

Inborn errors of carbohydrate metabolism

Inborn errors of carbohydrate metabolism are **inborn error of metabolism** that affect the catabolism and anabolism of **carbohydrates**. An example is **lactose intolerance**.

Carbohydrates account for a major portion of the human diet and are metabolized into three principal monosaccharides: galactose, fructose and glucose. The failure to effectively use these sugars accounts for the majority of the inborn errors of human carbohydrate metabolism.

Galactose

Galactosemia, the inability to metabolize **galactose**, is the most common monogenic disorder of carbohydrate metabolism, affecting 1 in every 55,000 newborns. When galactose is not possible to break down, it accumulates in tissues. The most common signs are **failure to thrive**, hepatic insufficiency, cataracts and developmental delay. Long term disabilities include poor growth, **mental retardation**, and ovarian failure in females.

Galactosemia is caused by mutations in the gene that makes the enzyme **galactose-1-phosphate uridylyltransferase**. Approximately 70% of galactosemia-causing alleles have a single missense mutation in exon 6. A milder form of galactosemia, called **Galactokinase deficiency**, is caused by a lack of the enzyme **uridine diphosphate galactose-4-epimerase** which breaks down a byproduct of galactose. This type of is associated with cataracts, but does not cause growth failure, mental retardation, or hepatic disease. Dietary reduction of galactose is also the treatment but not as severe as in patients with classical galactosemia. This deficiency can be systemic or limited to red blood cells and leukocytes.

Screening is performed by measuring GAL-1-P uridylyl transferase activity. Early identification affords prompt treatment, which consists largely of eliminating dietary galactose.

Fructose

Three autosomal recessive disorders involve the inability to metabolize fructose. The most common is caused by mutations in the gene encoding hepatic fructokinase, an enzyme that catalyzes the first step in the metabolism of dietary fructose. Inactivation of the hepatic fructokinase results in asymptomatic fructosuria.

Hereditary fructose intolerance (HFI) results in poor feeding, failure to thrive, hepatic and renal insufficiency, and death. HFI is caused by a deficiency of fructose 1,6-bisphosphate aldolase in the liver, kidney cortex and small intestine. Infants and adults are asymptomatic unless they ingest fructose or sucrose.

Deficiency of hepatic fructose 1,6-bisphosphate (FBPase) causes impaired gluconeogenesis, hypoglycemia and severe metabolic acidemia. If patients are adequately supported beyond childhood, growth and development appear to be normal.

Glucose

Diabetes mellitus type 1 is a genetic disorder caused by reduced or absent levels of insulin, a hormone that metabolizes glucose.

Lactose

The ability to metabolize lactose depends on an intestinal enzyme called lactase. In most mammals, production of lactase diminishes after infants are weaned from maternal milk. However, 5% to 90% of the human population possess an advantageous autosomal mutation in which lactase production persists after infancy. The geographic distribution of lactase persistence is concordant with areas of high milk intake. Lactase non-persistence is common in tropical and subtropical countries. Individuals with lactase non-persistence may experience nausea, bloating and diarrhea after ingesting dairy.

Glycogen

Carbohydrates are most commonly stored as glycogen in humans. Consequently, enzyme deficiencies that lead to impaired synthesis or degradation of glycogen are also considered disorders of carbohydrate metabolism. The two organs most commonly affected are the liver and the skeletal muscle. Glycogen storage disorders that affect the liver typically cause hepatomegaly and hypoglycemia. Those that affect skeletal muscle cause exercise intolerance, progressive weakness and cramping.^[2]

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Galactosemia

Galactosemia (British **Galactosaemia**) is a rare genetic metabolic disorder that affects an individual's ability to metabolize the sugar galactose properly. Galactosemia is not related to and should not be confused with lactose intolerance. Galactosemia follows an autosomal recessive mode of inheritance that confers a deficiency in an enzyme responsible for adequate galactose degradation.

Goppert first described the disease in 1917, with its cause as a defect in galactose metabolism being identified by a group led by Herman Kalckar in 1956.

Its incidence is about 1 per 60,000 births. It is much rarer in Japan and much more common in Italy, specifically the traveler region. Galactosemia is also very common within the Irish Traveller population. This is attributed to inbreeding within a relatively small gene pool.

Cause

Lactose in food (such as dairy products) is broken down by the enzyme lactase into glucose and galactose. In individuals with galactosemia, the enzymes needed for further metabolism of galactose are severely diminished or missing entirely, leading to

toxic levels of galactose in the blood, resulting in hepatomegaly (an enlarged liver), cirrhosis, renal failure, cataracts, brain damage, and ovarian failure. Without treatment, mortality in infants with galactosemia is about 75%.

