



Could the high consumption of high glycaemic index carbohydrates and sugars, associated with the nutritional transition to the Western type of diet, be the common cause of the obesity epidemic and the worldwide increasing incidences of Type 1 and Type 2 diabetes?

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ABSTRACT

The globally increasing incidences of Type 1 diabetes (T1DM) and Type 2 diabetes (T2DM) can have a common background. If challenged by the contemporary high level of nutritional glucose stimulation, the β -cells in genetically predisposed individuals are at risk for damage which can lead to the diseases. The fat to carbohydrate dietary shift can also contribute to the associated obesity epidemic.

Introduction

Our ancient genetic profiles are in the affluent societies of today challenged by exceptionally rapid changes in nutrition and life style. Simultaneously a panorama of non-communicable diseases is growing which can indicate a mismatch between the present-day human genetic profiles and current living conditions. Due to genetic heterogeneity human individuals and populations may have different risks for this.

T1DM and T2DM are two clinically defined diseases where such a mismatch may be involved. Their prevalence is now increasing epidemically in many parts the world [1,1b,2]. They were, like obesity, rare during the 1800s and to the middle of the 1900s, but in the decades following the second world war (WWII) their incidence started to increase. Their concomitant rise could indicate common triggering factors.

An increase of T1DM was observed already in the 1950s in Scandinavia, the U.K., the U.S. and Sardinia [3] and an increase of T2DM in the U.S. [4] and in some U.S. and Pacific island indigenous populations in the 1950s–1960s [5,6]. The epidemics run in parallel with rising rates of overweight and obesity in adults, adolescents and children beginning around the same time in most high income countries [4,7,8], and with the increased prevalence of new, more palatable, easy digested, sweet and energy-dense types of food and beverages which exploded in the U.S. and Western Europe after WWII. This new type of diet has subsequently through trade and marketing spread to other countries around the world in connection with their increase in wealth and per capita income [8b].

The post-war trends in carbohydrate consumption

A significant change in the Western food habits after WWII has been

in the carbohydrate consumption. The traditional food was, as in other parts of the world, largely based on products as they occur in nature, i.e. unrefined, starch- and fibre-rich vegetables like whole grains, legumes, roots, tubers and whole fruits - all characterized by a slow release of glucose during digestion.

In the U.S. carbohydrate consumption decreased during the 1900s. In 1909 it contributed 56% of the food energy, which towards the middle of the century had decreased to 45% accompanied by a considerable decrease in the intake of dietary fibre [9,10]. From the 1960s–1970s, and with acceleration in the 1980s and 1990s, carbohydrate consumption rose again, now due to increasing percentages of fibre-depleted, processed vegetable carbohydrates and sugars among the carbohydrates consumed [4]. Step by step these products then have become ingredients in a multitude of industrially processed foods causing a quality change in the Western diet. In the U.S. of today more than 60% of the caloric intake is estimated to come from processed or ultra-processed types of food [11]. A substantial contribution to these foods comes from the fast food industry [12].

Starting in 1977 official U.S. recommendations were to eat less fat and increase the consumption of carbohydrates [13]. This was followed by a considerable inflow of industrially-produced, low fat products to the food market in which carbohydrates were substituted for the fat.

According to a review of 10 US National Health and Nutrition Examination Surveys (NHANES) [14] the relative fat consumption dropped from 44,7% to 33,6% of the caloric intake between 1965 and 2011. The protein share of the intake was fairly constant 15–17%, while the carbohydrate share increased considerably from 39% to 55,5%. Main carbohydrates increasingly consumed from the 1960s and beyond were fibre-depleted refined grains, ready-to-eat cereals, wheat flour products, processed potato products, refined starches, added caloric sweeteners and sugars. This change in macronutrient composition

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correlated to a dramatic rise in obesity causing the percentage of overweight Americans to increase from 42.3% in 1971 to 66.1% in 2011. The average adult Body Mass Index (BMI) increased from about 24 kg/m² in 1965 to about 29 kg/m² in 2011.

There was an increase in the intake of energy from 1980 to 2000 with on average 480 kcal (adjusted for loss) per capita and day. Of the increase, refined grains and sugars accounted for around 70% and added fats for 24% (but with the total fat intake still substantially decreased in the percentage of caloric intake compared to 1965) [15,16]. Sugar-sweetened beverages (SSB), including 100% fruit juices, were a growing proportion of the caloric intake and contributed to the weight gain not only by their calorie content but also by limiting appetite control and not being compensated for by reduced food intake [17,18]. The increase in total energy (calorie) intake between 1971 and 2011 was however, in this study [14], found unlikely to have played any significant role in the increase in BMI. The macronutrient shift from fat to carbohydrate was due to an absolute increase of 30.6% (around 278 g/day) in the carbohydrate intake. Instead, a strong relationship was found between the increase in carbohydrate share of the intake and obesity. At the individual level this was reflected by a high correlation between caloric share from carbohydrate and adult BMI, suggesting that the carbohydrate fraction was the driving force for weight gain and obesity [14]. This is consistent with observations of Mozaffarian [19] and Brand-Miller [20] that the foods most associated with weight gain are high glycemic index foods rich in refined carbohydrates like potato products, refined grains, sweets and desserts. The weight gain associated with sweets and desserts seems to be equivalent to the weight gain associated with refined grains.

