HbA1c Levels Are Genetically Determined Even in Type 1 Diabetes
Evidence From Healthy and Diabetic Twins
Harold Snieder,1,2 Pamela A. Sawtell,3 Lesley Ross,4 James Walker,4 Tim D. Spector,1 and R. David Graham Leslie3

HbA1c, a measure of blood glucose regulation, reflects glucose levels in the preceding months. In diabetes, HbA1c levels predict the risk of microvascular complications. The aim of this study was to determine whether genetic factors could influence HbA1c levels in normal subjects and type 1 diabetic patients. We performed a classical twin study of HbA1c in healthy nondiabetic female twins and 42 monozygotic (MZ) and 47 dizygotic (DZ) pairs. Interclass correlations (r) were higher in MZ (r = 0.77) compared with DZ (r = 0.53) twin pairs, suggesting a substantial genetic effect; this was confirmed by quantitative genetic model fitting. Additive genetic effects (heritability) explained 62% (95% CI 47–75) of population variance in HbA1c; the remainder was attributable to the influence of unique environment (23% [15–36]) and age (14% [5–28]). Multivariate modeling showed that genetic factors also have a substantial influence on fasting glucose levels (51%). However, HbA1c heritability could not be explained by genes in common with fasting glucose. In the patients with type 1 diabetes, HbA1c levels were correlated in 33 MZ twins concordant for diabetes (r = 0.68; P < 0.001) but also in 45 MZ twins discordant for the disease (r = 0.52; P < 0.001). These significant correlations for HbA1c in both concordant and discordant pairs indicate a diabetes-independent familial effect. Thus, HbA1c levels are largely genetically determined and independent of the genes influencing fasting glucose. Even in type 1 diabetes, familial (i.e., diabetes-independent) factors influence protein glycation, implying that familial factors may explain, in part, the risk for microvascular complications, as indicated by high HbA1c levels. Diabetes 50: 2858–2863, 2001

Diabetes is a major cause of excess mortality and morbidity. It is now the single most common cause of blindness and renal failure in middle age. Recent studies have emphasized the importance of blood glucose levels in predisposition to these microvascular complications (1–3). The index of blood glucose levels used in these seminal studies was HbA1c, the levels of which were closely related to the frequency of diabetic microvascular complications (1–3). HbA1c is a stable minor hemoglobin variant formed in vivo via post-translational modification by glucose, and it contains predominantly glycated NH2-terminal β-chains (4). In early studies, HbA1c was thought to be genetically determined, but wide differences in levels of HbA1c between monozygotic (MZ) twins who were discordant (one twin affected) for diabetes suggested that levels reflected ambient blood glucose levels (5). Moreover, there was a strong relation between levels of HbA1c and the average blood glucose levels over the previous 3 months (4). Despite the present wide acceptance of HbA1c as the “gold standard” of blood glucose control, it has been recognized that levels may vary substantially between individuals, even those with similar blood glucose levels. Only one third or less of the variance in HbA1c levels in nondiabetic subjects can be explained by differences in blood glucose levels (6). The cause of this variability in levels of HbA1c is unclear, but a smaller difference in intraindividual than interindividual values suggests familial effects (7). In support of a familial effect, we noted that in one study, there was a correlation in HbA1c levels between MZ twin pairs who were discordant for diabetes (5). We therefore decided to examine whether HbA1c levels are influenced by genetic factors and, if so, whether genes in common with those controlling fasting glucose levels could explain such a genetic influence; to do this, we performed a twin study using data from MZ twins concordant and discordant for type 1 diabetes as well as healthy nondiabetic MZ and dizygotic (DZ) twins.