Types

Galactose is converted into glucose by the action of three enzymes, known as the Leloir pathway. Accordingly, there are 3 known types of Galactosemia; type 1, 2 and 3:

	galactose-1-phosphate uridyl transferase	classic galactosemia
	galactokinase	galactokinase deficiency
	UDP galactose epimerase	galactose epimerase deficiency, UDP-Galactose-4-epimerase deficiency

The order of these three types is not the same as the order that the enzymes are encountered by galactose on its metabolic path (which is closer to GALK, GALT, and then GALE, though many variations can occur.)

Diagnosis

Infants are now routinely screened for galactosemia in the United States, and the diagnosis is made while the person is still an infant. Infants affected by galactosemia typically present with symptoms of lethargy, vomiting, diarrhea, failure to thrive, and jaundice. None of these symptoms are specific to galactosemia, often leading to diagnostic delays. Luckily, most infants are diagnosed on newborn screening. A galactosemia test is a blood test (from the heel of the infant) or urine test that checks for three enzymes that are needed to change galactose sugar that is found in milk and milk products-into glucose, a sugar that your body uses for energy. A person with galactosemia doesn't have one of these enzymes. This causes high levels of galactose in the blood or urine.

Galactosemia is normally first detected through newborn screening, or NBS. Affected children can have serious, irreversible effects or even die within days from birth. It is important that newborns be screened for metabolic disorders without delay. Galactosemia can even be detected through NBS before any ingestion of galactose-containing formula or breast milk.

Detection of the disorder through newborn screening (NBS) does not depend on protein or lactose ingestion, and, therefore, it should be identified on the first specimen unless the infant has been transfused. A specimen should be taken prior to transfusion. The enzyme is prone to damage if the sample is delayed in the mail or exposed to high temperatures. The routine NBS is accurate for detection of galactosemia. Two screening tests are used to screen infants affected with galactosemia - the Beutler's test and the Hill test. In fact a third test, called the "Florida test", is also normally performed on all galactosemia positives. The Beutler's test screens for galactosemia by detecting the level of enzyme of the infant. Therefore, the ingestion of formula or breast milk does not effect the outcome of this part of the NBS, and the NBS is accurate for detecting galactosemia prior to any ingestion of galactose.

Treatment

The only treatment for classic galactosemia is eliminating lactose and galactose from the diet. Even with an early diagnosis and a restricted diet, however, some individuals with galactosemia experience long-term complications such as speech difficulties, learning disabilities, neurological impairment (e.g. tremors, etc), symptoms have not been associated with Duarte galactosemia, and many individuals with Duarte galactosemia do not need to restrict their diet at all. Infants with classic galactosemia cannot be breast-fed due to lactose in human breast milk and are usually fed a soy-based formula.^[3]

Galactosemia is sometimes confused with lactose intolerance, but galactosemia is a more serious condition. Lactose intolerant individuals have an acquired or inherited shortage of the enzyme lactase, and experience abdominal pains after ingesting dairy products, but no long-term effects. In contrast, a galactosemic individual who consumes galactose can cause permanent damage to their bodies.

Long term complication of galactosemia includes:

- Speech deficits
 - Ataxia
 - Dysmetria
 - Diminished bone density
 - Premature ovarian failure
 - Cataract
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Essential Fructosuria

Essential fructosuria, also known as **hepatic fructokinase deficiency** or **ketoheokinase deficiency**,^[1] is a hereditary metabolic disorder caused by a deficiency in hepatic fructokinase, leading to fructose being excreted in the urine (-*uria* denotes "in the urine"). It is essentially a benign condition, as fructose cannot be broken down, so it is simply excreted in the urine.^[2] Inheritance is autosomalrecessive.^[3]

Essential fructosuria should not be confused with *fructosemia*, which denotes fructose in the blood (also known as hereditary fructose intolerance). Fructosemia is a very serious condition, as fructose is converted into fructose-1-phosphate, using up ATP and building up fructose-1-phosphate in the blood. This prevents proper release of glucose from glycogen, uses up free phosphate, and causes a rise in uric acid, leading to growth abnormalities and, in severe cases, coma.

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Hereditary Fructose Intolerance

Hereditary fructose intolerance (HFI) or **fructose poisoning** is a hereditary condition caused by a deficiency of liver enzymes that metabolise fructose. It is also known as hereditary fructosemia.

Cause

The deficient enzyme is aldolase-B, which converts fructose-1-phosphate to DHAP and glyceraldehyde. This means that the fructose cannot be further metabolised beyond fructose-1-phosphate. This traps phosphates; which are needed to phosphorylate glycogen phosphorylase which carries on to release units of glucose-1-phosphate from glycogen. (Glucose-1-phosphate gets converted to glucose-6-phosphate and then dephosphorylated to form glucose).

In addition, Aldolase A plays an important role in gluconeogenesis, producing fructose-1,6-bisphosphate from glyceraldehyde-3-phosphate and DHAP. But, glucose may still be released through the breakdown of glycogen. Although, it cannot be synthesized from gluconeogenesis, resulting in severe hypoglycemia.

