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Review

Fructose, galactose and glucose – In health and disease

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SUMMARY

Background and aims: Monosaccharides are important components of the diet, where the sweetness of these common sugars draw animals to eat the tissue within which they are located - especially fruits. Higher (larger) saccharides, within which they are constituents, are ubiquitous throughout nature too - and include disaccharides, oligosaccharides and polysaccharides. These may be converted (hydrolysed) to monosaccharides by the plant tissue enzymes during ripening and stimulate consumption by a predator (whereupon seeds within the fruit are dispersed). Predators may have relevant enzymes in their digestive tract to effect conversion of the larger carbohydrates to its monosaccharides - which are then absorbed from the gut and like free monosaccharides in fruit/vegetables, provide an energy source. Starch is an important source of glucose. This review (on monosaccharides) is part one of a series of three which aim to link the role of carbohydrates in food through processing to health and disease related issues. The emphasis here is to understand the role of the three key monosaccharides from the diet - fructose, galactose and glucose - with perspectives in health and disease.

Methods: The review was based on a review of relevant databases for material (*e.g.* Pubmed, Science Direct, Web of Science, Wiley online library etc.).

Results: Data pertaining to the nutritional role of key dietary monosaccharides were evaluated together with their utilisation and role in health and disease. Disease states and their management in the context of monosaccharide consumption were considered.

Conclusions: The body is designed to utilise carbohydrates - where a physiological balance of ingestion, storage and utilisation is critical. In disease states, the balance is lost and a number of carbohydrate based metabolic disorders are established within the medical community. Overall, this review considers digestive and metabolic issues associated with free monosaccharides commonly consumed in the human diet. Further reviews will focus on common di-, oligo and polysaccharides relevant to digestive energy and overall health.

1. Structure and properties

Cyclic (Howarth) representations of the monosaccharides glucose, fructose and galactose are shown in Fig. 1. Glucose is an aldo-hexose (aldose-hexose). Hence there is an aldehyde group on the end carbon atom of the monosaccharide - by convention 'carbon 1'. The other carbon atoms within the monosaccharide contain hydroxyl groups. The D-unlike the L-form of glucose is found extensively in nature. It exists as a free sugar and within larger molecules (Table 1). Galactose is an isomer of glucose, specifically a carbon 4 epimer (Fig. 1 and Table 1). Fructose is a keto-hexose (ketose-hexose) isomer of glucose, with a ketone group on carbon 2 (Fig. 1 and Table 1). Both galactose and fructose occur in the D-form in nature like glucose and also occur as constituent units within larger molecules.

The physical properties of fructose, galactose and glucose are presented in Table 2. Fructose, which has a ketone rather than aldehyde group as in galactose and glucose, is less similar to the aldehydes than they are to each other in terms of melting points and solubility. The relatively high solubility of fructose means that solutions with greater osmotic pressures can be created than are possible for galactose or glucose. Fructose is also much sweeter than the other two sugars - more so than the disaccharide sucrose

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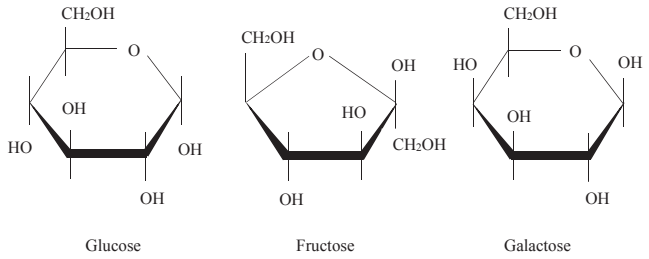


Fig. 1. Structure of glucose, fructose and galactose.

too. Invert sugar (inverted or hydrolysed sucrose with *invertase/sucrase/β-fructosidase* for example) contains equal proportions of fructose and glucose - which is found naturally in honey.

'Sucrose is the major transport form for photoassimilated carbon and is both a source of carbon skeletons and energy for plant organs unable to perform photosynthesis (sink organs)' as discussed by Lemoine [1]. For plants to utilise the carbon within the sucrose, it is transformed into glucose and fructose in relevant tissues by (i) *sucrose synthase* (a glycosyl transferase) which converts sucrose in the presence of uridine diphosphate (UDP) into UDP-glucose and fructose or (ii) *invertase* which generates glucose and fructose [2]. Galactose is less common than fructose and glucose in most fruits [3] with persimmons (Sharon fruit) the most galactose rich (~35 mg/100 g). Sugar contents of food products (including fruit and vegetables) can be found in the most recent edition of McCance and Widdowson's The Composition of Foods [4].

2. Absorption and transport in human

The human body can metabolise fructose, galactose and glucose and generate energy as a consequence. In infants, the capacity to absorb sugars is less developed than for adults and sugar consumption (*e.g.* syrups and honey) can lead to osmotic diarrhoea [5,6]. Babies will consume sugar in the form of lactose essentially from milk (with some free glucose, galactose and oligosaccharides in the milk) but will not be exposed to monosaccharides as extensively as adults are.

