

diabetes mellitus and thalidomide embryopathie

diabetes mellitus = high blood sugar

Definition:

Diabetes mellitus is a disorder of blood glucose regulation, which results from a deficiency in the action of the hormone insulin. This may be due to autoimmune destruction of the insulin-secreting cells of the pancreas (type 1 diabetes mellitus) or it may result from a problem in the responsiveness of tissues to insulin, known as insulin resistance (type 2 diabetes mellitus). With either disorder, the result is hyperglycemia, or high levels of glucose in the plasma.

History:

Diabetes mellitus is greek / latin for „honey-sweet flow“. With this description, the symptoms of diabetes were brilliantly described by Aretaios from Kappadokien (ca. 80 - 130 ac.) who stated, that in certain conditions where patients complained about having to go to the toilet frequently, some of the patients showed a sweet taste of the urine (the taste test of urine was a common diagnostic approach at that time).

First known therapeutic approaches to treat having to go to the toilet all the time were found on egypt papyrus from 1.500 bc which suggests that people have suffered from this condition since long ago.

Pathophysiologie:

Glucose („Sugar“) is an important energy supply, some tissues (e.g. brain) rely practically only on glucose for energy supply.

Insuline, a hormone of the pancreas, opens the cells for glucose. As a consequence, the glucose leaves the blood and enters the cell, leading to a good energy supply of the cells and a reduction of free glucose in the blood stream.

Insulin also inhibits glucose generation in the liver (the liver can produce about a pound of glucose per day).

A lack of insuline leads to energy deprived cells and elevated blood glucose levels.

Under normal circumstances, 100% of the glucose that is filtered in the kidneys is reabsorbed. Glucose reabsorption involves transport proteins that require specific binding. In a diabetic that has hyperglycemia, the filtered load of glucose (amount of glucose filtered) can exceed the capacity of the kidney tubules to reabsorb glucose, because the transport proteins become saturated. The result is glucose in the urine. Glucose is a solute that draws water into the urine by osmosis. Thus, hyperglycemia causes a diabetic to produce a high volume of glucose-containing and sweet tasting urine.

The reduced intracellular glucose levels lead to reduced physical performance and fatigue.

Complications:

The previously dreaded, often fatal complications such diabetic coma (severe hyperglycemia) or hypoglycemic shock (severe hypoglycemia) have become rare due to available diabetic treatment.

The main problem today are the blood vessel alterations in diabetes: Persistently high blood glucose levels lead to a non-enzymatic glycosylation (accumulation of saccharids in proteins) This leads to a loss of function in these proteins and to accumulation of those proteins in tissue.

In addition, high concentration of glucose in non-insulin-dependent tissues leads to osmotic organ damage (e.g., in the eye lens, diabetic cataract).

The long term complications of diabetes consist in complications from blood vessel or nerve damage. Leading to loss of function in the respective organs which clinically shows as heart attacks, strokes, kidney failure, necrosis of limbs, eye nerve damage. The altered protein structures, may lead to impairment of the immune system with the consequence of frequent infections.

Classification of forms of the disease:

The classification of the disease underwent different nomenclatures over the years. Currently the distinction may be simply put as follows:

- Diabetes mellitus type I:

Insulin deficiency due to destruction of the islet cells of the pancreas (which produce insuline) of unknown origin, manifestation time is within days to weeks and occurs mainly in children at around the age of 10. (Auto-)immunological processes, a genetic disposition or viral infections are suspected as triggering agent. Treatment consists of external administration of insuline and diabetic diet.

- Diabetes mellitus type II:

Here, an increasing insulin resistance of cellular receptors and a slow decrease in insulin production in the pancreas leads to an imbalance of blood sugar regulation. The detection of the disease can take years. As causes for this, genetic susceptibility, high-fat diet, obesity and lack of exercise are discussed.

The therapy consists of the administration of diabetes medications that are swallowed as a tablet and either inhibit glucose production or stimulate insulin production in the pancreas. External insuline administration may be necessary. Sports and weight loss are encouraged.

- Other causes: diabetes after surgical removal of the pancreas, diabetes in pregnancy, certain genetic syndromes, diabetes by drugs (eg cortisone)

Diagnostics:

Determination of blood glucose levels in the serum as well as assessment of the blood hemoglobin molecule (long term blood glucose marker HbA1c), Glucose stress test.

Prevalence:

Diabetes is considered as „the pest of the 21st century“. With hypercaloric nutrition as one of the main risks factors, diabetes is very common in western civilisation.

According to third party payers, prevalence in Germany was 8% in 2007, corresponding to a total of 6.3 million Germans [1] being treated for diabetes type 2 condition with a large number of not diagnosed cases.