Common Traits

- Refusal to eat or dislike of many fruits, vegetables, candies, and baked goods.
- Love of dextrose based candies.
- Primary beverages are: milk, water, unsweetened tea, unsweetened coffee.
- Feeling nauseated, sick, queasy, shaky, and/or foggy shortly after consuming fructose or sucrose.
- Kidney pain, hypoglycemia, shaky, weak, tired and inwardly focused (no real awareness of environment) a few hours to a couple days after consuming fructose or sucrose.
- Tendency to binge eat on "safe" foods after consuming fructose. Safe foods can include dairy, potato chips, pasta and/or rice.

Treatment

Treatment is with a fructose free diet, which if adhered to, is concordant with a good prognosis. ^[1]

Fructose and sucrose eliminated from diet.

Related Conditions

Hereditary fructose intolerance should not be confused with fructose malabsorption. The latter was formerly known as dietary fructose intolerance (DFI), a deficiency of fructose transporter protein in the enterocytes, which leads to abdominal bloating, diarrhea and/or constipation.

Diabetes Mellitus Type 1

Diabetes mellitus type 1 (Type 1 diabetes, IDDM, or juvenile diabetes) is a form of diabetes mellitus that results from autoimmune destruction of insulin-producing beta cells of the pancreas.^[2] The subsequent lack of insulin leads to increased blood and urine glucose. The classical symptoms of polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss result.^[3]

Type 1 diabetes is fatal unless treated with insulin. Injection is the most common method of administering insulin; insulin pumps and inhaled insulin have been available at various times. Pancreas transplants have been used to treat type 1 diabetes; however, this procedure is currently still at the experimental trial stage.^[4]

Most people who develop type 1 are otherwise healthy.^[5] Although the cause of type 1 diabetes is still not fully understood it is believed to be of immunological origin. There is a growing body of evidence that diet may play a role in the development of type 1 diabetes, through influencing gut flora, intestinal permeability, and immune function in the gut; wheat in particular has been shown to have a connection to the development of type 1 diabetes, although the relationship is poorly understood.^[6] Type 1 can be distinguished from type 2 diabetes via a C-peptide assay, which measures endogenous insulin production.

Type 1 treatment must be continued indefinitely in all cases. Treatment need not significantly impair normal activities, if sufficient patient training, awareness, appropriate care, discipline in testing and dosing of insulin is taken. However, treatment is burdensome for many people. Complications may be associated with both low blood sugar and high blood sugar. Low blood sugar may lead to seizures or episodes of unconsciousness and requires emergency treatment. High blood sugar may lead to increased tiredness and can also result in long term damage to other organs such as eyes and joints.

Signs and symptoms

The classical symptoms of type 1 diabetes include: polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), tiredness, and weight loss.

Cause

Environment

Environmental factors can strongly influence expression of type 1. A study showed that for identical twins, when one twin had type 1 diabetes, the other twin only had type 1 30%–50% of the time. Despite having the exact same genome, one twin had the disease, where the other did not; this suggests that environmental factors, in addition to genetic factors, can influence disease prevalence.

Genetics

Type 1 diabetes is a polygenic disease, meaning many different genes contribute to its expression. Depending on locus or combination of loci, it can be dominant, recessive, or somewhere in between. The strongest gene, *IDDM1*, is located in the MHC Class II region on chromosome 6, at staining region 6p21. This is believed to be responsible for the histocompatibility disorder characteristic of type 1: Insulin-producing pancreas cells (beta cells) display improper antigens to T cells.

Pathophysiology

The cause of type 1 diabetes is not fully understood. Some theorize that type 1 diabetes is a virally triggered autoimmune response in which the immune system attacks virus infected cells along with the beta cells in the pancreas. The Coxsackie virus family or German measles is implicated, although the evidence is inconclusive. In type 1, pancreatic beta cells in the islets of Langerhans are destroyed decreasing endogenous insulin production. This distinguishes type 1's origin from type 2 DM. The type of diabetes a patient has is determined only by the cause—fundamentally by whether the patient is insulin resistant (type 2) or insulin deficient without insulin resistance (type 1).

This vulnerability is not shared by everyone, for not everyone infected by the suspected organisms develops type 1 diabetes. This has suggested presence of a genetic vulnerability^[9] and there is indeed an observed inherited tendency to develop type 1. It has been traced to particular HLA genotypes, though the connection between them and the triggering of an auto-immune reaction is still poorly understood.