Sugars as monosaccharides are absorbed from the diet in the small intestine of man. The small intestine contains specific monosaccharide transporters (from the gut lumen, primarily within the jejunum, to the blood vessels pervading the gut) as discussed elsewhere [7–12]. Wright et al. [9] describe this process succinctly: 'The bulk of sugar absorption is mediated by specific sugar transport proteins in the apical (brush border) and basolateral membranes of the enterocytes lining the small intestine.' In fact, monosaccharide absorption from the small intestine is *via* both energy-coupled as well as non-energy coupled mechanisms. These transporters are specific small intestine located protein families (isoforms) of sodium-driven sugar co-transporters (SGLTs) and concentration gradient dependent glucose transporters (GLUTs). The basic features of these transporters (major transporters) in the small intestine, for the three monosaccharides, are as follows:

Fructose: Facilitated diffusion *via* GLUT2 and GLUT5.

Galactose: Co-transport sodium ions with galactose *via* SGLT1. Facilitated diffusion *via* GLUT2.

Glucose: Co-transport sodium ions with glucose *via* SGLT1. Facilitated diffusion *via* GLUT2.

In health, the gut absorption and utilisation of the monosaccharides functions very efficiently within the body [13–15]. However, in certain disease states disruption can occur to the absorption/utilisation of the sugars (discussed below). Where congenital metabolic pathway disruption (enzyme deficiency) occurs, the outcome can often be fatal.

3. Effect on health

Contemporary nutritional perspectives tend to consider the consumption of sugars *extracted* from plants or produced by

Table 1
Examples of D-fructose, D-galactose and D-glucose containing sources in nature.

	Monosaccharide	Disaccharide	Oligosaccharide (3–10 monosaccharide units)	Polysaccharide (>10 monosaccharide units)
Fructose	Fruits, vegetables and honey	Sucrose	Fructans in fruits and vegetables Raffinose Stachyose Verbascose	Fructans in fruits and vegetables
Galactose	Fruits, vegetables and dairy products	Lactose	Cell recognition (*e.g.* ABO) carbohydrates Floridoside Iso-floridoside Raffinose Stachyose Verbascose Dairy products	Agar Carrageenan Galactans Galactomannans Hemicellulose
Glucose	Fruits, vegetables, honey and dairy products	Maltose Isomaltose Lactose	Raffinose Stachyose Verbascose Dextrans and dextrins	Cellulose Glucomannans Glycogen Hemicellulose Laminaran Starch

Table 2
Physical properties of D-fructose, D-galactose and D-glucose.

	Melting point (°C)	Molecular weight (g/mol)	Density (g/cm^3)	Solubility (g/L @ 25 °C)	Sweetness (relative to sucrose = 1)	Energy (kcal/g)
Fructose	103	180.2	1.7	4000	1.73	3.75
Galactose	167	180.2	1.5	680	0.32	3.75
Glucose	146	180.2	1.5	909	0.74	3.75

polysaccharide hydrolysis (*e.g.* glucose from starch) negatively - but not so much so when the sugar resides in its original state as produced by nature (*e.g.* within fruits and vegetables). In some ways this is illogical as the sugar is the same molecular structure whether extracted or not. When sugars are extracted or most often generated from starch hydrolysis commercially and purified, other components of the plant are lost from the diet (*e.g.* fibre, minerals, vitamins, protein, antioxidants *etc*.). The energy source is thus more concentrated and potentially more readily absorbed from the gut.

As a contrast between (i) eating fruit or (ii) confectionery (which are both relatively sugar rich), these ingested sugar-containing dietary components provide an interesting nutritional comparison (w/w) in terms of:

- Water - fruit is typically ~90% water, confectionery is typically <5% (~3%).
- Sugar content - fruit is typically 10–16% (dates are ~65%), confectionery such as hard or pulled candy can be ~98%.
- Other nutrients - fruit will contain some protein, lipid, vitamins, minerals, acids, flavours, anti-oxidants *etc*. which will be absent from confectionery unless added as part of the recipe (which might include animal materials like gelatine and dairy products too). There is no cholesterol in plant materials.
- Processing induced modifications - although fruit undergoes enzymic browning reactions (as a defence mechanism), fruits are not in their native form, subject to heat and hence do not contain non-enzymic (Maillard) browning residues, *e.g.* acrylamide *etc*. Unusually, however, prune juice tends to contain a relatively high acrylamide content (caused by the drying process post-harvest) as discussed elsewhere [14–16]. Acrylamide does occur in other processed plant tissues too. Chocolate, for example, does contain acrylamide due to heat processing of the cocoa beans [14,15]. In heat processed foods and drinks more generally, N-glycosides (Schiff bases) formed by the reaction of reducing sugars with asparagine create significant levels of acrylamide.

Sugars provide energy/calories, which represent an absolute nutritional requirement for the body. Negativity associated with sugar consumption emanating from the medical and non-medical communities tends to focus on (i) teeth related issues, (ii) obesity, (iii) diabetes and (iv) deficiency of other nutrients in sugar rich foods and drinks. Because of the relative low cost of sugars and the sensory attractiveness, whole product categories such as confectionary and drinks have built up in demand [17].