RESEARCH DESIGN AND METHODS
We studied two groups of twin pairs: 1) healthy female nondiabetic MZ and DZ twins and 2) MZ twins concordant and discordant for type 1 diabetes. Healthy twins. Healthy twin pairs were drawn from the St. Thomas’ U.K. Adult Twin Registry in 1998. Twins from the registry are unselected, mainly female volunteers ascertained from the general population through national media campaigns in the U.K. (8). The 42 MZ and 47 DZ twin pairs (age range...
Diabetic twins. Diabetic twin pairs were selected from the British Diabetic Twin Study in 1989 (9). Twins from the registry were ascertained by referral through general practitioners and from hospital records. We selected 33 MZ pairs discordant for type 1 diabetes (12 male and 21 female pairs) and 45 MZ pairs discordant for type 1 diabetes (22 male and 23 female pairs). They were eligible according to the following criteria: 1) European origin, 2) affected twins had type 1 diabetes, 3) both twins of each pair were available for study, 4) the range in age of pairs discordant for type 1 diabetes was similar to those discordant for the disease, 5) neither twin was hypertensive, and 6) neither twin had evidence of overt renal impairment or microalbuminuria (overnight albumin excretion <1.4 mg/mmol creatinine), because renal disease can influence HbA1c levels (10).

Initially, we ascertained 48 discordant diabetic twin pairs and 36 concordant diabetic twin pairs; 3 discordant pairs and 3 concordant pairs were excluded because of microalbuminuria in at least one twin of a pair, leaving 45 discordant and 33 concordant pairs. Type 1 diabetes was defined according to the National Diabetes Data Group criteria, and diabetes was excluded in the nondiabetic co-twins by a 75-g oral glucose tolerance test and random whole-blood glucose <10.0 mmol/l (11). All diabetic twins had been treated from the time of diagnosis with insulin and were taking either highly purified porcine or human insulin at least twice daily. The duration (mean ± SD) of diabetes was as follows: in the concordant group, 21 ± 8 and 19 ± 8 years for the index twin and diabetic co-twin, respectively; and in the discordant group, 21 ± 9 years in the diabetic twin. The 45 nondiabetic twins were then followed from 1989 with periodic urine and blood tests and repeat oral glucose tolerance tests for 9 years until January 1999; 4 of the 45 twins developed diabetes (3 are on insulin treatment and 1 is on diet alone). We estimate that the risk of the remaining nondiabetic twins developing type 1 diabetes is now <2% (12,13). All subjects gave informed consent, and the respective hospital ethics committees approved the study.

Biochemical analyses and confirmation of zygosity

Healthy twins. Zygosity was determined by standardized questionnaire, and DNA fingerprinting was used for confirmation (14). Serum glucose was measured on an Enzymatic method (Johnson & Johnson). A high-performance liquid chromatography method (BioReX 70 variant analyzer; Biorad) was used to measure HbA1c, with a between-batch coefficient of variation of <2.5%.

Diabetic twins. Monozygosity was established in all twin pairs, using both clinical data and at least 22 blood groups, as described previously (15). The urinary albumin excretion rate was assessed on a fresh timed overnight urine sample on the day of study using radioimmunoassay (Beckman, High Wycombe, UK). Urinary albumin excretion, expressed as a function of urine creatinine, was raised if their ratio was >1.4 mg albumin/mmol creatinine. Serum and urinary creatinine were measured using a standard colorimetric method (Boehringer Mannheim). Blood glucose was estimated on venous whole blood (TSL, Yellow Springs, OH). The study of diabetic twins in 1989 used an electroendosmotic method (Corming, Medfield, PA) to measure HbA1c, with a normal range in nondiabetic control subjects of 4.5–5.3% and a between-batch coefficient of variation of 5%. This method to measure HbA1c is different from the one used in the healthy twins.

Analytical approach

The aims of our analyses were twofold. First, to estimate the influence of genetic factors on HbA1c levels and the extent to which this influence is dependent on glucose levels, we applied univariate and multivariate genetic model-fitting techniques in the healthy twins. Second, to examine the familial effect on HbA1c levels and the dependence of HbA1c, on disease status, we used a multiple regression approach in the diabetic twins.

