

## Healthcare industry BW

### Fatal relatives: adiposity and diabetes

**Martin Wabitsch was the first German pediatrician to investigate adiposity back when it was seen as a strange subject to study. Nowadays, in Germany the attitude towards adiposity has completely changed. More and more people are suffering from adiposity and diabetes and are consequently at risk of contracting other severe diseases as a result. In children and young adults the situation is alarming; many children are at risk of contracting diabetes mellitus type two at a very young age.**

This is a time bomb in terms of healthcare costs, a time bomb that the researcher from Ulm is hoping to deactivate. Extremely overweight people are at risk of contracting diabetes mellitus type 2 or its pre-stages very early on in life, according to an investigation carried out by Wabitsch on over 500 overweight children and young adults.

### Adiposity disrupts the sugar metabolism very early on

The children underwent an oral glucose tolerance test (OGTT) that assesses the function of the insulin-producing cells in the pancreas. Wabitsch concludes: "A large proportion of fat is one of the major reasons for disorders in the glucose metabolism, in particular the mass of fat in the abdominal area. About four percent of all children examined had an elevated fasting blood glucose level; in two percent of all children, the blood sugar content rose after the administration of sugar and 1.5 percent of the children revealed signs of diabetes type 2. The results show that being massively overweight might also lead to disorders in the glucose metabolism early on in life.

Through the establishment of medical research programmes into adiposity in German children and young adolescents, Martin Wabitsch, head of Paediatric Endocrinology and Diabetology at the University of Ulm, has standardised definitions and developed guidelines for the prevention of adiposity. He has also founded the 'adiposity in children and young adults work group' (AGA). Furthermore, in the research laboratory Wabitsch and his team have investigated the biology of fat cells.

### Adipose people can often do very little to combat the disease



Prof. Dr. Martin Wabitsch was head of a weight reduction programme (Obeldicks) for children. The photo shows him together with oecotrophologist Maleika Fuchs.  
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Twenty years ago, adipose people were not regarded as sick, instead they were stigmatised, and morally condemned (“you only have yourself to blame”). Stigmatisation continues – wrongly as researchers have found out: adiposity is a chronic disease that is biologically regulated. This means that, “individuals suffering from adiposity can only reduce their weight with difficulty.” This is due to the effect of genes and conditioning, says the researcher.

## Genes, conditioning and behaviour

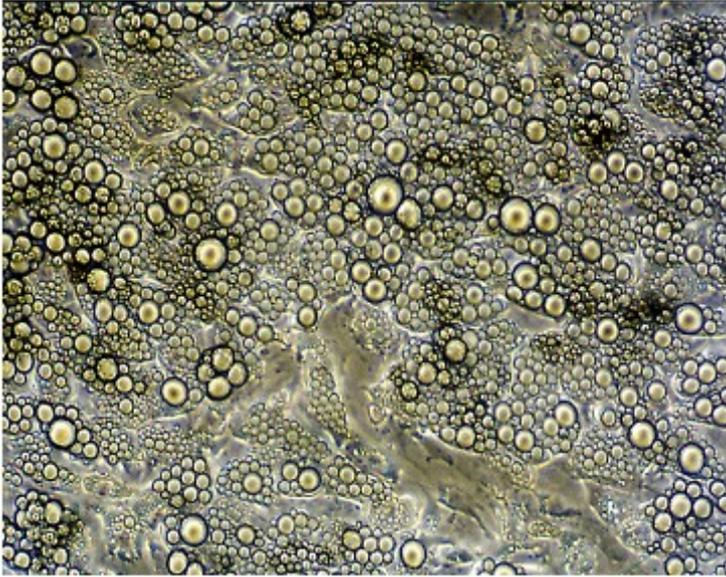
Children who have been breast fed for a long time have a far lower risk of becoming overweight than children who receive a protein- and sugar-rich diet at a very young age. Researchers have found out that the protein content of industrially produced baby food leads to a higher risk of adiposity.

There is also strong evidence pointing to the conditioning of unborn babies; pregnant women who smoke alter the blood supply of their child; this leads to deficient food supply, which in turn will lead to the conditioning of the metabolism. The body can store a lot when sugar is abundant, thus developing diabetes or a metabolic syndrome relatively quickly.