Production and use of specific carbohydrates

Sucrose

The increase in refined beet and cane sucrose consumption was impressive in many countries during the last century but started earlier. In England the yearly average intake of sucrose per capita was estimated to be 6.8 kg in 1815 which rose to 54.5 kg in 1970 [21]. Similar trends for refined sucrose consumption have been reported during the industrial era for Sweden, Norway, Denmark, the Netherlands and the U.S. [22]. A remarkable alteration in the food of mankind demasking an instinctive preference for the taste of sweetness.

Industrialization has made sucrose the world's predominant sweetener and one of the cheapest and important energy forms in the world whose main energy is transported as glucose in the blood.

However, in the U.S. the long time upward trend of sucrose consumption started to level out in the 1920s and remained relatively stable till the 1970s after which it decreased by being replaced as a sweetener, mainly of soft beverages, by the high fructose corn syrups (HFCS) [23]. But on the global level sucrose continued to be the dominant sweetener in use. Today, in developed countries, particularly in the EU the consumption of sucrose may have stabilized at high level. In the U.S., from around 2000 to 2016, there has been a 6% increase in the sucrose intake after the earlier decline, while the use of corn-derived sweeteners (HFCS) correspondingly has trended downward. In many developing countries sucrose consumption is steeply on the rise.

Starch

Starch, polymers of glucose, is a natural food component with cereals and potatoes being two of the most important sources. Wheat has today, on the global level, a 15% share of the caloric intake from all sources. But modern, almost universal, milling and refining techniques have profoundly changed wheat's (and other cereals) products for consumption. The result is loss of the structural properties of the cereal matrix, the intact cell walls and the integrity of the starch granules. Further refining results in calorie-dense white flours with small,

uniform granular particle size, mostly pure starch depleted of fibre, fat and protein [4,24].

Wheat flour consumption in the U.S., declining since the beginning of the 1900s, started to rise in the early 1980s and reached a peak in 1997 [25]. Between 1980 and 2000 the average per capita annual consumption (as availability) of wheat flour increased from around 50 kg to 66 kg [16]. From around 1997 there has however been a trend shift in the U.S. consumption of wheat flour which since then has been declining, but it was still around 18% higher in 2015 than in 1975 [26].

Beside wheat, corn and rice are the world's most important staple foods. The per capita annual average consumption (as availability) of corn products (flour and meal, hominy and grits and food starch) tripled between 1975 and 2015 from around 5 kg to 15 kg. Also rice consumption almost tripled from an average of around 3 kg per capita in 1975 to 8 kg per capita in 1995. Of the coarse rice about 70% is milled to polished rice which, with some variation because of rice type, contribute easily digested starch to the diet [26].

Potatoes are an important contributor of starch. The average annual per capita utilization of potatoes for food in the U.S. diet increased from 50 kg in 1980 to 63 kg in 1995, after which it has declined back to a level of around 50 kg in 2015, but potatoes are still the most consumed vegetable. Of the U.S. potato sales an increasing amount goes to processors of French fries, chips, dehydrated potatoes, canning and other potato products. In the 1970s the use of processed potatoes surpassed fresh use especially driven by the innovation of frozen-french-fry processing techniques and a huge demand for this product from the fast-food chains. This increased their use of French fries to account for 67% of this market followed by restaurants with a share of 13%. In 1980 the yearly average per capita utilization of French fries was around 16 kg which increased to around 26 kg in 1995 and was 22 kg in 2015 [27,28].

In parallel with the production of sucrose other industries have developed extracting the starch from ordinary food ingredients. Wheat, corn, potatoes, rice and tapioca are the most important sources. In an increasing trend the world's starch production reached around 66 million tonnes per annum in 2008, of which around 40% were used for the extensively growing market of processed foods and beverages [28b]. In 2012 the rising global starch production was 75 million tonnes [29]. Of the European production (9.4 million tonnes consumed 2017) a proportion (27%) is used in convenience foods, bakery, food ingredients and dairy products while 30% is used in sweet drinks and fruit processing [29]. In the U.S. most starch production is from corn and mainly destined for sweeteners, particularly HFCS [29]. Important commercial products of starch for food use are as glucose polymers, native starch, chemically-modified starches, starch syrups, glucose syrups, dextrins, maltodextrins and maltose. The addition to processed foods of various forms of starch is often not for their nutritional or sweetening properties but for their functional qualities. Examples are modified starches as temperature-stable thickeners, water retainers (in processed meats), for suspension of solids and stabilization of viscosity. Modified starches used in food are as a rule digestible, although some of them at a lower rate than pure starch [30].

Sweeteners

The global sweetener market developed during the latter half of the 1900s and has in the U.S. been dominated by sucrose and HFCS. The use of HFCS began to rise in the 1970s as it replaced sucrose in a vast array of nectars, still drinks and sodas. The HFCS and sucrose contribution to the individual energy intake was however relatively stable until the early 1980s when their combined consumption started to rise. In the 1970s the yearly average per capita U.S. availability of all added refined sugars was estimated to be 51 kg which rose to a peak of 68 kg in 1999. In 2005 the consumption had decreased to 58 kg but was still 19% higher than in the 1970s [31,31b,32].

