Determinants of HbA1c in non-diabetic children and adults

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HbA_{1c} is formed through the non-enzymatic attachment of glucose to the NH2-terminal of the β-chain of haemoglobin. This reaction, called glycation, begins during erythropoiesis and continues slowly throughout the lifespan of haemoglobin in the circulation. Because, erythrocytes are freely permeable to glucose, the level of HbA_{1c} in a blood sample provides a glycaemic history of the previous 120 days, the average erythrocyte lifespan.

HbA_{1c} has been firmly established as an index of long term glucose concentrations and as a measure of the risk for the development of complications in patients with diabetes mellitus. Recently, an international expert committee officially recommended using HbA_{1c} as indicator for the diagnosis of diabetes. In addition, several studies have shown an association between HbA_{1c} and cardiovascular risk in people without diabetes and it is known that cardiovascular risk accumulates over the life course. Consequently, an increased use and also a different way of using HbA_{1c} can be expected. Therefore, it is important to get better insight in the normal distribution of HbA_{1c} in non-diabetic children of all ages and to increase the knowledge about all the factors, environmental as well as genetic, determining HbA_{1c} in non-diabetic persons from childhood onwards.

The main aim of this thesis is to investigate determinants of HbA_{1c} in non-diabetic children and adults.

Chapter 2 presents the results of the study to the distribution of HbA_{1c} in 8-12 month-old non-diabetic infants and potential predictors of HbA_{1c} in this age group. In this study HbA_{1c}, measured in 86 non-diabetic infants participating in the Groningen Expert Center for Kids with Obesity (GECKO)-Drenthe birth cohort, was normally distributed with a mean (SD) HbA_{1c} 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 body mass index (BMI) were all not associated with HbA_{1c}. We conclude from this study that HbA_{1c} is normally distributed in non-diabetic infants, with a relatively high mean HbA_{1c} of 5.38%, and that there is no association between risk factors for type 2 diabetes and HbA_{1c} in non-diabetic infants at this age.

In **chapter 3** we describe the results of our study to the distribution and determinants of HbA_{1c} in non-diabetic Dutch children aged 8-9 years. In a group of 788 non-diabetic children aged 8-9 years participating in the PIAMA birth cohort study we found a normally distributed HbA_{1c} with a mean (SD) of 4.9% (0.33), range 3.5-6.0%. HbA_{1c} was significantly higher in boys and in children of mothers with gestational diabetes, and we found an inverse association between haemoglobin and HbA_{1c}. These results suggest that HbA_{1c} may not only reflect the preceding blood glucose levels, but seems to be determined by other factors as well.

Chapter 4 presents the associations of (lifestyle) determinants with HbA_{1c} at age 12 years and the effects of growth on change in HbA_{1c} between the age of 8 and 12 years. For this study HbA_{1c} was measured in 955 non-diabetic children participating in the PIAMA birth cohort study, of which in 363 children HbA_{1c} was also measured at the age of 8 years. No significant association between known risk factors for insulin resistance and HbA_{1c} was found at age 12 years. The mean (SD) change in HbA_{1c} between age 8 years and age 12 years was 0.6 (0.7) mmol/mol per year. HbA_{1c} showed to be fairly stable over time, since 68.9% of the children remained in the same quintile or had an HbA_{1c} one quintile higher or lower at age 8 years compared to age 12 years. Anthropometric measures at age 8 and the change in anthropometric measures between age 8 and 12 years were not associated with the change in HbA_{1c}. From this study can be concluded that HbA_{1c} in non-diabetic children is fairly stable over time, and seems to be determined by factors which are also fairly constant over time. The lack of association between know risk factors for insulin resistance and HbA_{1c} suggests again that HbA_{1c} in non-diabetic children is relatively unaffected by factors associated with glycaemia.