If the metabolism of a pregnant diabetic woman is badly adjusted, this affects the metabolism of the

unborn child: the child tries to regulate the glucose level itself and as a result increases its production of insulin. Such children are quite heavy at the time of birth. While the beta cells in the child's pancreas are trimmed for high performance, the children are suffering from nutritional deficiency although they have a high glucose level. Diabetes is transferred from mother to baby by way of conditioning.

## From a pure store to an organ



Wabitsch's work group has developed the sole human precursor and fat cell line (SGBS). The photo shows unstained differentiated 20-day-old fat cells in cell culture.

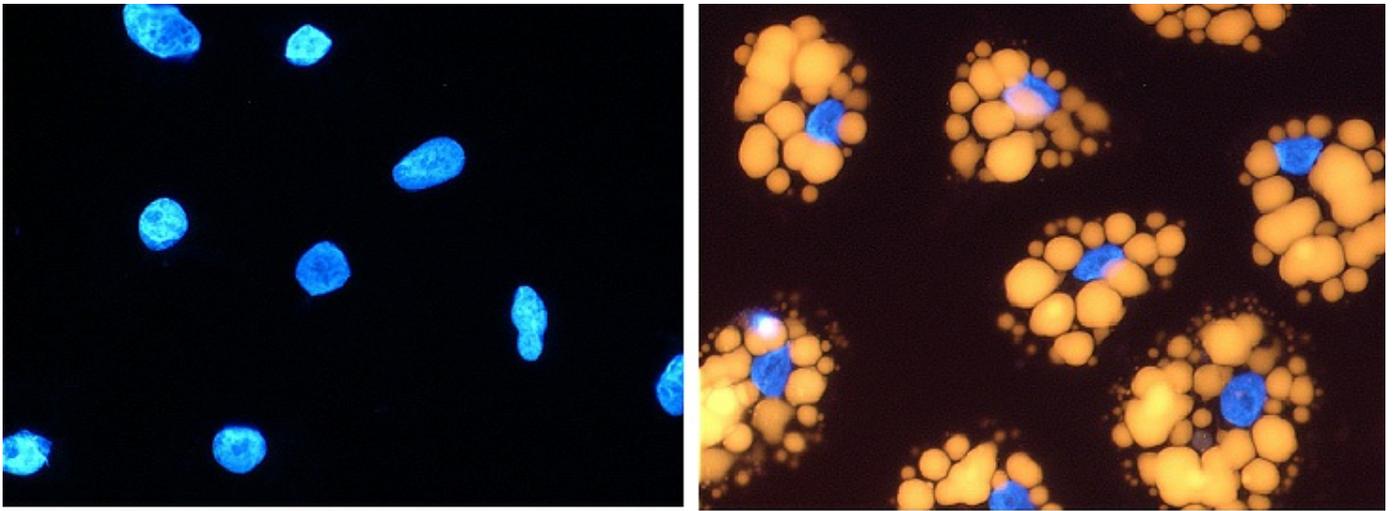
© Prof. Wabitsch, University Children's Hospital

It has recently been discovered that fatty tissue plays a much more important role than previously believed - rather than being just a fat producer and store, it is now recognised as an endocrine organ that plays a major role in the regulation of the energy equilibrium.

Fatty cells secrete products of which about 100 are known, including complex proteins, fatty acids, prostaglandins and steroid hormones that are generated and metabolised in the fatty tissue, before being released into the blood circulation. They are regarded as major contributors to adiposity-related diseases such as diabetes.

Little is yet known about the first differentiation steps of fat cells. However, the path of precursor adipocytes into mature fat cells is well understood. Only mature fat cells are capable of secretion.

## Only mature cells can release hormones



Precursor fat cells (preadipocytes) with stained nucleus (DAPI) (on the left) and fat cells with stained nuclei (DAPI) and Nile red-stained lipids.

© Prof. Martin Wabitsch, University Children's Hospital Ulm

Fatty tissue produces and stores lipids; it releases fatty acids in the case of negative energy balance (lipolysis), a process that is affected by a complex hormonal interaction. Both processes can happen simultaneously. The hormone that is most important for storage is insulin, which has an anabolic effect. It stimulates cellular glucose transport, the uptake of other metabolites and the synthesis of triglycerides. It inhibits the release of fatty acids into the blood.