Between 1977 and 1996 the increase in the consumption of caloric sweeteners has been estimated to be 83 kcal per capita and day for all

persons two years of age and older. Of this increase 80% was from soft drinks and sugared fruit drinks. There was also an increase in the consumption of 100% fruit juices with a similar carbohydrate content as sugar sweetened beverages. Around 20% was from desserts, snacks and candy amongst others [33].

Soft drink consumption among 6–16 year olds increased from 37% in 1977 to 56% in 1998 with an increasing share obtained from restaurants, fast-food establishments and vending machines. The mean amounts of the intake more than doubled [34]. Nearly half of American adults drink sugar sweetened beverage daily [34b].

The decline in sweetener intake observed after 1999 has been associated with a lower consumption of HFCS sweetened beverages along with an increased consumption of bottled water and artificially sweetened sodas. At the same time, however, other types of sweetener intake have remained unchanged or increased. There has been no reduction of added sugars in foods which still and increasingly are important contributors and sucrose consumption has started to increase and surpassed in 2010–2011 the declining consumption of HFCS. Despite the decline in consumption of added sugars in the U.S. during the current century there has been no reduction in the percentage of added sugars of total energy intake which has continued to exceed the consumption in the 1970s [35] and the recommended level of 10% of the total energy intake [32].

Fat-carbohydrate intake and weight gain

The current average fat intake in the U.S. is around 32% of total calories – a considerable decrease from around 45% in the 1960s. But between 1970 and 1999 there was a modest increase in the per capita availability of added fats and oils caused by an increased intake of vegetable oils. (After 1999 the statistics of oil availability are difficult to interpret due to a large number of new manufacturers reporting oil production coming into the market). Of total added fats in the diet 86% consisted of vegetable oils and related products around 2005 [31]. Fast-food use has increasingly been a contributor to vegetable oil consumption. The U.S. total fat intake (added and natural) is continuously exceeding recommended guidelines set to no more than 30% of fat in the daily caloric intake.

During the last quarter of the 20th century affluent countries were characterized by trends of increasing caloric intake and accelerating obesity in the context of a more sedentary lifestyle. In the U.S. there was a boost in the obesity epidemic in the early 1980s, shortly after the 1977 National recommendation of eating less fat and more carbohydrates. The average daily per capita increase of energy intake reached 400–500 kcal between 1980 and 2000. Fat had decreased considerably in its percentage of the caloric intake but there was a certain increase of intake in absolute amounts which contributed to the 32% level of the total caloric intake for a 2000 kcal/day diet [31]. Around 55% of the intake was attributed to high glycaemic index carbohydrates which since the 1960s successively had replaced the low glycaemic index carbohydrate intake in broad population groups.

A contribution to the increase in calorie intake was most probably also, in the wake of more easily accessible, more attractive, sweeter and palatable foods, more frequent eating/drinking occasions and expanding portion sizes [36–38]. The caloric intake may be proportional to the amount of carbohydrate in the food according to Swedish statistics [39], which lends support to the idea that it is the carbohydrate content (including sugars) of the diet that calls for more frequent eating occasions, larger portions at meals and larger cakes and desserts.

The macronutrient shift from fat to carbohydrates in the U.S. from around 1980 was paralleled not only by rapid increases in obesity but also in T2DM incidence in adults and younger individuals. In children (ages 2–19) overweight and obesity almost tripled during the following decades [40] but similar weight shifts were seen across all age groups [41].

The fat and the flour/cereal intake accounted for the major part of

the increase in daily caloric intake from 1970 to 2010 [42]. The increase of refined, high-glycaemic-index carbohydrates including caloric sweeteners and sugars consumed every day was extreme in the U.S. between 1980 and 2000 and although lowered during the current century it has continued to be on a level considerably above that of the 1960s and 1970s [42,43]. In the U.S., as in many other wealthy countries, it has, on a population basis, reached a level not earlier seen during human evolution. The composition of the actual carbohydrate intake is dominated by glucose in the body's provision of absorbable monosaccharides which by far exceeds the provision of other monosaccharides from the whole diet.

The high intake of SSB contributes to an additional increase in the glycaemic index of the meals. Per se SSB increases the blood glucose, and through the glycaemic surge on the β -cells also the insulin level, dramatically [43b]. The high glucose supply and the rapid absorption swiftly stimulates higher and more prolonged levels of circulating insulin compared to the traditional fibre-rich, low-glycaemic-index diets. More frequent eating and drinking contribute to longer periods daily spent in the postprandial state with the insulin level kept more or less continuously above the fasting level.

The increased level of food caloric intake but, importantly, with high glycaemic index carbohydrates, sweeteners and sugars as a major part of the energy consumed, coupled to insufficient compensating exercise is most probably the main reason for the development of the obesity epidemic in the U.S. and globally [44,45]. The drop in the consumption of wheat flour, potatoes, sweeteners etc. from the late 1990s may be the result of public interest in lowering carbohydrate and sugar intake, but at the same time there was an increase in the intake of corn products, rice and sucrose and, in spite of a drop in the caloric intake, the level of the total daily caloric intake remained 18–20% higher in 2010 than in the 1970s [40,46]. However, from around 2005, after decades of increase, there seems to be a stabilization in the obesity rates among men and only a slight increase among women in the U.S. – and after 2004 in children between two and 11 years of age there is a decrease or stabilization of obesity – which possibly can reflect a reduction in the carbohydrate intake [47,47b].