Short breast-feeding period and short attendance to day care is associated with the risk of type 1 diabetes in Czech children.^[10]

Some researchers believe that the autoimmune response is influenced by antibodies against cow's milk proteins.^[11] No connection has been established between autoantibodies, antibodies to cow's milk proteins, and type 1 diabetes. A subtype of type 1 (identifiable by the presence of antibodies against beta cells) typically develops slowly and so is often confused with type 2. In addition, a small proportion of type 2 cases manifest a genetic form of the disease called maturity onset diabetes of the young (MODY).

Vitamin D in doses of 2000 IU per day given during the first year of a child's life has been connected in one study in Northern Finland (where intrinsic production of Vitamin D is low due to low natural light levels) with an 80% reduction in the risk of getting type 1 diabetes later in life. The causal connection, if any, is obscure.

Type 1 diabetes was previously known as juvenile diabetes because it is one of the most frequent chronic diseases in children; however, the majority of new-onset type 1 diabetes is seen in adults. Scientific studies that use antibody testing (glutamic acid decarboxylase antibodies (GADA), islet cell antibodies (ICA), and insulinoma-associated autoantibodies (IA-2)) to distinguish between type 1 and type 2 diabetes demonstrate that most new-onset type 1 diabetes is seen in adults. A 2008 book, *Type 1 Diabetes in Adults: Principles and Practice*, says that adult-onset type 1 autoimmune diabetes is two to three times more common than classic childhood-onset autoimmune diabetes.^[12] In type 1 diabetes, the body does not produce insulin. Insulin is a hormone that is needed to maintain normal blood glucose levels (3.6 to 5.8 mM glucose) within the body, when spikes in blood glucose concentration occurs. One mechanism by which insulin does such is by causing the liver to take up glucose molecules and convert them to glycogen for storage in the liver.

Some chemicals and drugs preferentially destroy pancreatic cells. Pyrinuron (Vacor, N-3-pyridylmethyl-N'-p-nitrophenyl urea), a rodenticide introduced in the United States in 1976, selectively destroys pancreatic beta cells, resulting in type 1 diabetes after accidental or intentional ingestion. Vacor was withdrawn from the U.S. market in 1979, but is still used in some countries. Zanosar is the trade name for streptozotocin, an antibiotic and antineoplastic agent used in chemotherapy for pancreatic cancer; it also kills beta cells, resulting in loss of insulin production. Other pancreatic problems, including trauma, pancreatitis or tumors (either malignant or benign), can also lead to loss of insulin production.

The exact cause(s) of type 1 diabetes are not yet fully understood, and research on those mentioned, and others, continues.

Diagnosis

2006 WHO Diabetes criteria ^[13] edit		
Condition	2 hour glucose	Fasting glucose
	mmol/l(mg/dl)	mmol/l(mg/dl)
Normal	<7.8 (<140)	<6.1 (<110)
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:^[14]

- Fasting plasma glucose level at or above 7.0 mmol/L (126 mg/dL).
- Plasma glucose at or above 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test.
- Symptoms of hyperglycemia and casual plasma glucose at or above 11.1 mmol/L (200 mg/dL).
- Glycated hemoglobin (hemoglobin A1C) at or above 6.5. (This criterion was recommended by the American Diabetes Association in 2010; it has yet to be adopted by the WHO.)^[15]

About a quarter of people with new type 1 diabetes have developed some degree of diabetic ketoacidosis (a type of metabolic acidosis which is caused by high concentrations of ketone bodies, formed by the breakdown of fatty acids and the deamination of amino acids) by the time the diabetes is recognized. The diagnosis of other types of diabetes is usually made in other ways. These include ordinary health screening; detection of hyperglycemia during other medical investigations; and secondary symptoms such as vision changes or unexplainable fatigue. Diabetes is often detected when a person suffers a problem that is frequently caused by diabetes, such as a heart attack, stroke, neuropathy, poor wound healing or a foot ulcer, certain eye problems, certain fungal infections, or delivering a baby with macrosomia or hypoglycemia.

A positive result, in the absence of unequivocal hyperglycemia, should be confirmed by a repeat of any of the above-listed methods on a different day. Most physicians prefer to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test.^[16] According to the current definition, two fasting glucose measurements above 126 mg/dL (7.0 mmol/L) is considered diagnostic for diabetes mellitus.

Patients with fasting glucose levels from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) are considered to have impaired fasting glucose. Patients with plasma glucose at or above 140 mg/dL (7.8 mmol/L), but not over 200 mg/dL (11.1 mmol/L), two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these two pre-diabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus as well as cardiovascular disease.^[17]

Prevention

Type 1 diabetes risk is known to depend upon a genetic predisposition based on HLA types (particularly types DR3 and DR4), an unknown environmental trigger (suspected to be an infection, although none has proven definitive in all cases), and an uncontrolled autoimmune response that attacks the insulin producing beta cells.^[18] Some research has suggested that breastfeeding decreased the risk in later life;^{[19][20]} various other nutritional risk factors are being studied, but no firm evidence has been found.^[21] Giving children 2000 IU of Vitamin D during their first year of life is associated with reduced risk of type 1 diabetes, though the causal relationship is obscure.^[22]