Many ongoing studies are aimed at finding out whether the organ “fatty tissue” itself is involved in the development of adiposity-related diseases such as diabetes through its secretion products. This possibility is based on the assumption that the fatty acid maintains an active “dialogue” with other organs by way of its secretion products.

## Insulin is the pacemaker

Insulin is the pacemaker of adiposity. The metabolism of children is activated when they eat a diet that is fat- and carbohydrate-rich at the same time as being low-fibre (fast food, sugar-containing drinks). Beta cells increase the production of insulin. Since insulin is an anabolic hormone, the energy supplied is exploited highly efficiently and is quickly stored in the fatty tissue. In addition, insulin drives the formation of fat in the adipocytes. Wabitsch explains that adipocytes kept in culture dishes can live exclusively on glucose since they have the synthesis machinery that is required to metabolise glucose.

## Not eating at the right time causes problems

Adiposity might also result from not eating breakfast. There is growing evidence that this is the case although final evidence is still missing. Hunger-regulating hormones in the gastrointestinal tract play a role in this process; these hormones are released in large quantities in the morning. Children who do not eat breakfast become extremely hungry, consume higher amounts of energy and distort their appetite control. The paradoxical consequence: people who try to lose weight by skipping breakfast will most likely consume higher energy levels of food than they would have done had they eaten breakfast.

Which fat cell secretion products potentially lead to diabetes? Researchers have not yet discovered

the trigger, but they have gained insights into the individual steps of the pathophysiology. It is certain that the fatty tissue releases substances that promote the development of diabetes. Wabitsch assumes that this is the result of the interaction between several cells in the fatty tissue.

## It all started with leptin

These issues all arose from the discovery of leptin in 1994. Leptin is a hormone that is released by fat cells; it regulates the energy equilibrium and informs the CNS about the current energy stocks. It regulates insulin sensitivity and Wabitsch assumes that it is also involved in the development of diabetes.

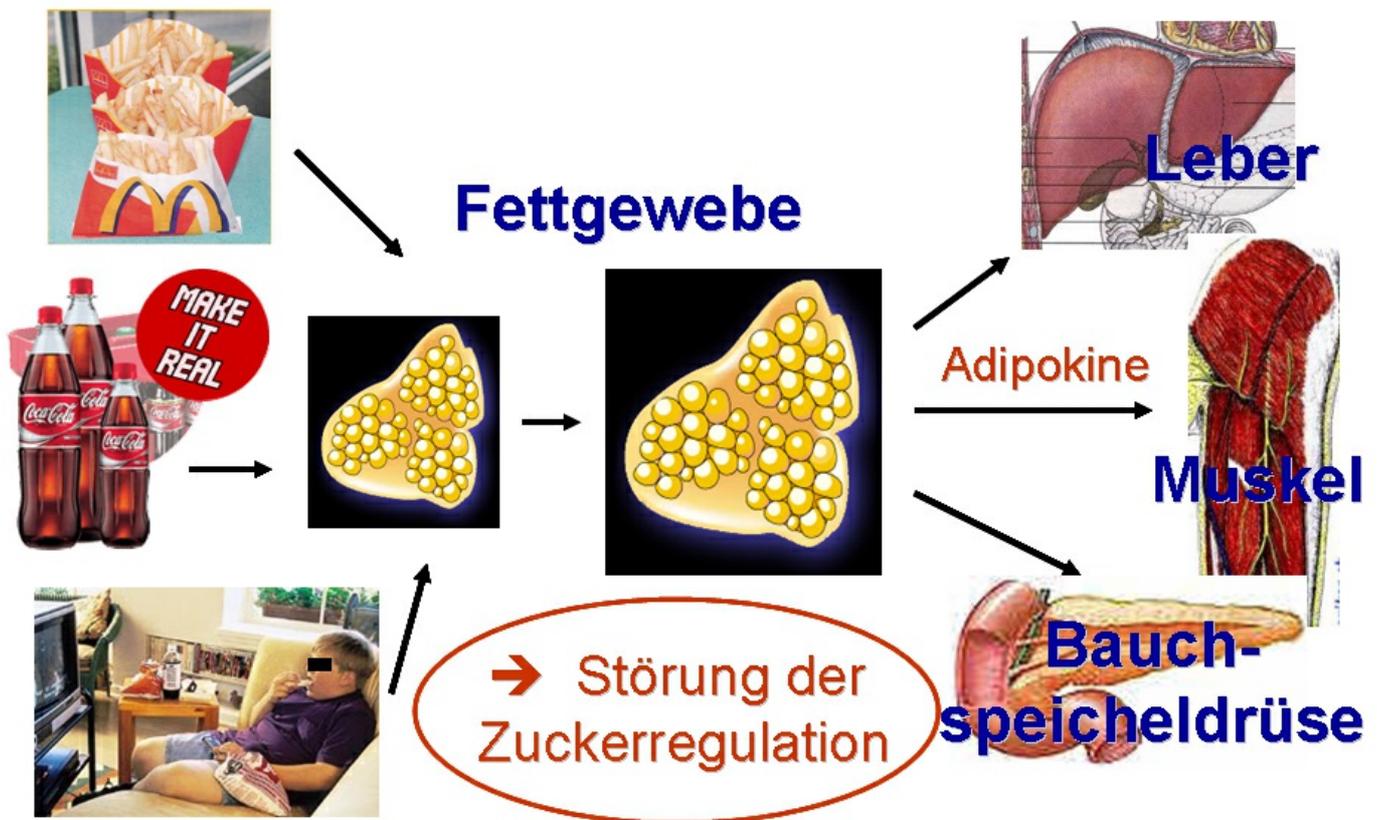
Patients suffering from primary leptin deficiency (there are 12 worldwide) have a resistance to insulin which can be corrected following the administration of leptin. Patients with lipoatrophy or lipodystrophy suffer from leptin deficiency, thus confirming Wabitsch's idea that leptin is relevant for protection against diabetes.