Carbohydrates in children's food

Industrially produced food for infants and children has become a profitable global market after WWII which has grown into a multi-billion-dollar business and plays an increasing role in meeting the nutritional demands of infants and toddlers worldwide. The products include alternatives to breast milk, follow-on formulas and complementary baby and infant foods. Other foods are directed to older children.

Despite the WHO recommendation that babies be exclusively breastfed for the first 6 months of life on average only 38% of infants below this age are exclusively breastfed for this time, worldwide. In the U.S. around 75% of infants initiate breastfeeding from birth but by the age of six months only 30% and at 12 months 16% still rely on breastfeeding. The six months “any breastfeeding” rate among new mothers in the U.S. is 43% with only 13% of the babies being exclusively breastfed for the first 6 months [48,50].

Formulas

The natural food for children during the first period of life, human breastmilk, contains as carbohydrates lactose around 7%, oligosaccharides 1–2% and minimal amounts (0.5–1 g/l) of monosaccharides. Starch is not present in breastmilk. In commercially available cow's-milk-based infant formulas around 7% added lactose is the major carbohydrate. Small amounts of glucose are present emanating from cow's milk. Earlier rapidly metabolised sugars like maltose, sucrose, glucose and precooked starch were allowed in formulas. Today maltodextrin is the substance added usually up to a total carbohydrate maximum of 14 g/100 kcal. Maltodextrin consists of a number of

different glucose-polymers in varying mixtures in different preparations which after digestion increases the child's uptake of glucose [49]. From four months of age also canned puréed fruit and fruit flavoured soft drinks are given as supplements to the milk formula according to recommendations from the producers. 100% juice is also frequently given before a recommended age of six months as well as French fries before 12 months of age [50].

After six months of age the infant's exposure to cereals increases. Commercial follow-on formulae (among them gruels and porridges) can, beside added lactose, contain starches, maltodextrin, sucrose, glucose syrup, fructose or other sugars [51]. This is on the top of the added precooked, easily digested starches from refined cereal flours of corn, oats, wheat, rye or other grains aimed at increasing the energy content of the formula. A typical composition is per 100 g dry powdered formula around 60 g carbohydrates of which 58% is flour and 42% sugars. Around 15 g of the powder is fat and 14 g is protein. The flours are usually derived from totally or partially malted grains where the starch content is broken down to malto-oligosaccharides by the action of amylolytic enzymes generated during the germination. The grains are then dried, toasted and milled to flour. Many flours are processed as such by toasting, boiling, enzymatic or other type of hydrolytic process and drying. These processes are in order to improve digestibility, increase dispersibility in water and increase shelf life. The resulting products mixed with water consist mainly of glucose polymers more or less completely gelatinized which rapidly releases glucose during digestion. The follow-on formulas are usually also devoid of basic food texture and structure and are often relatively low in fibre [52]. Due to residual enzyme activities rapidly digestible oligosaccharides are continuously being formed during gruel preparation [53].

Prepared cereal-containing formulas differ from breastmilk and milk-based formulas by the higher amount of glucose per calorie that an infant consumes at each feeding. Infants formula-fed daily generally have a higher energy intake than breastfed infants. The increased inflow of glucose, the glucose and amino acid stimulated insulin secretion and the high energy intake increase the risk for more rapid weight gain of formula-fed children compared with breastfed children [53b]. At nine months of age it has been shown that breastfed infants have a significant lower blood insulin response than infants not breastfed and a lower body weight [54]. If also receiving solid food from five months of age the formula-fed infants are at risk for a significantly higher BMI even at six years of age compared with exclusively breastfed infants. [55,56]

In spite of the increased uptake of glucose from formulas like gruel and porridge meals the result is a lower blood glucose response than expected [54b]. A comparatively more increased insulin level keeps the blood glucose low but instead causes an increased rate of glucose metabolism in the body cells which through the signaling effects of insulin could support growth and weight gain [54]. Not only glucose but insulinotropic amino acids from added skim milk powder is most probably the cause of the high insulin response.

Infant and toddler foods

The prevalence of childhood overweight follows, with some disparities, the general global upward trend. The Feeding Infants and Toddlers Study Survey 2008 in the U.S. [57] describes a consistent excessive energy intake for infants beginning before four months of age and continuing at least up to four years of age (where the study ends). The carbohydrate share of the caloric intake was found to be constantly over 50% except for the very first few months of life. Introduction of energy-dense sweets (i.e. desserts, cookies, candy, etc.) and sweetened beverages appeared early in the diet, sometimes earlier than 4–5 months of age and preferentially in formula-fed infants. Almost half of the infants consumed some type of dessert, candy or sweetened beverage at least once daily, a number that increased to over 70% among the toddlers. The rise in the intake of these foods and

beverages continued into the preschool age [57].

Among toddlers juices and fruit-flavored drinks can be the second and third most important source of energy after breastmilk, formula or milk [58]. A systematic review of controlled trials and cohort studies of the association between consumption of SSB, including 100% juice, and excess weight gain among children under 12 years of age showed a significant consistent association with total adiposity among children under five years of age and with central adiposity among children less than 12 years old [59].

