable, it is possible that reduced TRF length in WBCs in IDDM is also determined by genetic factors that establish the expression and function of subsets of WBCs in this disorder.

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