## A high number of baddies

Adiponectins, which protect against diabetes in the same way, also have an endocrine effect, and improve insulin sensitivity. The "good" secretions are outnumbered by the bad ones, which include cytokines, interleukin 6 and TNF alpha. It is believed to be invaded inflammation cells rather than adipocytes that either produce these substances or trigger adipocytes to produce them. Another assumption is that preadipocytes develop into immune cells (macrophages).

It is clear that the substances (adipokines) released by the tissue have an effect on other organs: in the liver, they affect gluconeogenesis, glycogenolysis, insulin degradation and insulin sensitivity. They also affect insulin sensitivity in the muscles. In the pancreas, adipokines have an effect on beta cells. Leptin and adiponectin inhibit the apoptosis of these cells, while a degradation product of adiponectin, free fatty acids, interleukin-6 and TNF-alpha stimulate the apoptosis of beta cells.

# Altersdiabetes und Übergewicht - Stand der Forschung -



## Speeding up regeneration

Fat cells renew once every eight years. Young adipocytes have a "good" secretion profile whilst larger, old ones have a "bad" secretion profile. Improving the regenerative ability of adipocytes might therefore improve the secretion profile of adipocytes.

Pure chance helped researchers move on a step further. A group of researchers found that a diabetes drug of the thiazolidinedione class (of which rosiglitazone is a representative) not only affects insulin sensitivity, but is also responsible for the differentiation of fat cells.

Diabetes patients treated with rosiglitazone had a greater total body fat mass and showed improvements. The patients who showed improvements had many young fat cells. Wabitsch assumed that the bigger and older cells had disappeared as a result of apoptosis. He therefore concludes that fat tissue is not a bad thing in itself, but it must be healthy.

## Drugs to improve the secretion profile

Since adiposity prevention has only a limited chance of success, Wabitsch is convinced that drugs are necessary to make the fatty tissue healthier. All the big global pharmaceutical companies are doing research on substances that have the potential to improve the secretion profile of adipocytes.

In his doctoral thesis, Wabitsch once refuted a dogma according to that held that the number and volume of fat cells is determined during childhood. The Ulm researcher showed that children, and even adults, had a large pool of fat precursor cells. Nowadays, it is assumed that the number of fat

cells can either be reduced by dedifferentiation, during which fat is withdrawn from the fat cell, or by apoptosis.

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#### Article

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#### The article is part of the following dossiers



Diabetes, a danger that is still underestimated