Children with antibodies to beta cell proteins (i.e. at early stages of an immune reaction to them) but no overt diabetes, and treated with vitamin B₃ (niacin), had less than half the diabetes onset incidence in a 7-year time span as did the general population, and an even lower incidence relative to those with antibodies as above, but who received no vitamin B₃.^[23]

Management

Type 1 is treated with insulin replacement therapy—usually by insulin injection or insulin pump, along with attention to dietary management, typically including carbohydrate tracking, and careful monitoring of blood glucose levels using glucose meters. Today the most common insulins are biosynthetic products produced using genetic recombination techniques; formerly, cattle or pig insulins were used, and even sometimes insulin from fish. Major global suppliers include Eli Lilly and Company, Novo Nordisk, and Sanofi-Aventis. A more recent trend, from several suppliers, is insulin analogs which are slightly modified insulins which have different onset of action times or duration of action times.

Untreated type 1 diabetes commonly leads to coma, often from diabetic ketoacidosis, which is fatal if untreated. Continuous glucose monitors have been developed and marketed which can alert patients to the presence of dangerously high or low blood sugar levels, but technical limitations have limited the impact these devices have had on clinical practice so far.

In more extreme cases, a pancreas transplant can restore proper glucose regulation. However, the surgery and accompanying immunosuppression required is considered by many physicians to be more dangerous than continued insulin replacement therapy, and is therefore often used only as a last resort (such as when a kidney must also be transplanted, or in cases where the patient's blood glucose levels are extremely volatile). Experimental replacement of beta cells (by transplant or from stem cells) is being investigated in several research programs. Thus far, beta cell replacement has only been performed on patients over age 18, and with tantalizing successes amidst nearly universal failure.

Pancreas Transplantation

Pancreas transplants are generally performed together with or some time after a kidney transplant. One reason for this is that introducing a new kidney requires taking immunosuppressive drugs such as cyclosporin. Nevertheless this allows the introduction of a new, functioning pancreas to a patient with diabetes without any additional immunosuppressive therapy. However, pancreas transplants alone can be wise in patients with extremely labile type 1 diabetes mellitus.^[24]

Islet cell Transplantation

Islet cell transplantation is expected to be less invasive than a pancreas transplant which is currently the most commonly used approach in humans.

In one variant of this procedure, islet cells are injected into the patient's liver, where they take up residence and begin to produce insulin. The liver is expected to be the most reasonable choice because it is more accessible than the pancreas, and islet cells seem to produce insulin well in that environment. The patient's body, however, will treat the new cells just as it would any other introduction of foreign tissue, unless a method is developed to produce them from the patient's own stem cells or there is an identical twin available who can donate stem cells. The immune system will attack the cells as it would a bacterial infection or a skin graft. Thus, patients now also need to undergo treatment involving immunosuppressants, which reduce immune system activity.

Recent studies have shown that islet cell transplants have progressed to the point that 58% of the patients in one study were insulin independent one year after islet cell transplant.^[25] Ideally, it would be best to use islet cells which will not provoke this immune reaction. Scientists in New Zealand with Living Cell Technologies are currently in human trials with Diabecell, placing pig islets within a protective capsule derived of seaweed which enables insulin to flow out and nutrients to flow in while protecting the islets from immune system attack via white blood cells.

Prognosis

Complications of poorly-managed type 1 diabetes mellitus may include cardiovascular disease, diabetic neuropathy, diabetic retinopathy among others. Overweight or obese people having T1DM are especially likely to have these problems if substandard diet is involved or the cholesterol or blood pressure is not well-controlled.^[26] There is some evidence that cardiovascular disease^[27] as well as neuropathy^[28] may, in fact, have an autoimmune basis as well.

Prevention

"Immunization" approach

If a biochemical mechanism can be found that prevents the immune system from attacking beta cells, it may be administered to prevent commencement of diabetes type 1. Several groups are trying to achieve this by causing the activation state of the immune system to change from Th1 state ("attack" by killer T Cells) to Th2 state (development of new antibodies). This Th1-Th2 shift occurs via a change in the type of cytokine signaling molecules being released by regulatory T-cells. Instead of pro-inflammatory cytokines, the regulatory T-cells begin to release cytokines that inhibit inflammation.^[30] This phenomenon is commonly known as "acquired immune tolerance".