Today's infants and children are at risk of being exposed to a much sweeter nutritional environment than previous generations due to the high percentages of calories from sugar in common food products like puréed desserts (51% sugars) and snacks (33% sugars) [60]. Infant mixed grains and fruits can contain more than 35% of calories from sugar [61]. Grain-based dessert, candy and ready-to-eat cereals are large contributors of added sugar among children two to 18 years old [62]. In Finland there is an exceptionally high children's consumption of puréed fruit [Semper Reports]. Laboratory analysis of food products marketed towards and consumed by infants and young children in the U.S. showed that of 100 samples analyzed 74% contained 20% or more of total calories per serving from added sugars [63]. There are also various packed foods for children that can have 73–93% of the caloric content from sugars [60].

Fast food consumption in children, adolescents and adults

Food eaten away from home has increased dramatically in the U.S. after WWII. The contribution of this sector to total energy intake increased from 18% in 1977 to 34% in 2012. Of this share the amount obtained from fast food climbed from around 6% in 1977 to 16% in 2012 [64]. Reports indicate fast food use in 37% of adults and 42% of children between 1994 and 1998 [65,66].

A survey conducted in California public schools found that more than 855 of the school districts responding sold fast food items. Pizza, hamburgers, submarine sandwiches, French fries, chips, cookies, yoghurt, bagels, ice cream and sodas accounted for up to 70% of all food sales in the high schools. More than half of the schools surveyed carried Taco-Bell, Subway, Dominos, Pizza Hut or other branded fast foods [67].

Fast food consumers, compared with non-consumers have a higher intake of energy as fat, carbohydrates and added sugars and a lower intake of milk, fruits and non-starchy vegetables compared with meals eaten at home. The fast-food meals have in general a high glycaemic index and cause a high glycaemic load. [68,69]. The affordable well-marketed food tempts to large portions. Popular at reasonable prices are supersized burgers, cheeseburgers, pizzas, large servings of French fries and free servings of sugar sweetened beverages [70].

The expansion of the fast food businesses in the U.S. has in essential aspects paralleled the obesity and diabetes epidemics [71]. Eating fast food more than twice rather than less than once per week has in young adults been associated with an 86% increased risk of becoming obese and to develop insulin resistance [72]. The U.S. fast food chains have subsequently spread globally and contribute to the rise of obesity in frequent users of their products also in other parts of the world [73].

Sugar, acceleration of growth and weight gain

Eugene Ziegler was the first to suspect a relationship between the secular trend of modern sugar (sucrose) consumption increase and the secular trend in the stature of adults, as well as a gradual increase in both pregnancy weight gain, birth weight and accelerated growth in children and adolescents that had occurred in specific populations in the 1900s [22,74]. His idea about sugar as a driving force for growth identified sugar metabolism and the demand for insulin supply as central to this process. Ziegler's concept has been supported by a study on Canadian Eskimo children which showed that an observed pre- and

postnatal growth acceleration runs in parallel with increased sugar consumption independently of the protein intake [75].

That sugar via glucose in blood can play a part in the increase of body growth is also supported by observations like the macrosomic child of a prediabetic mother. And even without diabetic criteria, maternal intake of a high glycaemic index diet results both in maternal weight gain and foeto-placental overgrowth [76]. Also in children born preterm carbohydrate intake is the main determinant of growth under the presumption that protein intake is adequate [77]. Undesirable weight gain because of overtreatment with insulin in diabetes is a known phenomenon for clinicians. In children with a glycogen storage disorder (GSD I) an enzyme deficiency impairs the liver to release free glucose to the blood which leads to a severely stunted growth. Treatment of this inborn error with raw corn starch per os increases the blood glucose level which is followed by the catching up of growth in height and weight [78] indicating that glucose is integral and central to the metabolism maintaining cellular proliferation and growth.

A systematic review and meta-analysis of randomized controlled trials and cohort studies on the influence of dietary sugars on body weight showed that the intake of free sugars or sugar sweetened beverages leads to rapid weight gain. The results indicated a special role for sugar in the metabolic process of growth since an isoenergetic exchange with other carbohydrates was not associated with weight gain [79]. An increase in obesity was observed to be parallel to an increase in the consumption of sugar in a study of Johnsson et al. in 2007 [78b]. The parallelism of the upward trend in the consumption of fibre-depleted refined carbohydrates and the upward trend of obesity (and T2DM) has also been accounted for in a study by Gross et al. in 2004 [4]. The focus in these studies is on the intake of fructose corn syrups (HFCS) and their eventual role in obesity and T2DM. But similar and simultaneous trends of obesity and T2DM on the global level are concomitant with an almost complete dominance of sucrose as a sweetener which makes it less probable that HFCS per se play any specific role in these developments [42].

A special role for glucose in cell proliferation and growth is supported by experimental research.

Studies in yeast show that glucose is required for cellular proliferation because lack of glucose in the culture media induces cell cycle arrest. Experimental inhibition of glycolysis stops cell cycle progression linking the requirement of glucose for proliferative control [80]. In vitro studies of thymocytes have shown that induction of glycolytic enzymes (mediating transition from oxidative to glycolytic energy production) and subsequent cell proliferation strictly depends on glucose [81]. High glucose and insulin levels influence cell cycle progression in myoblasts and the onset of myogenesis with effects similar to IGF-1 [82]. A glucose to gene link may also exist suggesting that glucose can affect transcription of genes of importance in glucose metabolism [83].