3.1. Diabetes

Diabetes mellitus represents a metabolic disorder where blood glucose concentrations are elevated (hyperglycaemia) due to impaired insulin (i) secretion, (ii) physiological action or (iii) both as discussed elsewhere [18,19].

Fructose produces a lower insulinaemic response than glucose (due at least in part to slow absorption) and was once, consequently, recommended as a desirable sweetener for people with diabetes [20]. However, there is an association between diets high in any sugars and the overall risk of the disease state. Fructose (over 100 g/d) specifically for example can reduce insulin sensitivity [21]. Although glucose, galactose and fructose are metabolised differently in the body they all serve as substrates for glycogen synthesis [22]. From the gut, these three monosaccharides enter the portal vein and are carried to the liver - which removes fructose from the circulation where much is stored consequently as glycogen [22]. Galactose is also removed from the circulation by the liver while glucose enters the peripheral circulation where it stimulates insulin secretion [22]. Due to hepatic metabolism, the blood glucose and insulin responses to fructose or galactose are attenuated in comparison to glucose ingestion [23]. The relative nutritional significance of dietary monosaccharides has been discussed in some details elsewhere [21].

3.2. Energy

Bodily functions require energy - although the intake of dietary energy from fat should not exceed 35% with 50% from plant carbohydrates [24]. Saturated fat and refined carbohydrate consumption have been linked to risks associated with cardiovascular disease, diabetes and obesity [24], as discussed above and below.

Unlike glucose, both fructose and galactose are almost completely metabolised upon first pass (from the gut) through the liver where they are converted into glucose, lactate, glycogen and lipids [23,25]. The energy cost of converting fructose into glucose and other substrates may account for the greater postprandial thermogenesis for fructose versus glucose [23]. According to Clemens et al. [20], fructose and glucose provide the same amount of energy upon metabolism although 'sugar', when consumed under iso-caloric conditions, is no more likely to contribute to weight gain than any other source of dietary energy. Fructose has the greatest impact on energy expenditure [26] although like glucose is linked to increased liver and muscle fat deposition due (in the most part) to calorie over consumption [21].

3.3. Glycaemic index

According to [14,15,27], the glycaemic index of a food can be defined as follows:

'The glycaemic index is defined as a measure of the blood-glucose-raising ability of the available carbohydrate in foods. It is expressed as a percentage of the incremental area under the glycaemic response curve elicited by a portion of food containing 50 g available carbohydrate in comparison with the area under the glycaemic response curve elicited by 50 g glucose in the same subject. The glycaemic index is a system of classifying carbohydrate containing foods according to glycaemic response. The principle is that the slower the rate of carbohydrate absorption, the lower the rise of blood glucose level and the lower the glycaemic index value. A glycaemic index value of $\geq$70 is considered high, a glycaemic index value 56–69 inclusive is medium and a glycaemic index $\leq$55 is low, where glucose = 100.'

Glucose has the greatest glycaemic index of the simple sugars whilst fructose has the lowest [20]. Fructose has long been known to have a minimal effect on blood glucose - reflecting its slow rate of absorption [20]. The glycaemic index of glucose is 100 and fructose 23 with sucrose 65 - an average of the constituent monosaccharides [28]. Lactose (galactose and glucose) has a glycaemic index much lower than sucrose (46) reflecting the low glycaemic index of the galactose component. In babies and adults, intravenous galactose injections raise blood glucose a fraction of that of intravenous glucose while ingestion of glucose and galactose (50 g) in adults causes very little impact on blood glucose [28].

3.4. Laxative

Laxatives promote the transit of the bowel contents but work differently [29]. They are defined as (i) lubricants, (ii) stool softeners, (iii) fibre supplements, (iv) bulk forming, (v) stimulants or (vi) osmotic [29].

Sugars can act as osmotic laxatives [30] - which can be dangerous if babies in particular are fed sugar solutions/honey.

Ladas et al. [5] have suggested that the laxative effect of honey in adults is due primarily to incomplete fructose absorption.

3.5. Teeth

Sugars are associated with tooth decay and dental caries [31–33]. Although the World Health Organisation has recommended that sugars should not exceed 10% of dietary energy, halving this limit is justified to reduce caries [34]. It is difficult to define which sugars are most cariogenic although galactose is often considered to be less cariogenic than fructose or glucose [31] perhaps because it tends to be present in milk which is less acidic than fruit juices.

4. Related diseases/disorders of monosaccharides metabolism

4.1. Fructose

In Table 3, disorders of fructose absorption and metabolism (inborn errors of metabolism) are presented. Fructose (unlike glucose) in humans is metabolised almost completely in the liver as discussed previously (Fig. 2). Also, as discussed previously it can be converted to liver glycogen and used for triglyceride synthesis. Since fructose is not a component of baby milk, it is relatively easy to manage the dietary exclusion of fructose in babies (and to a large extent children and adults). As a naturally occurring sugar, it is ubiquitous in fruit and vegetables [4] and especially high in grapes [35]. Often there are no obvious signs that fructose absorption or metabolism is an issue until the infant gets older (if indeed exhibited then).

