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Determinants of HbA1c in non-diabetic children and adults

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HbA_{1c} in non-diabetic Dutch infants aged 8-12 months The GECKO-Drenthe birth cohort study

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ABSTRACT

Objective: An international committee of experts recommended using HbA_{1c} for diagnostic testing for diabetes. Little is known about normal values of HbA_{1c} in infants. The aim of this study is to describe the distribution of HbA_{1c} in 8- to 12-month-old non-diabetic infants.

Research design and methods: HbA_{1c} was measured in 86 infants participating in the Groningen Expert Center for Kids with Obesity (GECKO)-Drenthe birth cohort study. Anthropometric measurements were performed at Well Baby Clinics. Data on parents and children were collected prospectively using questionnaires.

Results: HbA_{1c} was normally distributed with a mean (SD) HbA_{1c} level of 5.38% (0.24), range 4.8–6.0% or 35.29 mmol/mol (2.65), range 29.1–42.1 mmol/mol. Age, sex, birth weight, duration of breastfeeding, anthropometric measurements, and maternal BMI were not associated with HbA_{1c}.

Conclusions: We found a normal distribution of HbA_{1c} with a relatively high mean HbA_{1c} of 5.38%. No significant association between risk factors for type 2 diabetes and HbA_{1c} levels was found.

BACKGROUND

An international committee of experts recommended using HbA_{1c} as an indicator for diagnosing diabetes, and, with the prevalence of type 2 diabetes rising, an increase in use of HbA_{1c} can be expected¹. Accordingly, reference levels for HbA_{1c} will need to be developed for all age groups. This study's aim is to describe the distribution of HbA_{1c} in non-diabetic infants aged 8–12 months, and to investigate predictors of HbA_{1c}.

RESEARCH DESIGN AND METHODS

The study population consisted of 86 Dutch infants participating in the Groningen Expert Center for Kids with Obesity (GECKO)-Drenthe study. This population-based birth cohort study within the GECKO was designed to examine risk factors for developing childhood obesity². A random subgroup (N = 100) of this study population, aged about 8 months, was invited to participate in the current study. Eighty-seven parents agreed to participate, and in eighty-six infants, an HbA_{1c} value could be assessed. This study was approved by the Medical Ethics Committee of the University Medical Center Groningen.

HbA_{1c} was measured in a capillary blood sample using a turbidimetric inhibition immunoassay on a Cobas Integra 800 CTS analyzer (Roche Diagnostics, Nederland BV, Almere, the Netherlands). This method has been standardized against the reference method of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Results (mmol HbA_{1c}/mol Hb) were converted to units (% HbA_{1c}) traceable to the Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program (DCCT/NGSP) using the Roche master-equation. Between-batch imprecision (coefficient of variation) was 2.1% for a mean HbA_{1c} of 5.5% and 1.9% for a mean HbA_{1c} of 10.6%.

Anthropometric measurements were performed by trained staff at Well Baby Clinics². Forty-eight percent of the infants did not visit the Well Baby Clinic within 2 weeks around blood sampling. For these infants, weight, length, and waist circumference were determined by linear interpolation. Weight, waist circumference, and weight-for-length z-scores were calculated using Growth Analyzer 3.5 (Growth Analyzer B.V., Rotterdam, the Netherlands), based on Dutch reference values^{3,4}. Growth velocity was defined as increase in weight between birth and time of blood sampling, in grams per week. Data on gestational age, birth weight, infant feeding, gestational diabetes, maternal BMI, and parental educational level were obtained through questionnaires, and missing data was obtained from Well Baby Clinic files. Small for gestational age (SGA) and large for gestational age (LGA) were

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defined as birth weight below the 10th percentile and above the 90th percentile, respectively, for gestational age compared with Dutch reference values by parity and sex⁵.

We used ANOVA to test for differences in mean HbA_{1c} between groups and linear regression to test the relationship between continuous variables and HbA_{1c}. For all analyses, a level of significance of $P < 0.05$ was applied. Statistical analyses were performed using SPSS 16.0 for Windows (SPSS, Chicago, IL).

RESULTS

Of the 86 infants included, 43 were girls and 43 were boys, with a mean (SD) age of 9.42 months (1.14). Mean (SD) HbA_{1c} was 5.38% (0.24), range was 4.8–6.0%, with a skewness (SE) of 0.215 (0.260) and a kurtosis (SE) of -0.004 (0.514). According to IFCC values, mean (SD) HbA_{1c} was 35.29 mmol/mol (2.65), range 29.1–42.1 mmol/mol (Figure 1).