Quantitative genetic model fitting. The technique is based on the comparison of the covariances (or correlations) in MZ and DZ twin pairs and quantifies sources of individual differences by separation of the observed phenotypic variance into additive (A) or dominant (D) genetic components and shared (C) or unique (E) environmental components (16). The latter also contains measurement error. Dividing each of these components by the total variance yields the different standardized components of variance, such as heritability (h2), which can be defined as the proportion of the total variance attributable to genetic variation. By incorporating age as a linear regression into the model, the influence of age on the phenotype can also be quantified (17). Estimates of genetic variation in the quantitative genetic model applied here represent the influence of the sum of several genes on the trait (i.e., the polygenic effect). The number of genes influencing the trait, their separate effects, and the mode of inheritance cannot be evaluated in the present twin design. Extension of the univariate HbA1c model to a bivariate (or Cholesky) model (18,19), including both glucose and HbA1c, also allows exploration of the extent to which the correlation between glucose and HbA1c can be explained by common genes (i.e., the genetic correlation [rE]) or a common environment (i.e., the environmental correlation [rC]). In other words, this model enabled us to quantify which part of the variance components (genetic or environmental) was specific to HbA1c, and which part was attributable to the influence of glucose (or age).

Table 1 shows the Cholesky decomposition of the genetic and environmental factors for the two phenotypes (and age) included in the analysis. The observed phenotypes are shown in squares, and latent factors are shown in circles. The number of latent factors equals the number of variables. The first factor (A1, E1) contributes to both variables, and the second factor (A2, E2) reflects influences specific to HbA1c. Factor loadings (cf. regression coefficients) of observed variables on the different latent factors are represented by the arrows.

Model-fitting procedure. For both univariate and multivariate model fitting analyses, a series of submodels nested within the full-parameter model were fitted to the variance-covariance matrices. The significance of variance components A, C, D, and age were assessed by testing the deterioration in model fit after each component was dropped from the full model, leading to a model in which the pattern of variances and covariances is explained by as few parameters as possible. Standard hierarchical χ2 tests were used to select the best-fitting model (16). Before all data analyses, both HbA1c and glucose values were log transformed to obtain normal distributions.

Statistical software. Data handling and preliminary analyses were done with STATA software (20). Univariate and multivariate quantitative genetic modeling were carried out using Mx software (21).

RESULTS

Healthy twins. Table 1 shows the characteristics of the healthy female twin pairs. Mean HbA1c values were similar in MZ and DZ twins, as were all other characteristics. HbA1c was significantly correlated with age (r = 0.38; P < 0.001). Twin correlations for HbA1c levels were significantly (P < 0.02) higher in MZ (r = 0.77; SE 0.064) compared with DZ (r = 0.53; SE 0.106) twin pairs, suggesting a substantial genetic effect, and were confirmed by univariate genetic model fitting (Table 2). In the best-fitting model, additive genetic effects (heritability) explained 62% (95% CI 47–75%) of the population variance in HbA1c levels. The remaining part was attributable to the influence of unique environment (23% [15–36]) and age (14% [5–28%]). Variance components C and D did not contribute significantly and were thus excluded from the model (Table 2).

For the multivariate analysis, including both HbA1c and fasting glucose, we only used pairs in which both twins were fasting, which reduced the sample size to 38 MZ and 41 DZ pairs. The phenotypic correlation between HbA1c and fasting glucose was 0.31 (P < 0.001). Correlations with age were still significant for both HbA1c (r = 0.26; P = 0.001) and fasting glucose (r = 0.28; P < 0.001). Results of the multivariate analysis are shown in Table 3 and Fig. 2.
Table 3 shows variance component estimates for the best-fitting model. Estimates for HbA1c changed only slightly compared with the univariate analysis because of the smaller number of twin pairs. The heritability for fasting glucose was estimated at 51% (29–67).

The amount of overlap in genetic and environmental influences on glucose and HbA1c was small, as indicated by low genetic ($r_g = 0.16$) and environmental ($r_e = 0.36$) correlations. The same result is reflected in a different way in Fig. 2, which shows sources of individual differences in HbA1c levels (expressed as a percentage of the total population variance) based on the best-fitting multivariate model. It illustrates that almost all of the variance in HbA1c could be explained by genetic and environmental factors specifically influencing HbA1c. Only a very small part of the total variance in HbA1c could be attributed to genes in common with fasting glucose (1.6%).