Exclusion is the key therapeutic approach to treat fructose related metabolic disorders. This is (as discussed above) a relatively easy nutrient/energy source to avoid - especially at concentrations that are likely to cause health specific problems. However, sucrose (the common fructose-glucose disaccharide and most common source of dietary fructose) is more ubiquitous and is potentially more difficult to avoid in the diet. Sorbitol (common in fruit and vegetables [35]) is converted to fructose in the liver by *sorbitol dehydrogenase* and is hence also a source of fructose.

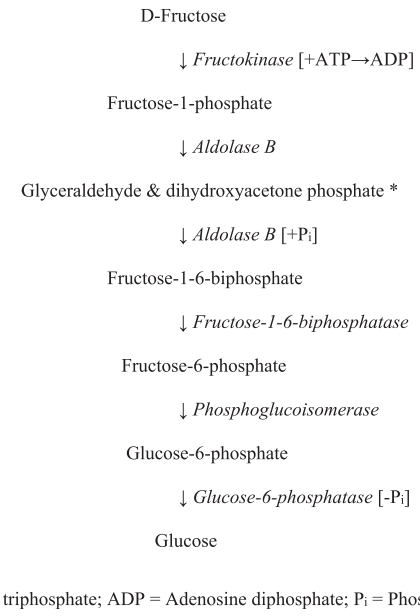


Fig. 2. Fructose metabolism.
*Dihydroxyacetone phosphate alone (not glyceraldehyde) is a substrate for the *aldolase B*.

The incidences of the inborn errors of fructose metabolism are (see for example Steinmann et al. [36]):

Fructosuria: *Fructokinase* deficiency, 1/130,000 births.

Hereditary fructose intolerance: *Fructose-1-6-biphosphate aldolase* deficiency, 1/18,000 to 1/30,000 births (depending on population).

Table 3
Disease states associated with fructose absorption from the small intestine and associated metabolism in the body.

Disease state	Cause and consequence on health	Reference
Absorption		
Fructose malabsorption	May be greater than 50% of the population depending on how it is tested - 25 or 50 g test does of fructose. Possible that the fructose loading in some modern foods outstrips the capacity of the transporters to transport the fructose. Possible specific defects in GLUT2 and GLUT5. Leads to flatulence and diarrhoea.	Latulippe and Skoog [63]; Ebert and Witt [64]
Sorbitol	Converted to fructose in the liver by *sorbitol dehydrogenase* and is hence a source of fructose.	Steinmann et al. [36]; Jovanovic-Malinovska et al. [35]; Tran [65]
Metabolism		
Fructosuria	Due to *fructokinase* (*ketohexokinase*) deficiency. Elevated fructose in the urine. No significant impact on health.	Steinmann et al. [36]; Tran [65]
Hereditary fructose intolerance	Due to aldolase B (*fructose-1-6-biphosphate aldolase*) deficiency. Causes elevation of fructose-1-phosphate. This leads to blocked gluconeogenesis and glycogenolysis causing hypoglycaemia. Adenosine *tri* phosphate (ATP) is depleted too. Protein metabolism *etc*. is then affected. Leads to nausea, vomiting, agitation, pallor, sweating, trembling, lethargy, apathy, convulsions and coma if fructose (plus sucrose and sorbitol) is not excluded from the diet.	
Fructose-1-6- bisphosphatase deficiency	Due to the gluconeogenic enzyme *fructose-1-6-bisphosphatase* deficiency. Impairs the flow of glucose precursors *via* the metabolic pathway. Can lead to hypoglycaemia with the build-up of lactate, alanine and glycerol. Multiple heart related and broader physiological effects leading to coma and death potentially. Fructose, sucrose and sorbitol should be avoided. Treatment is usually *via* glucose administration. Slowly digested starch is a very useful therapeutic approach.	

Fructose-1-6-biphosphatase deficiency: 1/350,000 births (some populations).

Hence the conditions are relatively rare. None the less, their impact for relevant members of the population affected can be very significant - especially if not diagnosed early in life.

4.2. Galactose

Galactose is a far greater problem to exclude from the diet than is fructose. This is especially true for babies and infants due to the galactose presence (as lactose mainly) in milk (below). Non-dairy sources of milk can be used to resolve this problem - usually soya based - although the non-dairy milks do not exclude galactose derived from the plant source completely. Adult foods based on milk such as milk as a liquid, yoghurts and cheese are relatively easy to avoid in the diet. However, dairy products/ingredients are incorporated into many foods and are very often less visible.

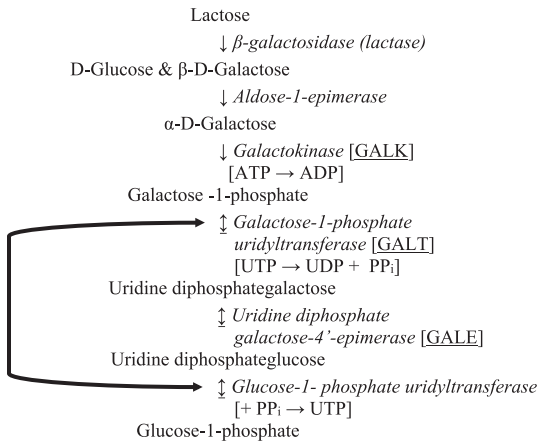
The main metabolic pathway for galactose utilisation in the body is the Leloir pathway (Fig. 3). This pathway converts D-galactose to uridine diphosphate glucose (UDP-glucose). Disorders associated with galactose metabolism are shown in Table 4.