HbA_{1c} was unrelated to age or sex. Birth weight, growth velocity, anthropometric measurements, duration of breastfeeding, gestational diabetes, maternal BMI, and parental educational level were all unassociated with HbA_{1c}. HbA_{1c} did not differ between infants born SGA and infants not born SGA, or between infants born LGA and those not born LGA.

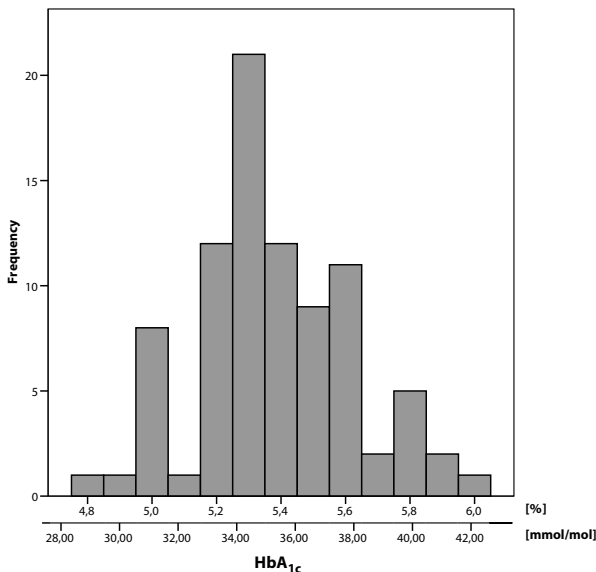


Figure 1. Distribution of HbA_{1c} in infants aged 8-12 months. Mean (SD) = 5.38 (0.24) % or 35.29 (2.65) mmol/mol

CONCLUSIONS

In this non-diabetic infant population, aged 8–12 months, HbA_{1c} was normally distributed, with a mean (SD) HbA_{1c} of 5.38% (0.24), range 4.8–6.0%.

The mean HbA_{1c} of 5.38% observed in the current study is higher than that found by studies in adults and older children^{6,9}. Because HbA_{1c} below 6% is considered normal, the clinical relevance of the difference between an HbA_{1c} level of 4.9% seen in adults and children, compared with 5.4% in our study population, is arguable. However, because the rate of formation of HbA_{1c} is directly proportional to ambient glucose concentration, our results could indicate higher glucose levels in 8- to 12-month-old infants. The predominant fuel for human cells is glucose, and survival of the brain depends on a continuous supply, yet the brain cannot synthesize glucose nor store more than a few minutes supply as glycogen. The infant brain is large relative to body mass and, especially in this period, rapid brain growth and differentiation takes place. To meet the high demand for glucose, the rate of glucose production in infants and young children is two to three times that of older children and mature adults¹⁰. This high demand for glucose by the brain and the subsequent higher rate of glucose production might explain the higher HbA_{1c} levels observed in this study. Another explanation for the relatively high HbA_{1c} levels might be the higher percentage of infant fat mass compared with older children; fat mass is known to be positively related to insulin resistance^{11,12}. Unfortunately, glucose and insulin levels were not assessed, so we could not test these hypotheses.

At birth, between 55 and 65% of total hemoglobin synthesis consists of HbF. After birth, the production of the γ -chain declines to values of <5% by the age of 6 months; normal adult HbF values of <1% are usually reached by age 1 year¹³. Because our study population's age ranged from 8.1–12.3 months, somewhat higher levels of HbF might be expected. Glycated HbF is not detected by the turbidimetric inhibition immunoassay we used; HbF, however, is included in total hemoglobin determination. Because HbA_{1c} is expressed as a proportion, infants with high amounts of HbF (<10%) may have lower than expected HbA_{1c} values¹⁴. However, this does not explain the relatively high HbA_{1c} levels found in our study.

The life span of a fetal erythrocyte is approximately 60–80 days, and the life span of erythrocytes in infants is still less than the 120-day life span of erythrocytes in adults¹⁵. A shorter life span for erythrocytes should show lower HbA_{1c} levels instead of the higher levels we found. To our knowledge, this is the first study describing the distribution of HbA_{1c} in non-diabetic infants. Compared with known HbA_{1c} levels in older children, we found a relatively high mean HbA_{1c} of 5.38%. No significant association between known risk factors for type 2 diabetes and HbA_{1c} was found.

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