The blood glucose level is the primary regulator of the postprandial insulin release and it is a feature of the β -cells that their metabolic activation is governed by substrate availability and not being able to downregulate the transport of glucose inside the cell when exposed to high glucose levels. Amino acids, fatty acids, incretins and other substances can act as potentiators of insulin secretion but in a glucose dependent way requiring a threshold stimulatory level of glucose in the blood to have an effect [84–87]. Glucose is the predominant energy source in the human body and all cells express glucose transporters and glucose-metabolizing enzymes. Under optimal conditions glucose metabolism is the mainstay for metabolic energy generation and anabolic process production.

The high cellular flow of glucose and its metabolites caused by the Western type of food habits thus can induce or support processes promoting growth. One such process is the non-oxidative lactic-acid-producing aerobic glycolysis (the Warburg effect). This glycolytic metabolic pathway was originally observed in fast growing malignant cells but may be functional also in normal proliferating cells and can be a

process selected for proliferating cells throughout Nature [88]. Important biosynthetic pathways diverge from this glycolytic pathway which provide carbon-atoms to cell building substances such as nucleotides, amino acids and lipids, which through the growth-signaling effects of insulin, and the presence of other essential nutrients, can be critical contributors to the synthesis of biomass, acceleration of growth and weight gain [89,19].

Weight gain, acceleration of growth and diabetes risk

There is an association between body weight gain in adults and the risk of T2DM, which may be of a dose-response type [90]. But the T2DM risk is not necessarily bound to obesity. Studies have shown that weight gain can increase T2DM risk even among lean individuals [91]. Studies in the Japanese population have observed that long term weight/BMI gain since the age of 20 years and through adulthood, even within the normal weight range and independently of attained weight status, is a significant predictor of T2DM [92]. Other Japanese studies have confirmed that weight increase within the non-obese level increases the T2DM risk [93]. In Asian countries obesity rates do not generally correspond with diabetes rates, but even a modest amount of weight gain in adults increases the risk of diabetes [94]. Also, in U.S. adults there is an increased risk of T2DM with weight gain already at modest levels of overweight [95].

The increasing incidence of T1DM in children in many countries can be seen in this context. Being overweight is not prominent in T1DM but a number of studies have shown that accelerated growth is a risk factor for the disease. In a 1974 study Drayer found that diabetic boys may be taller than the average for their age at the onset of T1DM [96]. Baum et al. observed in 1975 that weight gain in infancy is also a risk factor for T1DM [97]. Blom et al. 1992 found rapid linear growth to be a risk factor for T1DM in childhood [98] and Johansson et al. in 1994 observed a significantly greater weight gain in children diagnosed with T1DM compared to reference children. Weight gain in children who never had been breast-fed was more marked than that of breast-fed children in both probands and reference children [99]. This is consistent with the observations of Almquist-Tangen of an association between frequent intake of cereal-containing formula and weight gain [53b]. The lower weight gain of breast-fed children was suggested to explain the protective effect of breast-feeding against T1DM [99]. Also, prenatal weight gain and high birthweight as well as rapid weight gain during the first year of life have been found to be risk factors for T1DM [100]. The ongoing secular trend in height and BMI increase among children and young people in industrial countries is also suggested to contribute to the T1DM risk [101].

Weight gain is a risk predictor not only for T2DM and T1DM but also for early islet autoimmunity in children belonging to the HLA risk subgroups [102]. Early β -cell damage can then be part of the pathogenesis of both T2DM and T1DM. But only individuals with the HLA risk factors have today the known laboratory manifestations that reflect this damage.

Sugar, obesity, acceleration of growth and diabetes risk

A recent study at the population level found sugar intake to be uniquely correlated to T2DM prevalence independently of the overweight and obesity prevalence rates. The duration and degree of sugar exposure correlated with diabetes prevalence in a dose-dependent manner [103]. A dose-response relation of dietary glycaemic load to T2DM risk was also observed in a meta-analysis of prospective cohort studies [104]. Another study including 165 countries has presented results showing independent associations between T2DM prevalence and the per capita consumption of sugar worldwide. A prominent correlation between diabetes and sugar consumption was noted in the Asia-Pacific region where the contribution of obesity rates to T2DM prevalence also was minimal. The patients developed T2DM at a

younger age and at a lower threshold of BMI [105]. A meta-analysis of prospective cohort diets with high glycaemic index and load showed significantly increased risk of T2DM without any conclusive relation to body mass index [106]. A study of U.S. younger and middle-aged women has shown that a diet high in rapidly-absorbed carbohydrates and low in cereal fibre is associated with an increased risk of T2DM without significant modification by the BMI [107]. Habitual consumption of sugar-sweetened beverages has been associated with a greater incidence of T2DM, independent of obesity [108]. High SSB intake in combination with weight gain is associated with the development of T2DM and the metabolic syndrome [109,110].

Development of T1DM in childhood is also associated with a high intake of sugars. A Swedish matched case-control study found the intake of disaccharides (including sucrose) associated not only with the T1DM risk but also with a more rapid growth [111]. Another study has found that a high frequency intake of foods rich in carbohydrates increase the risk for T1DM with a non-linear dose response curve possibly indicating a threshold effect [112].

Overweight and obesity seem not necessarily per se to be risk factors for T2DM. The disease is neither always associated with obesity nor do most overweight/obese persons develop T2DM [113]. But, in accordance with Wilkins [114], processes driving weight gain and/or acceleration of growth may be the distinct risk factors for T2DM and T1DM. Even if they seem to follow a common path the physiological mechanisms leading to weight gain and growth acceleration must be apart from the pathophysiological mechanisms leading to the diabetic diseases.