DiaPep277

A substance designed to cause lymphocyte cells to cease attacking beta cells, DiaPep277 is a peptide fragment of a larger protein called HSP60. Given as a subcutaneous injection, its mechanism of action involves a Th1-Th2 shift. Clinical success has been demonstrated in prolonging the "honeymoon period" for people who already have type 1 diabetes.^[31] The product is currently being tested in people with latent autoimmune diabetes of adults (LADA). Ownership of the drug has changed hands several times over the last decade. In 2007, Clal Biotechnology Industries (CBI) Ltd., an Israeli investment group in the field of life sciences, announced that Andromeda Biotech Ltd., a wholly owned subsidiary of CBI, signed a Term Sheet with Teva Pharmaceutical Industries Ltd. to develop and commercialize DiaPep277.^[32]

Intra-nasal insulin

There is pre-clinical evidence that a Th1-Th2 shift can be induced by administration of insulin directly onto the immune tissue in the nasal cavity. This observation has led to a clinical trial, called INIT II, which began in late 2006, based in Australia and New Zealand.

BCG research

Tumor necrosis factor-alpha, or TNF- α , is part of the immune system. It helps the immune system distinguish self from non-self tissue. People with type 1 diabetes are deficient in this substance. Dr. Denise Faustman theorizes that giving Bacillus Calmette-Guérin (BCG), an inexpensive generic drug used to immunize against *Mycobacterium tuberculosis*, would have the same impact as injecting diabetic mice with Freund's Adjuvant, which stimulates TNF- α production. TNF- α kills the white blood cells responsible for destroying beta cells, and thus prevents, or reverses diabetes.^[33] She has reversed diabetes in laboratory mice with this technique, but was only able to receive funding for subsequent research from The Iacocca Foundation, founded by Lee Iacocca in honor of his late wife, who died from diabetes complications. Human trials are set to begin in 2008.

Diamyd

Diamyd is the name of a vaccine being developed by Diamyd Medical. Injections with GAD65, an autoantigen involved in type 1 diabetes, has in clinical trials delayed the destruction of beta cells for at least 30 months, without serious adverse effects. Patients treated with the substance showed higher levels of regulatory cytokines, thought to protect the beta cells. Phase III trials are under way in the USA ^[35] and in Europe, with most sites actively pursuing participants. Two prevention studies, where the vaccine is given to persons who have not yet developed diabetes are underway

Lactose Intolerance

Lactose intolerance is the inability to metabolize lactose, because of a lack of the required enzyme lactase in the digestive system. It is estimated that 75% of adults worldwide show some decrease in lactase activity during adulthood.^[1] The frequency of decreased lactase activity ranges from as little as 5% in northern Europe, up to 71% for Sicily, to more than 90% in some African and Asian countries.^[2]

Overview

Disaccharides cannot be absorbed through the wall of the small intestine into the bloodstream, so in the absence of lactase, lactose present in ingested dairy products remains uncleaved and passes intact into the colon. The operons of enteric bacteria quickly switch over to lactose metabolism, and the resulting in-vivo fermentation produces copious amounts of gas (a mixture of hydrogen, carbon dioxide, and methane). This, in turn, may cause a range of abdominal symptoms, including stomach cramps, bloating, and flatulence. In addition, as with other unabsorbed sugars (such as sorbitol, mannitol, and xylitol), the presence of lactose and its fermentation products raises the osmotic pressure of the colon contents.

Diagnosis

To assess lactose intolerance, the intestinal function is challenged by ingesting more dairy than can be readily digested. Clinical symptoms typically appear within 30 minutes but may take up to 2 hours, depending on other foods and activities.^[29] Substantial

variability of the clinical response (symptoms of nausea, cramping, bloating, diarrhea, and flatulence) is to be expected, as the extent and severity of lactose intolerance varies between individuals.

When considering the need for confirmation, it is important to distinguish lactose intolerance from milk allergy, which is an abnormal immune response (usually) to milk proteins. Since lactose intolerance is the normal state for most adults on a worldwide scale and is not considered a disease condition, a medical diagnosis is not normally required. However, if confirmation is necessary, three tests are available.

Managing lactose intolerance

For persons living in societies where the diet contains relatively little dairy, lactose intolerance is not considered a condition that requires treatment. However, those living among societies that are largely lactose-tolerant may find lactose intolerance troublesome. Although there are still no methodologies to reinstate lactase production, some individuals have reported their intolerance to vary over time (depending on health status and pregnancy^[38]).

Lactose intolerance is not usually an all-or-nothing condition: the reduction in lactase production—and hence, the amount of lactose that can be tolerated—varies from person to person. Since lactose intolerance poses no further threat to a person's health, managing the condition consists of minimizing the occurrence and severity of symptoms. Berdanier and Hargrove recognise four general principles: avoidance of dietary lactose, substitution to maintain nutrient intake, regulation of calcium intake, and use of enzyme substitute.

Avoiding lactose-containing products

Since each individual's tolerance to lactose varies, according to the US National Institute of Health, "Dietary control of lactose intolerance depends on people learning through trial and error how much lactose they can handle."^[39] Label reading is essential, as commercial terminology varies according to language and region.^[31]

Lactose is present in two large food categories: conventional dairy products, and as a food additive (in dairy and non dairy products).