**Diabetic twins.** Table 4 shows characteristics of MZ twin pairs concordant and discordant for type 1 diabetes. There were no differences in mean HbA1c between men and women and no differences in mean age between men and women or diabetic and nondiabetic twins. As expected, HbA1c levels were significantly higher in diabetic than nondiabetic twins ($\chi^2[1] = 64.41; P < 0.0001$).

![Path diagram showing the influence of age and variance factors A and E on glucose and HbA1c (Cholesky decomposition). The observed phenotypes are shown in squares, and latent factors are shown in circles. Factor loadings of observed variables on the different latent factors are represented by the arrows. The correlation between A variance factors is 1 and 0.5 for MZ and DZ pairs, respectively. For clarity, C and D latent factors are not included in the model, and arrows loading on the latent A factors are omitted.](image)
Correlations for HbA1c in MZ twin pairs concordant and discordant for type 1 diabetes are shown in Table 5. Figure 3 shows that the scatterplot of log transformed HbA1c values for discordant pairs (Fig. 3B) is shifted downwards compared with the concordant plot (Fig. 3A) because of the lower HbA1c levels in the healthy twin (twin 2). However, the positive slope of the regression line reflecting the strength of the relation between the twins is similar for discordant and discordant pairs. Significant correlations for HbA1c in both discordant and discordant pairs indicate a diabetes-independent familial effect.

Of the 45 nondiabetic twins from the discordant pairs, 4 subsequently developed diabetes, but their mean HbA1c levels (6.9 ± 2.6%) were similar to that of the 41 twins who remained nondiabetic (6.6 ± 1.1%).

DISCUSSION

We performed a twin study using data from both normal subjects and patients with type 1 diabetes to determine the heritability of HbA1c levels and that heritability’s dependence on fasting glucose levels. Genetic effects explained 62% of the population variance in HbA1c; the remainder was attributable to the influence of unique environment (23%) and age (14%). Although genetic factors have a substantial influence on fasting glucose levels (51%) in healthy twins, the HbA1c heritability could not be explained by genes in common with fasting glucose because they explained only 1.6% of the total variance in HbA1c.

The amount of overlap in genetic determinants of HbA1c and fasting glucose in diabetic individuals could not be studied in our data and may possibly be different.

For the bivariate analysis, only fasting twin pairs were included, whereas all twin pairs were used in the univariate analysis. However, heritability estimates of HbA1c in the univariate and bivariate analysis were very similar (62 and 63%). We therefore think it unlikely that the possible inclusion of undiagnosed diabetic patients in the univariate analysis might have biased the results.

MZ twins concordant and discordant for type 1 diabetes showed substantial HbA1c correlations of similar size, despite the majority of these twins living apart, attending different physicians, and receiving different insulin treatment regimens. The similarity of the correlations in concordant and discordant twin pairs indicates that a considerable portion of the variance of HbA1c levels in patients with type 1 diabetes must be due to shared familial factors, which are not diabetes-dependent. Given the results in the healthy twins, it is likely that most of this familial effect is attributable to genetic factors rather than shared environment.

Our data emphasizes the importance of familial factors as determinants of HbA1c variation in type 1 diabetic patients. However, this by no means implies that type 1 diabetes is unimportant in determining HbA1c levels, as is illustrated by the large difference in HbA1c levels between diabetic and healthy twins shown in Table 4 and Fig. 3.

Genetic factors could influence glycation of proteins by glucose-dependent or glucose-independent mechanisms. Glucose metabolism is, in part, genetically determined, and our study is in line with other twin and family studies that have shown substantial heritability of fasting glucose and postload glucose levels (22). Our heritability estimate of 51% for fasting glucose is comparable with another recent twin study that reported a heritability of 50% (19). However, fasting glucose plays only a small role in determining HbA1c levels in normal subjects, just as it does not

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<th>Twin 2</th>
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<td>Concordant</td>
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<td>36.7 ± 10.4</td>
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Data are means ± SD. N = number of twin pairs. *Twin 1 is the diabetic twin and twin 2 is the healthy twin.