With respect to incidences of galactosaemia in the human population (see for example Pyhtila et al. [37]):

- Type 1: *Galactose-1-phosphate uridyltransferase* (GALT) deficiency - defects in both paired gene copies, where about 1/30,000–1/60,000 births carry this 'classic galactosaemia' disease.
- Duarte variant Type 1: *Galactose-1-phosphate uridyltransferase* deficiency - one of the gene pairs is defective whilst another one is only partially defective, affects about 1/4000 births.
- Type 2: *Galactokinase* (GALK) deficiency (less severe than Type 1, about 1/100,000–1/130,000 births).
- Type 3: *Uridyldiphosphate galactose-4′-epimerase* (GALE) deficiency (two major forms, 1/7000 to 1/70,000 which tends to be race dependent).

As discussed above, galactose is ubiquitous in fruit and vegetables where it is especially high in persimmons (at around 35 mg per 100 g [3]) and red peppers (approximately 40 mg per 100 g [38]). However, these are mg/100 g concentrations unlike fructose and glucose which are often xg/100 g.

The lactose contents of commonly consumed animal sources of liquid milk compared to human milk have been reported by Pereira



ATP = Adenosine tri phosphate; ADP = Adenosine di phosphate; UTP = Uridine tri phosphate; UDP = Uridine di phosphate; PP_i = Pyrophosphate

Fig. 3. Galactose metabolism (Leloir Pathway).

[39] to be as follows: Goat 4.1%, Sheep 4.9%, Cow 4.7% and Human 6.9%. It is apparent that the human milk is especially lactose rich compared to these other mammals (that supply milk into the human food chain commonly). The galactose represents 50% of the lactose mass and hence milk, regardless of origin, provides a considerable load for babies (and adults) that cannot metabolise galactose. This galactose source must be excluded from the diet [37,40–46] for those metabolically compromised people. However, it should be noted that galactose is an impotent nutrient - *e.g.* for brain development [44] and hence exclusion is not without some loss of health benefits in other areas.

According to Welling et al. [43], the clinical guidelines for galactosaemia therapy are:

'Clinicians should immediately commence a galactose restricted diet (*e.g.*, soy-based, casein hydrolysate or elemental formula) if classical galactosaemia is suspected in an infant, without waiting for confirmation of the diagnosis.'

and

'We recommend allowing any amount and type of fruits, vegetables, legumes, unfermented soy-based products, mature cheeses (with galactose content <25 mg/100 g), and the food additives sodium or calcium caseinate, in the diet for classical galactosaemia. Although higher in galactose, all fermented soy-based products can be allowed in the small quantities that are typically used in the diet.'

Babies with galactosaemia are fed soya-based milks or elemental diets that have proven to be effective alternatives to mammalian milk [41,47]. In terms of strategies to remove galactose from milk as an alternative to using non-mammalian milk, it is not a simple matter. However, possible approaches to achieve this (alone or in combination) are:

- Chemical conversion: *To convert lactose or galactose within milk to a molecular form which is not handled like galactose by the body using chemical modification.*

  Advantages: Low cost; many possible modifications to sugar structures; relatively easy to do; rapid.

  Disadvantages: Generation of new chemical entities; potential toxicity; unspecified reactions with other components of the milk; destabilisation of the milk structure overall; possible loss of nutritional benefits due to modification of non-sugar molecules; probable reaction with prebiotic oligosaccharides; batch processing; regulatory barriers.
- Enzymatic conversion: *To convert lactose or galactose in milk to a molecular form which is not handled like galactose by the body using enzymes. For example*:

  Galactose oxidase

  D-Galactose + O_2 → D-galacto-hexodialdose + H_2O_2

  Galactose dehydrogenase

  D-Galactose + NAD^+ → D-galactonic acid + NADH

  *Arabinose (Galactose) Isomerase*w

  D-Galactose ↔ Tagatose

  Advantages: Relative selectivity; enzymes can be produced commercially at relatively low cost; enzymes themselves are usually non-toxic; can be inactivated by processing; could be undertaken in the home to treat human milk samples.

  Disadvantages (general which apply to different enzymes more or less): Nutritional properties/toxicity of products; fermentation of products in the colon; end product reactivity; impact on pH; need for co-enzymes or co-factors; equilibrium position of the enzyme (substrate-product ratio at equilibrium); reversibility.
- Genetic engineering: *To make dairy milk products lactose/galactose free.*

  Advantages: Could be used theoretically for mammalian milk.

Table 4
Disease states associated with galactose monosaccharide absorption from the small intestine and metabolism in the body.