Hypothesis

Genetic assumptions

The full picture of the genetic risks for T2DM and T1DM is not known. For T2DM a large number of genetic susceptibility loci have been identified. The known risk variants are however calculated to collectively account for only 10% of the overall hereditary risk [115,116]. There are also indications of a considerable genetic heterogeneity among the diabetic diseases. [117].

In T1DM genetic factors in the HLA system are considered to account for the major part of the disease risk. There is however an ongoing temporal change in the proportion of different HLA types in children who develop T1DM. More children than previously with low risk HLA genotypes acquire the disease in association with increasing body mass index. This could indicate that other factors connected to weight gain have a greater impact on the pathogenic process in T1DM than the HLA genotypes [118]. In addition to the known HLA-risk factors more than 50 non-HLA polymorphisms have been identified which can contribute to the disease risk [119].

The genetic backgrounds of T2DM and T1DM are suggested here to be various clusters of gene variants existing in β -cells with normal function, but forming a spectrum of different degrees of individual β -cell susceptibility, eventually representing extremes of the normal distribution, to damaging effects deriving from environmental factors not adapted to during evolution. Individuals as well as populations and subgroups of different racial/ethnic or geographic origin are supposed to have different genetic susceptibilities to the same damaging environmental agents rather than specific pre-diabetic genotypes, although genetic susceptibility factors can be shared across individuals and populations and definable clusters can vary in prevalence among different populations and population groups [119,120,120b]. The most important constellations of genetic risk factors for T1DM and T2DM and their specific interactions as well as their interaction with other genes is today unknown.

T2DM and T1DM are by this definition polygenic and genetically heterogeneous disorders. This can be a reason for the blurred age distinction between them. Population-specific genetic susceptibility traits

can also explain the ethnic/racial, geographic and migration-associated variations in disease incidence and prevalence seen globally and in multi-ethnic societies. In certain constellations the genetic factors are supposed to have a more dominant pathogenic role and then can contribute to earlier clinical onset of the diseases.

The genotypic patterns behind different degrees of vulnerability in the β -cells have not, according to this hypothesis, been of earlier survival value.

Disease precipitation

Chronic exposure of the human β -cells to glucose under diabetic conditions is known to exert toxic effects on these cells and causes defective insulin gene expression followed by decreases in insulin content and insulin secretion after administration of glucose [121].

The current Western type of diet, dominantly based on fibre-depleted, high-glycaemic-index carbohydrates including a substantial proportion of sugars and sweeteners, mostly in the form of soft beverages, is a new phenomenon in the history of human nutrition. It causes a glycaemic effect on the body which by far exceeds that of earlier diets. The easily digested starches from wheat, rice, corn, potatoes and other starch-rich products result in glucose as the dominant monosaccharide for absorption, to which glucose from the caloric sweeteners is added. Low fibre content of the meals and high intake of SSB facilitate rapid passage and digestion of the carbohydrates and promote rapid absorption of large amounts of glucose to the blood exposing the β -cells to a high glucose inflow and high glucose levels inside the cells. A corresponding insulinaemia keeps the blood glucose under a defined level thereby causing a rapid cellular turnover of glucose and a considerable up-regulation of the glucose metabolic pathways in insulin-sensitive body cells compared with the intake of traditional fibre-rich low-glycaemic-index diets [4,122]. A subset of body cells involved in diabetic late complications (vascular endothelial cells, kidney mesangial cells, neurons and neuroglia), share with the pancreatic β -cells the inability to down-regulate the inflow of glucose inside the cell [122b].

Catabolism of glucose is under normal conditions the main provider of energy in the β -cells and in other tissues through the ATP-generating flux of glucose and glucose metabolites through the glycolytic pathways the tricarboxylic acid (TCA) cycle and the electron transport chain. The rate of glucose metabolism regulates insulin secretion. By diabetic glucose excess this flux however also has the potential to cause mitochondrial dysfunction through overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the mitochondria [123]. In the β -cells the antioxidative defence mechanisms are particularly low and among the lowest of all mammalian tissues [123b]. Accumulation of oxidants above a certain level can cause severe and irreversible damage to the cells by reacting with cellular proteins and DNA thus interfering with cellular processes [124]. This causes among other disturbances decreased binding of the specific nuclear transcription factors for insulin (MAFA and PDX1) to the gene initiating β -cell dysfunction [129]. Islets have been shown to have a poor DNA repair capacity against oxidative damage [129b]. According to animal experiments oxidative stress also can disrupt β -cell mass and function by inducing endoplasmic reticulum stress through initiation of pro-apoptotic levels of interleukins in the islets [129c]. Oxidative stress is considered to be the central mechanism for the toxicity of glucose. The presence of a high level of fatty acids can contribute to the destruction of glucose-damaged β -cells [128,128b,148,149].

The post-War Western diet, generating exceptional amounts of glucose for rapid absorption is suggested to boost mitochondrial oxidative stress as a damaging agent to the β -cells. Not only the magnitude but also the rate of glucose inflow to the blood can be critical for eliciting this reaction. Significant fluctuations in the glucose inflow have also been shown to contribute to formation of oxidative species [125].

