Already for many years we have been confronted with a worldwide increasing tendency of children who become obese. At the same time, there is also evidence that obesity in childhood is on the basis of the metabolic syndrome in adulthood with the well-known pathology of hypertension, cardiovascular disease, diabetes mellitus and stroke. In this study we tried to gain better insight in the development of obesity, the possibilities of prevention and what obesity means in terms of body composition.

The first question to study concerned the epidemiology of obesity. Although it is well-known that the origin of obesity in adulthood often has to be found in childhood, we did not find any increase in weight of the neonate born during the last decades. In other words, there is no increase in prenatal growth despite a mean increase in weight and length of the mothers known as the secular trend. In explanation may it be stated that it is assumed that the intrauterine environment and the placental nutrition supply prevent the fetus from becoming overgrown to protect the mother herself. The placenta is not simply a passive conduit for nutrients but also responds to both maternal and fetal signals, altering placental transport and metabolic function\(^1\,^2\). On the other hand, it is described that maternal weight gain in early pregnancy has an influence on fetal weight probably mediated through raised placental mass\(^3\,^4\). Nevertheless, the general idea is that if a child has the tendency to achieve a weight and height outside the physiological borders, there might be a mechanism to restrict the further intrauterine growth as is shown in our data of birth weight and length gathered during the last years.

The main concerns of obesity are the comorbidities like the metabolic syndrome and numerous psychosocial problems, which transfer obesity into a serious disease. Because the roots of obesity can often be found in childhood, it is significant to discern those children who are becoming obese just based on abnormal food intake often combined with a less degree of physical exertion and those who suffer from insulin resistance from birth onwards. The last group is especially recognized in the infants born after intrauterine growth retardation, the small for gestational age (SGA) children. Thanks to the longitudinal growth study during the first four years of age of a healthy Dutch population\(^5\), we were able to analyze the postnatal growth of individual children during this period.

We realize that the reference population was taken ten years ago but at the same time these reference data compared to the last Dutch nationwide growth study show that the so-called secular trend has come to a stop for height. However, it did not come to a stop for weight. This tendency of becoming taller and heavier was originally an important indication of a population whose health gained thanks to better feeding and less disease. While the mean increase in height stopped already since more than ten years, weight gain is still going on for the population as a whole. For that reason a comparison with an older reference population it is signifi-
cant to be informed about the start of the discrepancy between height and weight of the Dutch population. Taking into account the information that height does not increase anymore, the increase in Body Mass Index (BMI), which was seen in the postnatal data, means a higher increase in weight.

**Methods of analyzing growth of children**

There are several methods to analyze the growth of a child and to determine overweight or obesity. One can compare particular children of the same age, gender and population to judge if its weight and height are within the normal range for the population. Usually weight and height are expressed as a function of age. Weight can also be expressed in relation to height as the BMI defined as weight (kg) divided by squared height (m²). However, the above-mentioned tendency of the population to become heavier with steady size led to an increase in the BMI as followed from the formula. In case of an equal weight to height ratio a child (below the age of 10 years) with a taller height has a higher BMI in contrast to a child (below the age of 10 years) with a smaller height, taking the P3, P50 and P97 values into account. Therefore the expression of weight versus height is more reliable in children. A limitation of the anthropometric approach of weight is that the BMI as well as weight for height does not distinct between fat mass (FM) and fat-free mass (FFM). In adipose children it is reasonable to ascribe the weight gain to an increase in FM. At the same time in relatively lean children a lower weight is largely due to a shift from FM to FFM. Because a large part of the FM is situated in the abdominal region, Fredriks stated that waist circumference can be used as a better tool to screen for increased abdominal fat in children.

To measure total body fat one needs the use of other methods. A rather complex method is the underwater weighing. The difference of weight in the open air and under water gives a good indication of the FM. An easy and reliable method is the measurement of the FFM by means of Deuterium. Deuterium is a stable isotope of hydrogen of which the natural presence in the body fluids is knowable by measuring Deuterium in the urine. After a known gift of Deuterium the new concentration in the urine after equilibration of the Deuterium in all body segments, is equivalent with the total body FFM. Distracting the result from total body weight delivers a good estimate of total body fat. Minimal changes in body composition can be found by using the Deuterium method.
Small for gestational age children