Disease state	Cause and consequence on health	Reference
Absorption		
Glucose galactose malabsorption	SGLT1 gene mutation. Leads to severe diarrhoea which is fatal within weeks unless lactose (glucose and galactose) is removed from the diet. Fructose absorption is unaffected.	Wright [66]
Metabolism		
Galactokinase (GALK) deficiency	Galactose and galactitol build up (*aldose reductase* converts the galactose to the galactitol) throughout the body and cause cataracts to develop relatively rapidly.	Lai et al. [67] Berry et al. [40] Coelho et al. [44]
Galactose 1 phosphate uridyltransferase deficiency (GALT, biochemical, classic (severe) and clinical variant galactosaemia)	Apparent symptomatically in babies due to galactose in milk response. Leads to many symptoms including lack of feeding, vomiting, jaundice, lethargic behaviour, hypotonia (decreased muscle tone), liver disease, kidney disease, brain damage and cataracts. Multiple effects throughout the body with the development if untreated of sepsis and death.	Coelho et al. [45] Demirbas et al. [46]
Uridine diphosphate galactose-4′- epimerase (GALE, generalised (severe form), intermediate and peripheral) deficiency	Multiple symptoms including lack of feeding, vomiting, jaundice, lethargic behaviour, hypotonia, liver disease, *etc.* - similarly to GALT for the generalised form (the two other forms are relatively asymptomatic).	
Fanconi-Bickel Syndrome	Due to GLUT2 deficiency. Glycogen accumulates in the liver and kidneys. Have rickets, failure to thrive, kidney dysfunction, swelling of the liver and spleen and hypoglycaemia.	

Disadvantages: Requisite genetic engineering steps are complex; genetically modified organisms (GMOs); animal welfare issues.

- Microbiological conversion: *To convert lactose to another entity such as lactic acid.*
  Advantages: Relatively low cost; efficient; accessible.
  Disadvantages: Production of microbiological mass; non-specificity in terms of substrate utilisation in most/many cases; metabolites such as lactic acid affect pH, milk stability and taste.
- Synthetic and semi-synthetic milk: *Replacement for dairy.*
  Advantages: Lactose, galactose and fructose free options.
  Disadvantages: Key nutrients may need to be added; potential issues with other components in the milk - *e.g.* phytoestrogens in soya, protease inhibitors *etc.* (although the latter are essentially destroyed by heat); allergens; does not have the sensory profile of milk.
- Physical processing: *To remove the sugars in milk using filtration processes.*
  Advantages: Ultra-filtration and reverse osmosis.
  Disadvantages: Cost; selectivity.

Exclusion of human milk and dairy products is by far simpler, effective and cost-effective way to manage galactose exclusion from the diet at this time.

4.3. Glucose

Glucose is the universal energy transport molecule within the body. It is key to the maintenance of life and is consequently, impacted on by many control mechanisms which regulate its absorption, storage and utilisation. Glucose is stored in a compact form in the body (especially the liver) as glycogen in discrete granules. There are physical and molecular similarities between glycogen and starch granules, where starch occurs as an energy storage reserve in plants.

Since glucose is essential for life, problems associated with glucose utilisation (especially congenital metabolic problems) are often very difficult to manage. Glycolysis and glycogenesis are presented in Fig. 4a.

4.3.1. Haemolytic anaemia (erythrocyte congenital enzyme deficiencies only)

The enzyme deficiencies associated with haemolytic anaemia have been described in detail by others [48–51] where the conditions are due predominantly to three key enzyme deficiencies.

1. *Glucose-6-phosphate dehydrogenase* deficiency: Affects about 400 million people in the world - not very often in Caucasians but common in African males. Five classes of the disease are reported - with different degrees of severity and deficiency. With enzyme deficiency, the reduced form of nicotine amide