Assessment of the question if diabetes mellitus was part of the thalidomide syndrome

The medical commission of the „Conterganstiftung“ is frequently confronted with this question. The questions always concern diabetes mellitus type 2 and a manifestation in adulthood.

As of today (8/2014) search of *pubmed* does not yield any hits concerning studies or observations of a positive correlation between diabetes and thalidomide embryopathy.

As mentioned above, diabetes is a very frequent condition.

With today's knowledge, prenatal thalidomide exposure does not lead to diabetes mellitus in adults as a classic intrinsic side effect of thalidomide.

Why is it unlikely that thalidomide causes diabetes directly?

The pancreatic gland is an organ with endocrine function (insulin production in the beta cells, insulin is released into the blood) and an exocrine function (production of various hormones that are released into the duodenum). In all applications of thalidomide where it was claimed that pancreatic function was impaired, only the endocrine function was impaired, leading to a diabetes mellitus. **With onset at the age of 40-50 years.** If this was caused by thalidomide, it would imply a cell-selective damage by thalidomide during pregnancy in a manner that would leave the affected cells to function 40-50 years normally and then failing at the age of 40-50 years.

According to current medical understanding, the selective formation of the hypoplastic islets is hard to imagine and even a hypoplastic cell line can fulfill its function for life under certain circumstances. The reason for the damage of the beta cells in the adult can not be caused by a growth inhibition during pregnancy. There is no single case of a congenital diabetes known to the thalidomide foundation.

As of today, the medical commission of the foundation assumes that the cases of diabetes mellitus in the thalidomiders are caused by the same agents that cause diabetes in non-thalidomiders all over the world, whatever these agents are.

Why is the combination of diabetes and thalidomide a frequent one?

Diabetes is a frequent disease in all western populations.

In Germany, prevalence of diabetes (Type I and II) in the „normal“ population is under 5% in the age group of 40-49 years and over 9% in the age group of 50-59 years (Robert Koch Institute ²)

¹ Deutscher Gesundheitsbericht Diabetes 2010, http://profi.diabetesde.org/fileadmin/users/Patientenseite/PDFs_und_TEXTE/Infomaterial/Gesundheitsbericht_2010_Gesamt_28_10_2009.pdf, p 9

² Publikation des Robert Koch Institutes 03/2011: Diabetes mellitus in Deutschland. Aus: Zahlen und Trends aus der Gesundheitsberichterstattung des Bundes, Seite 2: http://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsK/2011_3_diabetes.pdf?__blob=publicationFile

There is no publication about the prevalence of diabetes in the thalidomide group and so it is hard to say if thalidomiders develop diabetes more frequently than non-thalidomiders.

Assumption of an identical prevalence of diabetes mellitus, regardless of thalidomiders or not leads to the observation, that wherever 11 people in the age of 50-59 years meet, one of them will suffer diabetes statistically.

So, the impression that many thalidomiders have diabetes is correct, for statistic reasons it would be expected that more than 200 of the 2.700 thalidomiders in Germany will have diabetes.

As stated above, as of today, there is no evidence of diabetes caused **directly** by thalidomide.

On the other hand, development of diabetes can most certainly be fostered by being a thalidomide victim and living a certain, physically inactive lifestyle since a physically inactive lifestyle is one of the known risk factors for diabetes. .

The phantastic sport achievements of some thalidomiders which we see in the media from time to time should not lead to the assumption of a sportive thalidomide community.

People with damaged extremities do have immense problems to pursue a sport activity and many thalidomiders are very obese.

So, the assumption of thalidomide as an **indirect** source for diabetes since a handicap itself may lead to a non healthy lifestyle may be correct if we take a look at the following chain of action:

thalidomide embryopathy -> handicap -> impaired ability to pursue a sport activity -> - obesity-> diabetes

As of today, the medical commission of the thalidomide foundation does not see a reason for financially compensating a diabetic condition in thalidomiders as it must be assumed that the diabetes is caused by a different agent than thalidomide and the case of diabetes caused by overweight caused by lack of sports caused by a physical handicap caused by thalidomide is an indirect chain of action, not a direct cause and effect principle.

On the other hand it must be assumed, that during the time of the founding of the thalidomide foundation, when the handicap/compensation guidelines were determined, development of diabetes at the age of 50 years secondary to lack of sport activity of the handicapped person was definitely not an issue. First, no one assumed at that time that thalidomiders would achieve an age where diabetes was an issue. Second, a lifestyle with lack of physical activity as a major risk factor for diabetes was not known at that time.