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**TABLE 3**

<table>
<thead>
<tr>
<th>Component</th>
<th>h² (95% CI)</th>
<th>E² (95% CI)</th>
<th>Age² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>0.51 (0.29–0.67)</td>
<td>0.43 (0.28–0.65)</td>
<td>0.06 (0.005–0.17)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.63 (0.45–0.76)</td>
<td>0.31 (0.20–0.48)</td>
<td>0.06 (0.005–0.18)</td>
</tr>
</tbody>
</table>

h², genetic variance component (heritability); age², variance component due to age.

**TABLE 4**

Characteristics of MZ twin pairs concordant and discordant for type 1 diabetes

<table>
<thead>
<tr>
<th>Component</th>
<th>N</th>
<th>Age</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ concordant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>12</td>
<td>36.7 ± 10.4</td>
<td>10.6 ± 2.2</td>
</tr>
<tr>
<td>Women</td>
<td>21</td>
<td>35.2 ± 8.3</td>
<td>10.4 ± 2.7</td>
</tr>
<tr>
<td>MZ discordant*</td>
<td>22</td>
<td>40.2 ± 12.1</td>
<td>10.2 ± 2.0</td>
</tr>
<tr>
<td>Women</td>
<td>23</td>
<td>41.9 ± 13.7</td>
<td>9.1 ± 1.5</td>
</tr>
</tbody>
</table>

Data are means ± SD. N = number of twin pairs. *Twin 1 is the diabetic twin and twin 2 is the healthy twin.

**TABLE 5**

Twin correlations in MZ pairs concordant and discordant for type 1 diabetes

<table>
<thead>
<tr>
<th>Component</th>
<th>Concordant</th>
<th>P</th>
<th>Discordant</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.52</td>
<td>0.085</td>
<td>0.54</td>
<td>0.010</td>
</tr>
<tr>
<td>Women</td>
<td>0.74</td>
<td>&lt;0.001</td>
<td>0.50</td>
<td>0.014</td>
</tr>
<tr>
<td>Combined</td>
<td>0.68</td>
<td>&lt;0.001</td>
<td>0.52</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
precisely predict HbA1c levels in diabetic patients (6,23). Therefore, postprandial glucose may play a more important role in determining HbA1c levels. Although glycation of proteins is nonenzymatically determined, it is possible that genetic factors influence events upstream or downstream of the glycation process. What is surprising is that diabetes-independent familial factors appear to influence HbA1c levels in type 1 diabetic patients. These diabetes-independent factors are likely to affect the levels of both blood glucose and HbA1c and, hence, the risk of developing diabetic microvascular complications.

Alternatively, genetic factors could influence glycation of proteins by glucose-independent mechanisms. Thus, levels of HbA1c can be influenced by rates of hemoglobin glycation, red cell survival, oxygen tension, 2,3-diphosphoglycerate levels, intra-erythrocyte pH, and erythrocyte glucose permeability (24–26). Certainly, HbA1c reproducibility is improved by testing blood samples taken within 4 months (i.e., within the normal erythrocyte life span) (24).

We studied levels of glycated protein in our normal twins (data not shown), but the assay was not sensitive enough to the variation in the normal range of these healthy individuals. Protein glycation is widespread, and the physical properties of proteins are closely related to glycation, which can influence their folding, trafficking, packing, stabilization, protease protection, quaternary structure, and organization. Glycation of proteins is probably important in leading to diabetic microvascular complications, and inhibition of protein glycation can prevent their development (27). These diabetic microvascular complications tend to cluster in families, partly because of genes that remain unidentified (28).

Clinically, it will be important to establish the extent to which HbA1c levels reflect genetically determined protein glycation as distinct from genetically determined glucose metabolism, which could account for the occasional anomalies between HbA1c levels and blood glucose levels, microvascular complications, or both (1,2,26). Our present observations explain the tendency for HbA1c to “track” at certain levels in particular individuals. Because much of the variation in HbA1c levels between individuals is inherited, elevated HbA1c levels may indicate an increased familial risk of diabetic microvascular disease.

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