Dairy products

Lactose is a water-soluble molecule. Therefore fat percentage and the curdling process have an impact on which foods may be tolerated. After the curdling process, lactose is found in the water portion (along with whey and casein) but is not found in the fat portion. Dairy products which are "fat reduced" or "fat free" generally have a slightly higher lactose percentage. Additionally, low fat dairy foods also often have various dairy derivatives such as milk solids added to them to enhance sweetness, increasing the lactose content.

Milk. Human milk has the highest lactose percentage at around 9%. Unprocessed cow milk has 4.7% lactose. Unprocessed milk from other bovids contains similar lactose percentages (goat milk 4.1%,^[40] buffalo 4.86%,^[41] yak 4.93%,^[42] sheep milk 4.6%)

Butter. The butter-making process separates the majority of milk's water components from the fat components. Lactose, being a water soluble molecule, will still be present in small quantities in the butter unless it is also fermented to produce cultured butter.

Yogurt and kefir. People can be more tolerant of traditionally made yogurt than milk, because it contains lactase enzyme produced by the bacterial cultures used to make the yogurt. However, many commercial brands contain milk solids, increasing the lactose content.

Cheeses. Traditionally made hard cheese (such as Swiss cheese) and soft ripened cheeses may create less reaction than the equivalent amount of milk because of the processes involved. Fermentation and higher fat content contribute to lesser amounts of lactose. Traditionally made Swiss or Cheddar might contain 10% of the lactose found in whole milk. In addition, the traditional aging methods of cheese (over 2 years) reduces their lactose content to practically nothing.^[43] Commercial cheese brands, however, are generally manufactured by modern processes that do not have the same lactose reducing properties, and as no regulations mandate what qualifies as an "aged" cheese, this description does not provide any indication of whether the process used significantly reduced lactose.

Sour cream and **ice cream**, like yogurt, if made the traditional way, may be tolerable, but most modern brands add milk solids.^[44] Consult labels.^[45]

Examples of lactose levels in foods. As scientific consensus has not been reached concerning lactose percentage analysis methods^[46] (non-hydrated form or the mono-hydrated form), and considering that dairy content varies greatly according to labeling practices, geography and manufacturing processes, lactose numbers may not be very reliable. The following are examples of lactose levels in foods which commonly set off symptoms.^[39] These quantities are to be treated as guidelines only.

Lactose In non-dairy Products

Lactose (also present when labels state lactoserum, whey, milk solids, modified milk ingredients, etc.) is a commercial food additive used for its texture, flavour and adhesive qualities, and is found in foods such as processed meats^[47] (sausages/hot dogs, sliced meats, pâtés), gravy stock powder, margarines^[48] sliced breads,^{[49][50]} breakfast cereals, potato chips,^[51] processed foods, medications, pre-prepared meals, meal replacement (powders and bars), and protein supplements (powders and bars).

Kosher products labeled *pareve* are free of milk. However, if a "D" (for "Dairy") is present next to the circled "K", "U", or other hechsher, the food likely contains milk solids (although it may also simply indicate that the product was produced on equipment shared with other products containing milk derivatives).

Alternative Products

Plant based milks and derivatives are inherently lactose free: soy milk, rice milk, almond milk, hazelnut milk, oat milk, hemp milk, peanut milk, horchata.

The dairy industry has created low-lactose or lactose-free products to replace regular dairy. Lactose-free milk can be produced by passing milk over lactase enzyme bound to an inert carrier; once the molecule is cleaved, there are no lactose ill-effects. A form is available with reduced amounts of lactose (typically 30% of normal), and alternatively with nearly 0%.

Finland, where approximately 17% of the Finnish-speaking population has hypolactasia,^[52] has had "HYLA" (acronym for *hydrolysed lactose*) products available for many years. These low-lactose level cow's milk products, ranging from ice cream to cheese, use a Valio patented chromatographic separation method to remove lactose. The ultra-pasteurization process, combined with aseptic packaging, ensures a long shelf-life.

Recently, the range of low-lactose products available in Finland has been augmented with milk and other dairy products (such as ice cream, butter, and buttermilk) that contain no lactose at all. The remaining about 20% of lactose in HYLA products is taken care of enzymatically. These typically cost slightly more than equivalent products containing lactose. Valio also markets these products in Sweden and in Estonia.

In the UK, where an estimated 15% of the population are affected by lactose intolerance, Lactofree produces milk, cheese, and yogurt products which contain only 0.03% lactose.

Alternatively, a bacterium such as *L. acidophilus* may be added, which affects the lactose in milk the same way it affects the lactose in yogurt (see above).