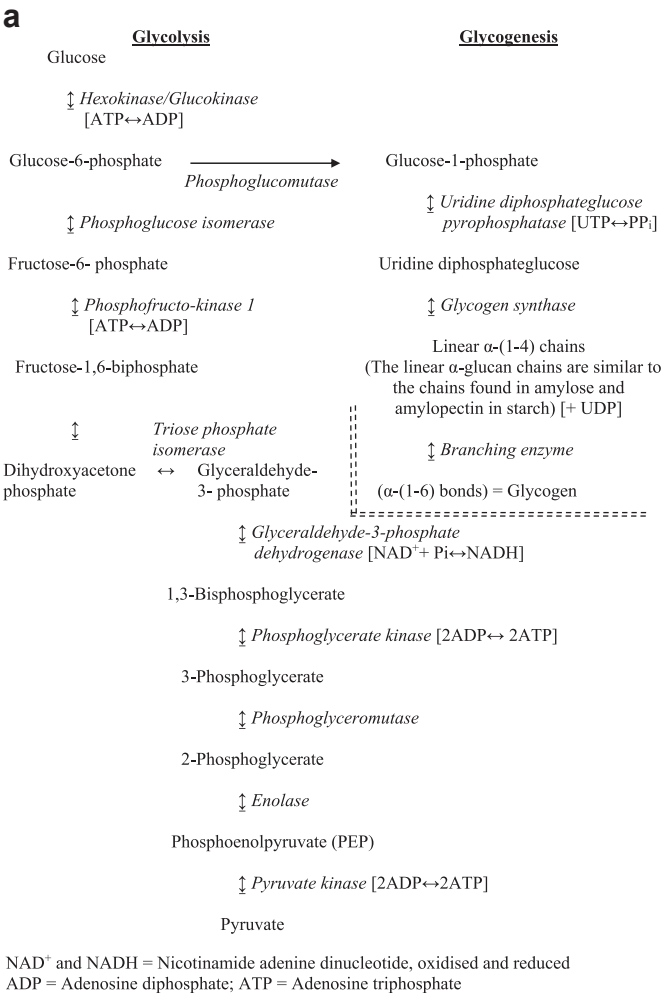
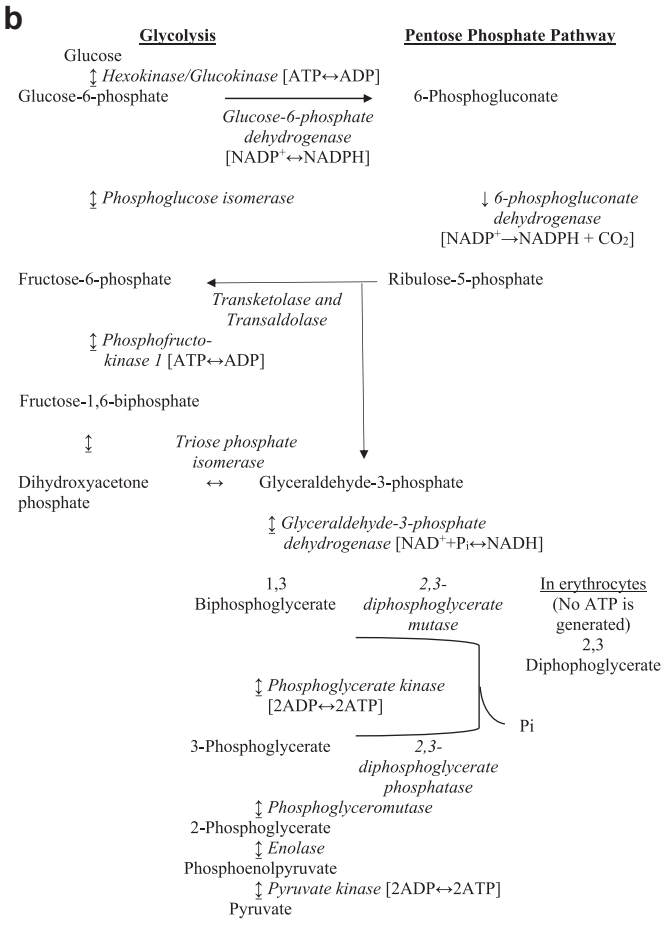


Fig. 4a. Glucose metabolism – Glycolysis and Glycogenesis.



NAD^+ and NADH = Nicotinamide adenine dinucleotide, oxidised and reduced
$NADP^+$ and NADPH = Nicotinamide adenine dinucleotide phosphate, oxidised and reduced
ADP = Adenosine diphosphate; ATP = Adenosine triphosphate

Fig. 4b. Glucose metabolism – Glycolysis and Pentose Phosphate Pathway.

adenine dinucleotide phosphate (NADPH) cannot be generated from the pentose phosphate pathway (Fig. 4b). This means that in the erythrocytes the cells themselves and the haemoglobin in particular are not protected against oxidative stress. Jaundice, haemolytic anaemia and intravascular haemolysis can develop.

2. *Hexokinase* deficiency: Very rare - presumably as deficiencies (Fig. 4a and b) can be lethal even before birth. The key initial step for the utilisation of glucose to glucose-6-phosphate in the Glycolytic Pathway is compromised. About 20 cases of the disease have been reported where severe jaundice, anaemia, fatigue and lethargy are present. People living with the disorder may require regular blood transfusions.
3. *Pyruvate kinase* deficiency: Probably 1/20,000 of people originating in Europe. Symptoms range from fatigue, shortness of breath, asymptomatic to transfusion-dependent haemolytic anaemia, jaundice and splenomegaly. Enzyme deficiency (Fig. 4a and b) leads to decreased levels of erythrocyte adenosine triphosphate (ATP), disturbing many cellular processes creating energy failure and dehydration. Intermediates of metabolism such as 2,3-diphosphoglycerate accumulate - which enhances tissue oxygenation and in part compensates for any anaemia that develops.

4.3.2. Pyruvate dehydrogenase deficiency

The prevalence of this condition is uncertain but probably ~1/1,000,000 people. There is an accumulation of lactic acid in the body (as pyruvate is not metabolised through the tricarboxylic acid cycle) which can cause nausea, vomiting, plus breathing and heartbeat problems. There are usually neurological problems too. The pyruvate dehydrogenase enzyme converts pyruvate in the presence of coenzyme A to acetyl coenzyme A.

Lactate	↔Lactate dehydrogenase NAD^+ ↔ NADH	Pyruvate	Co Enzyme A → Pyruvate dehydrogenase NAD^+ → NADH	Acetyl Co Enzyme A + CO_2

Patel et al. [52] have reviewed this enzyme (complex) deficiency in detail. Other authors [53] have also reviewed this enzyme deficiency together with other disorders associated with pyruvate metabolism and the tricarboxylic acid cycle.