Besides the evidence of the origin of the metabolic syndrome in SGA children, it is also remarkable that their growth in length and height often stay behind the norm. One of the factors mentioned with respect to the stunted growth SGA children is reduced sensitivity for the insulin-like growth factor 1 (IGF-1)⁸. IGF-1 is mainly secreted by the liver as a result of stimulation by growth hormone. IGF-1 expression is required for achieving maximal growth. Short SGA children show plasma IGF-1 levels that are in the lower normal range⁹. For that reason these children are treated with recombinant human growth hormone (rhGH) nowadays. In general they respond very good on this treatment and correct their height towards their genetically defined percentile. At the same time it is known from that treatment of growth hormone deficient (GHD) children with rhGH results in a change of the metabolism¹⁰. This change is assumed to be an effect of IGF-I what is a primary regulator of systemic anabolism and muscle growth¹¹. Growth hormone deficiency is associated with increased body fat and a lower lean body mass. These changes in body composition are associated with metabolic derangements including insulin resistance. They normalize with growth hormone replacement therapy¹².

In this thesis we showed that treatment with rhGH has also a positive metabolic effect on body composition of SGA children. The treatment with rhGH causes a shift in body composition of FM towards FFM. After treatment with rhGH, SGA children show an increase in height but also in weight. The detected increase in weight is based on an increase in FFM and not in FM. This means, as mentioned before, that the body composition in SGA children improves after receiving rhGH treatment. In SGA children rhGH treatment prevents overweight and thereby the metabolic syndrome.

To evaluate adequate and inadequate responders to rhGH therapy, with respect to height, changes in body composition can be measured. The change in body composition is an actual tool in predicting the individual response on rhGH treatment. By using this method rhGH therapy can be given only to adequate responders and it is possible to prevent aimless administration.

In obese children there exists a decrease in growth hormone (GH) secretion what is fully reversible when body weight is normalized¹³. A decrease in spontaneous GH release in obesity has been confirmed in several comparative studies on the 24-hour secretion of GH in normal weight¹⁴ and obese children¹³,¹⁵. In obese children, GH secretion may be as low as in poorly growing children with classical GHD¹⁶. Investigation of the pattern of factors potentially influencing GH secretion confirmed a significant and independent impact of fat mass. Relative adiposity acts as a negative determinant of the frequency and amplitude of GH secretory bursts. They are associated with an increased GH clearance leading to a lower GH half-life time,
suggesting a defect both in secretion and clearance. Alterations in GH receptors and circulating GH-binding proteins support these changes.

Bocca et al showed that insulin resistance and cardiovascular risk factors are already evident in overweight and obese children with a mean age of 4.7 years. An association exists between insulin resistance and BMI, waist circumference and percentage body fat. The question arises if obesity will improve by rhGH treatment. It is dubious to give rhGH treatment to obese children. However, if a child suffers from obesity due to an insulin resistance, rhGH therapy is theoretically indicated but, as in all cases of insulin resistance known as diabetic type II, the first step is lowering weight by means of dietary measures.

One can discuss if rhGH treatment is indicated in very obese children. Like bariatric surgery, these treatment options are controversial in pediatric patients. Bariatric surgery in children results in clinically significant weight loss, but also has the potential for serious complications. Therefore, this is not a usual treatment option. But in the case of severe obesity, where other treatment options failed, it is questionable if more risky therapies, under strict monitoring, are indicated if we take the severe comorbidities of obesity into account.

**Costs**

Not only the health consequences of overweight in childhood are a serious problem, but also the financial aspect. Consequences and comorbidities of obesity like cardiovascular diseases, DM type II, orthopedic problems, skin abnormalities and psychosocial problems such as underachievement in school and lower self-esteem, will lead to rising health care costs if the incidence of obesity is increasing in the future. Treating obesity and obesity-related conditions costs billions of dollars a year. By one estimate, the United States spent $190 billion on obesity-related health care expenses in 2005, double previous estimates. The medical costs of obesity-related illnesses in the United States have been estimated at $209.7 billion annually (in 2008).

Not only these direct costs have to be taken into consideration, but also indirect costs like absence from work due to illness. Obese employees miss more days from work due to short-term absences, long-term disability, and premature death than non-obese employees. Some studies show that obese employees have also lower wages. One can imagine that obese persons with possible psychosocial problems and lower self-esteem due to their weight are less likely to ask for increment in salary or improvement of career options. One can imagine that these problems also apply for children at school. Obese children suffer from bullying, are less self-assured and therefore probably less motivated to go to school.