Chapter 5 provides the associations of "environmental" factors, genetic loci, and gene-environment interactions with HbA_{1c} in 2,921 non-diabetic Dutch adults from the LifeLines cohort study. In this study population, we found age, gender, BMI, fasting plasma glucose (FPG), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), current smoking and alcohol consumption to be independently associated with HbA_{1c}. A full predictive model with these eight "environmental" factors explained 26.2% of the variance in HbA_{1c} and FPG contributed only less than half to this explained variance namely 10.9%. In addition, association between three out of 12 previously identified single-nucleotide polymorphisms (SNPs) could be replicated in our study population. The calculated genetic risk scores (GRSs) (calculated by adding up the weighted effect of HbA_{1c}-increasing alleles) were also independently associated with HbA_{1c} and explained 0.2% of the variance in HbA_{1c}. We categorized the 12 previously identified SNPs in "glycaemic" and "non-glycaemic" SNPs according to the presumed way they act on HbA_{1c} and calculated GRSs for these two groups of SNPs separately. The effect of the "non-glycaemic GRS" appeared to be lower in females compared to males and there was an attenuation of the effect of the GRS of all 12 SNPs with increasing BMI. All these results suggest that HbA_{1c} is determined by other factors besides preceding glucose levels which raises serious questions about the use of HbA_{1c} for diagnosing diabetes.
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Chapter 6 comprises the general discussion in which I discuss important limitations of HbA_{1c} as diagnostic test for diabetes. Finding the best way to diagnose diabetes has been a challenge for many years. The diagnosis based on the development of complications caused by the hyperglycaemia

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instead of the hyperglycaemia itself is probably most clinical useful, and since HbA_{1c} is firmly established as a measure of the risk for the development of complications, the use of HbA_{1c} for diagnosing diabetes seems to be a logical step. But there are important limitations of the use of an HbA_{1c} level ≥ 6.5% for diagnosing diabetes.

Firstly, evidence suggests that there is a continuous relationship between HbA_{1c} levels and cardiovascular complications, even in the non-diabetic range. A cut point at 6.5% would lead to under treatment of a lot of people at risk for cardiovascular disease.

In addition, other factors besides glycaemia seem to determine HbA_{1c} including e.g. the "glycation gap". But also genetic factors, erythrocyte lifespan, age and ethnicity influence HbA_{1c} independent of plasma glucose levels. Substantial effects of these factors on HbA_{1c} levels, independent of glycaemia, will have important consequences for the use of HbA_{1c} as diagnostic tool for diabetes. And finally, some practical considerations like variant haemoglobins, assay imprecision and costs, and the delay in diagnosis argue against the use of HbA_{1c} for diagnosing diabetes.

In conclusion, HbA_{1c} has great perspectives for the use as a continuous marker for cardiovascular risk, probably even in patients without as well as in patients with diabetes. But, the results presented in this thesis show that the observed variation in HbA_{1c} caused by other factors besides glycaemia makes it not suitable for dichotomizing and thereby diagnosing diabetes.

Child and adolescent obesity is increasingly prevalent, and can be associated with significant short- and long-term health consequences. It is acknowledged as an important determinant of insulin resistance and thereby higher levels of glycaemia and HbA_{1c}. There is only limited evidence on risk factors and treatment of obesity in children.

Chapter 7 and chapter 8 are two supplemental chapters concerning childhood obesity.

Chapter 7 covers a summary of the results of the Cochrane review we conducted to assess the efficacy of a range of interventions designed to treat obesity in children and adolescents. For this review eight databases were searched from 1985 to may 2008. Randomised controlled trails (RCTs) of lifestyle (i.e. dietary, physical activity and/or behavioural therapy), drug and surgical interventions for treating obesity in children with a minimum of six months follow up were selected and two reviewers independently assessed trial quality and extracted data. We included 64 RCTs with 5,230 participants. Meta-analyses indicated a reduction in overweight at 6 and 12 months follow up in: i) lifestyle interventions involving children (<12 years); and ii) lifestyle interventions in adolescents (> 12 years) with or without the addition of orlistat or sibutramine. A range of adverse effects was noted in drug RCTs. While there is limited quality data to recommend one treatment program to

be favoured over another, this review shows that combined behavioural lifestyle interventions can produce a significant and clinically meaningful reduction in overweight in children and adolescents. In obese adolescents, consideration should be given to the use of either orlistat or sibutramine, as an adjunct to lifestyle interventions, although this approach needs to be carefully weighed up against the potential for adverse effects.

Chapter 8 provides the results of our study to energy intake and physical activity during treatment for acute lymphoblastic leukaemia (ALL) with intermittent dexamethasone (DEXA), to explain the weight gain seen in children treated for ALL. For this study BMI, energy intake, and physical activity were measured in 16 ALL patients on maintenance treatment and in 17 healthy controls. ALL patients were measured during ("on DEXA") and in between ("off DEXA") DEXA treatments. We found a mean (SD) increase in BMI z-score of 1.4 (1.1) in ALL patients. Energy intake on DEXA was higher and energy intake off DEXA was lower compared to healthy controls. Physical activity on DEXA was lower compared to healthy controls, while no difference was found between physical activity off DEXA and healthy controls. We concluded from these results that the weight gain seen in patients on ALL treatment might be owing to increased energy intake and decreased physical activity during treatment with DEXA.