The high glucose flow in insulin-sensitive somatic cells can, beside

supplying energy, also provide cell proliferative components which through the insulin signalling can contribute to acceleration of growth and weight gain. (This phenomenon is not associated with other putative causes to T1DM for example virus, gluten or cow's milk.) The effect on growth and weight gain could contribute to the secular trend of increase of height, weight and body mass index among adolescents that has been observed in developed countries over several decades – a trend which correlates positively with the ongoing increase in the incidence of T1DM [126] – and to the obesity epidemic which correlates with T2DM incidence. Acceleration phases of linear body growth and weight gain most probably mirror a β -cell apparatus exerting its capacity for insulin production and secretion at the utmost, which at the same time can increase the risk for generation of oxidative species.

Under high insulin-glucose load oxidative stress may occur in all cells of the body – the risk of damage, however, may be highest in the β -cells due to their deficient antioxidant defences [123b,127] and will be fatal for β -cell metabolic systems which for genetic reasons could be abnormally susceptible to this type of damage.

There is also accumulating evidence that a high blood insulin level is the key causal factor in the development of obesity [142,143,144]. The degree of weight gain and obesity associated with the Western diet may depend on the total energy intake while the diabetes risk may depend on an imminent β -cell glucotoxic effect associated with this intake. Diet quality can have independent effects on the prevalences of both T2DM and obesity.

Oxidative stress as a possible damaging factor in T1DM and T2DM

In T1DM oxidative stress is present at onset in children and adults [130,131], and may have been present already before the clinical onset of the disease, as markers of oxidative stress have been demonstrated in non-diabetic family members of T1DM patients having shared the same diabetogenic environment [132].

Seroconversion to islet antibodies has a peak at 9 months to 2 years of age in most children with HLA-related risk for T1DM [133]. Rapid weight gain during this period of life is a predictor of the autoimmune reaction [134–136]. But the main genetic traits in T1DM hypothesized to cause a pre-destined vulnerability of the β -cells are suggested here to lie outside the HLA-gene related risk agents in the immune system. The appearance of autoantibodies preceding the onset of disease can be an epiphenomenon seen in individuals with certain HLA-types but caused by an immune reaction against β -cell tissue damaged by nutrition. The autoimmune reaction could be initiated by oxidatively- modified post-translational molecules recognized as “non-self” epitopes by the immune system [138]. A high carbohydrate intake leading to a glucose stimulated high rate of insulin secretion can promote expression of such autoantigens from the β -cells as experimentally exemplified by glutamic acid decarboxylase (GAD) [139,139b]. GAD, experimentally modified by reactive oxygen species (ROS), is recognized by antibodies from patients with T1DM [140]. Recently also the presence of oxidatively modified post-translational insulin has been demonstrated in vivo and shown to serve as an autoantigen in most individuals with newly diagnosed T1DM [141].

The early appearance of autoantibodies may occur in individuals with the genetically most vulnerable type of β -cells when challenged by a high glucose load. Anticipated from the duration of presence of autoantibodies there can be a period (years) of silent β -cell damage proceeding before the onset of clinical symptoms [137]. When the oxidative/autoimmune destruction of the insulin-producing tissue has reached a critical level, ongoing glucose overload will contribute to a rapid clinical precipitation of the disease. If physiological blood glucose levels are restored during this process the β -cells will recover for a period of time.

In T2DM, pancreatic islet markers of oxidative stress are significantly higher compared with control islets, and the level of these markers correlates positively with the degree of glucose-stimulated

impairment of insulin secretion [152,152b]. Experimentally, antioxidants can protect the β -cells [151,153]. The initial glucose-induced oxidative β -cell damage could in predisposed individuals occur early in life in sensitive periods of β -cell development and cause permanent changes in systems of importance for future β -cell mass and/or function [150]. By the cumulative effect of repeated oxidative challenges hitting their loci minoris the initial damage can aggravate with time and contribute to a progressive β -cell damage finally leading to overt T2DM [146]. Mitochondrial dysfunction, in the presence of elevated levels of fatty acids, as in obesity, has been suggested to play a central role in the pathogenesis of the associated insulin resistance [146b]. But the increased risk for T2DM in obesity most probably emanates from a fraction of genetically susceptible obese individuals. Most obese persons can adapt to the presence of insulin resistance by increasing insulin secretion.

The etiology of T2DM may be independent of insulin resistance and obesity [145] although these can influence the clinical course. But it seems less probable that an individual can develop the disease without genetically predisposed malfunctioning β -cells [147]. Inability of the β -cells to maintain appropriate insulin secretion is most probably the key factor and a prerequisite for developing the disease. In genetically susceptible individuals, when a β -cell oxidative damage becomes aggravated beyond a certain point the β -cell damage will be irreversible. If however physiological blood glucose concentrations are restored before that point the pathogenetic process could probably be reversed permanently. With ongoing oxidative damage T2DM will ensue.

Hyperglycaemic complications

Oxidative stress caused by hyperglycaemia is the most significant factor in the development of the diabetic complications that are observed several years after the onset of the diabetic illnesses [154]. The increase of rapidly absorbed glucose to the blood, associated with the transition to the Western type of nutrition can also involve β -cell oxidative stress which may be a factor in causing β -cell complications in individuals adapted to a lower level of glucose load from their available food.

Conflicts of interest

None to declare

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