Lucerne, Safeway's dairy brand, produces 100% lactose-free milk. The milk's only noticeable difference from regular milk is a slightly sweeter taste due to the adding of the lactase enzyme. It does not however contain more sugar, and is nutritionally identical to regular milk.

Lactase Supplementation

When lactose avoidance is not possible, or on occasions when a person chooses to consume such items, then enzymatic lactase supplements may be used.^{[53][54]}

Lactase enzymes similar to those produced in the small intestines of humans are produced industrially by fungi of the genus *Aspergillus*. The enzyme, β -galactosidase, is available in tablet form in a variety of doses, in many countries without a prescription. It functions well only in high-acid environments, such as that found in the human gut due to the addition of gastric juices from the stomach. Unfortunately, too much acid can denature it,^[55] and it therefore should not be taken on an empty stomach. Also, the enzyme is ineffective if it does not reach the small intestine by the time the problematic food does. Lactose-sensitive individuals can experiment with both timing and dosage to fit their particular needs.

While essentially the same process as normal intestinal lactose digestion, direct treatment of milk employs a different variety of industrially produced lactase. This enzyme, produced by yeast from the genus *Kluyveromyces*, takes much longer to act, must be thoroughly mixed throughout the product, and is destroyed by even mildly acidic environments. Its main use is in producing the lactose-free or lactose-reduced dairy products sold in supermarkets.

Enzymatic lactase supplementation may have an advantage over avoiding dairy products, in that alternative provision does not need to be made to provide sufficient calcium intake, especially in children.

Nutritional concerns

Primary lactose intolerance

Populations where primary lactose intolerance is the norm have demonstrated similar health levels to westerners (outside of malnutrition issues; see the History of genetic prevalencesubsection above), or better health.

Secondary lactose intolerance

Dairy products are relatively good and accessible sources of calcium and potassium and many countries mandate that milk be fortified with vitamin A and vitamin D. Consequently, in dairy-consuming societies, dairy is often a main source of these nutrients and, for lacto-vegetarians, a main source of vitamin B₁₂. Individuals who reduce or eliminate consumption of dairy must obtain these nutrients elsewhere. However, Asian populations for whom dairy is not part of their food culture do not present decreased health and sometimes present above average health, as in Japan.

Plant based milk substitutes are not naturally rich in calcium, potassium, or vitamins A or D (and, like most non-animal products, contain no vitamin B₁₂). However, prominent brands are often voluntarily fortified with many of these nutrients.

An increasing number of calcium-fortified breakfast foods — such as orange juice, bread, and dry cereal — have been appearing on supermarket shelves. Many fruits and vegetables are rich in potassium and vitamin A; animal products like meat and eggs are rich in vitamin B₁₂, and the human body itself produces some vitamin D from exposure to direct sunlight. Finally, a dietitian or physician may recommend a vitamin or mineral supplement to make up for any remaining nutritional shortfall.

Lactose-reduced dairy products have the same nutritional content as their full-lactose counterparts, but their taste and appearance may differ slightly.

Most infants with gastroenteritis due to rotavirus do not develop lactose intolerance,^[59] so these infants do not benefit from being put on a lactose-free diet unless symptoms of lactose intolerance are severe and persistent.

Congenital lactase deficiency

Congenital lactase deficiency, or CLD, is an autosomal recessive disorder which prevents the expression of lactase.^[60] Before the 20th century, infants with this disease rarely survived. As substitute and lactose-free infant formulas later became available,

nursing infants affected with CLD could now have their normal nutritional needs met. Beyond infancy, individuals with CLD usually have the same nutritional concerns as those affected by secondary lactose intolerance.

Glycogen storage disease

Glycogen storage disease (GSD, also glycogenosis and dextrinosis) is the result of defects in the processing of glycogen synthesis or breakdown within muscles, liver, and other cell types.^[1] GSD has two classes of cause: genetic and acquired. Genetic GSD is caused by any inborn error of metabolism (genetically defective enzymes) involved in these processes. In livestock, acquired GSD is caused by intoxication with the alkaloid castanospermine.^[2]

Overall, according to a study in British Columbia, approximately 2.3 children per 100 000 births (1 in 43,000) have some form of glycogen storage disease.^[3] In the United States, they are estimated to occur in 1 per 20,000-25,000 births.^[4] A Dutch study estimated it to be 1 in 40,000.^[5]

Types

There are eleven distinct diseases that are commonly considered to be glycogen storage diseases (some previously thought to be distinct have been reclassified). (Although glycogen synthase deficiency does not result in storage of extra glycogen in the liver, it is often classified with the GSDs as type 0 because it is another defect of glycogen storage and can cause similar problems.)

- GSD type VIII: In the past, considered a distinct condition.^[6] Now classified with VI.^[7] Has been described as X-linked recessive.^[8]
- GSD type X: In the past, considered a distinct condition.^{[9][10]} Now classified with VI.^[7]