Chapter 10

Summary
Chapter 1 provides background on the adult consequences of intrauterine growth retardation that is considered as the cause of low birth weight. Associations between low birth weight and insulin resistance and cardiovascular risk factors are described. The rationale for studying infancy and childhood growth patterns, insulin sensitivity and cardiovascular risk factors in preterm born children is explained. Background is provided on the metabolic consequences of obesity. The rationale for studying insulin sensitivity, type 2 diabetes mellitus and the metabolic syndrome in children and adolescents with obesity is described.

Chapter 2 consists the aims to study infant and childhood growth patterns, insulin sensitivity and cardiovascular risk factors in preterm born subjects. In addition, the aims to study insulin sensitivity, type 2 diabetes mellitus and the metabolic syndrome in obese children and adolescents are described.

In chapter 3 insulin sensitivity and blood pressure are studied in preterm born young adults, using the hyperinsulinaemic euglycaemic clamp technique. Furthermore, the influence of growth during infancy and childhood is taken into account. The hyperinsulinaemic clamp shows a reduction in insulin sensitivity in preterm born subjects. Blood pressure measurements show increased blood pressure in preterm born subjects. Preterm born subjects with the highest increments of height and weight during childhood have lower insulin sensitivity and higher blood pressure compared to preterm born subjects with the lowest increments in height and weight during childhood. It is concluded that infant and childhood growth patterns are a modifying factor in the decreased insulin sensitivity that is observed in preterm born subjects.
In chapter 4 insulin sensitivity is studied in young adults born small for gestational age at term that have been treated with growth hormone and compared to preterm-born subjects as well as with term-born control subjects with normal birth weight using the hyperinsulinaemic euglycaemic clamp technique. A reduction in insulin sensitivity in the preterm born subjects similar to that in term born small for gestational age treated with growth hormone is observed, compared to control subjects. It therefore is concluded that the cause for the decreased insulin sensitivity in the growth hormone treated SGA subjects is not known, but that growth hormone should be used with caution in preterm born subjects that already have decreased insulin sensitivity.

In chapter 5 postprandial lipid metabolism and beta cell response are studied in young adult preterm born subjects, using the mixed meal test (MMT). The MMT shows that postprandial triglyceride levels are higher in preterm born males with a low birth weight for gestational age compared to control subjects. Preterm born subjects with a low birth weight for gestational age have higher insulin levels during the MMT.

It is concluded that the mixed meal test provides additional information on cardiovascular risk factors that cannot be observed in the fasting state.

In chapter 6 childhood growth patterns and insulin sensitivity, measured by the hyperinsulinaemic euglycaemic clamp, were studied in preterm-born young adults. Subjects born preterm small for gestational age (SGA), subjects born preterm appropriate for gestational age with postnatal growth retardation, and subjects born
preterm appropriate for gestational age without postnatal growth retardation were
compared. The hyperinsulinaemic clamp shows that insulin sensitivity is lower in
preterm born subjects born appropriate for gestational age with a normal postnatal
growth pattern than in preterm born subjects born small for gestational age and tends
to be lower than in preterm born subjects with normal birth weight and a retarded
postnatal growth pattern. These differences disappeared after adjustment for body
size. It is concluded that early growth patterns in preterm born subjects are
associated with differences in insulin sensitivity.

In chapter 7 is an assessment of the number of children with type 2 diabetes
mellitus, diagnosed by pediatricians, in the Netherlands in 2003 and 2004. The Dutch
Pediatric Surveillance Unit (DPSU), a nation-wide pediatric register, was used to
assess new cases of diabetes mellitus. Data on socio-demographic and clinical
characteristics were collected by means of a questionnaire. A second questionnaire
was sent to the reporting pediatrician if the diagnosis was inconclusive or if the
diagnosis was type 1 diabetes mellitus in combination with overweight or obesity,
according to international criteria. During the 24 months of registration 1142 new
cases of diabetes were reported. The study shows a discrepancy between the
number of patients with type 2 diabetes mellitus diagnosed by pediatricians in daily
practice and the number of patients diagnosed according to the ADA criteria.
Moreover, it was obvious that a considerable amount of reported patients were
misclassified. Finally, 2.4% patients were classified as (very likely) type 2 diabetes
mellitus. It is concluded that type 2 diabetes mellitus should be considered especially
in overweight and obese children. Because type 2 diabetes mellitus remains a
challenging diagnosis, the development of and adherence to diagnostic guidelines is warranted.

In chapter 8 insulin sensitivity, glucose intolerance and the metabolic syndrome are studied in 512 obese children and adolescents, using fasting insulin sensitivity indexes as well as oral glucose tolerance tests (OGTT). The fasting insulin sensitivity indexes show that the majority of the obese children and adolescents are insulin resistant and that 12.1% has impaired fasting glucose. The metabolic syndrome is present in 13.9% of obese children ≥ 10 years of age and 5.3% of children < 10 years of age. The OGTT showed that 7.4% of obese children and adolescents has impaired glucose tolerance. It is concluded that risk factors for cardiovascular disease are present in many obese children and adolescents. For the detection of high-risk groups the OGTT is needed.

In chapter 9 the results of the studies described in this thesis are discussed. It is concluded that differences in insulin resistance and high blood pressure in preterm born subjects are associated with preterm birth, early postnatal growth, childhood growth velocity and adult body composition. Impaired lipid handling in young adult preterms that cannot be detected in the fasting state can be detected with meal tests. In The Netherlands, type 2 diabetes mellitus is now a differential diagnosis that should be considered in a child with new onset diabetes. The metabolic syndrome and glucose intolerance are present in a significant proportion of obese children. Not all high risk groups can be detected without the use of an oral glucose tolerance test. Suggestions for future research are made.