4.3.3. Pyruvate carboxylase deficiency

$$\text{Pyruvate} + HCO_3^- + \text{ATP} \rightarrow \text{oxaloacetate} + \text{ADP} + \text{Pi}$$

This biochemical reaction replenishes oxaloacetate withdrawn from the Krebs cycle for different metabolic pathways. It controls metabolic flux through gluconeogenesis, lipogenesis and insulin secretion [54]. About 1/250,000 live birth experience this condition. Enzyme deficiency (there are three types- A, B and C) can cause lactate build up in the body. Normally, excess pyruvate enters gluconeogenesis *via* conversion into oxaloacetate. With this enzyme deficiency, however, excess pyruvate is converted into lactate. Due to its role in gluconeogenesis and blood sugar maintenance, the deficiency can cause hypoglycaemia. Type A (infantile form, often fatal as infants) presents as developmental delay, intellectual disability, mixed acid-base disturbance, lactic acidosis/ketoacidosis, abdominal pain, vomiting, tiredness and muscle weakness. Type B (severe neonatal form, usually fatal with a few months of birth) presents as lactic acidosis, ketoacidosis and hyper-ammonaemia. Liver failure, hypotonia, intellectual disability, abnormal eye movements, irregular signs and reflexes, seizures and coma are common. Type C is less severe than types A or B with mildly delayed development where lactic acidosis is mild and occasional.

4.3.4. Phosphoenolpyruvate carboxykinase deficiency

$$\text{Oxaloacetate} + \text{GTP} \leftrightarrow \text{Phosphoenolpyruvate} + \text{GDP} + CO_2$$

Oxaloacetate in the presence of guanosine triphosphate (GTP) is converted into phosphoenolpyruvate and guanosine diphosphate (GDP) with the loss of carbon dioxide. This reaction supports gluconeogenesis. There are two forms of the enzyme deficiency which are focused and located in the cytosol and mitochondria. Symptoms of this rare disorder include lactic acidaemia, hypotonia, hepatomegaly, growth disorder and hypoglycaemia. The course of this disorder can be very rapid. The condition is very rare - probably ~10 cases have been reported in the literature. For more details see Yang et al. [55].

Table 5
Glycogen storage diseases.

Code for specific disorder and incidence	Defect enzyme	Tissue	Conversion	Deficiency symptoms
0 Liver [<30 known] 0 Muscle [<10 known]	*Glycogen synthase*	Liver Muscle	UDP-Glucose + $Glycogen_n$ → $Glycogen_{n+1}$ + UDP	Hypoglycaemia
Ia (Von Gierke) [~80,000]	*Glucose-6-phosphatase α-subunit*	Liver Kidney	Glucose-6-phosphate → Glucose + Pi	Hepatomegaly Hyperlipidaemia Hypoglycaemia Hypotrophic muscles Glycogen accumulation Lactataemia Protruded abdomen Renomagaly Stunted growth
Ib [~20,000]	*Glucose-6-phosphate translocase*	Endoplasmic reticulum sited.		Hepatomegaly Hyperlipidaemia
Possibly also: Ic	*Phosphate-translocase deficiency*	Liver Kidney Leucocytes		Hypoglycaemia Hypotrophic muscles Glycogen accumulation Infections
Id	*Glucose transporter*	Small intestine Pancreas Gallbladder		Lactataemia Neutropenia Protruded abdomen Renomagaly Stunted growth
II (Pompe) [~1/40,000]	*Lysosomal α-glucosidase (acid maltase) deficiency*	Lysosomal General Muscle Heart Glycogen accumulates in the tissues	α-(1−4) $glucan_n$ → α-(1−4) $glucan_{n-1}$ + Glucose	Infant (usually fatal), juvenile and adult. Enlarged heart (infants) Hypotonia Hyporeflexia (especially infants) Large tongue (infants) Motor dysfunction Respiratory dysfunction
IIb (Danon disease or pseudo-Pompe)	*Lysosomal associated membrane protein [glycoprotein] 2 deficiency*	Lysosomal Heart Muscle Glycogen accumulates in the tissues		Cardiac muscle Skeletal muscle Mental issues
Also Lafora disease	*Uncertain* 	Lafora bodies in neural tissues, muscle, liver, heart, skin and eyes	Glycogen deposition and utilisation	Seizures Myoclonus Dementia Death by 25 years old
III (Cori or Forbes disease)	*Glycogen debranching enzyme(s)*	Liver Muscle Heart Leukocytes	The human glycogen debranching enzyme has two catalytic domains which can function independently of each other providing: (i) transferase activity - which transfers three of four glucose residues from a glycogen branch to other chains. This reveals single glucose units linked to the modified molecule through α-(1−6) bonds and (ii) glucosidase activity - which hydrolyses α-(1−6) bonds liberating glucose from the modified glycogen molecules.	IIIa Hepatic symptoms Hepatomegaly Hypoglycaemia Hyperlipidaemia Myopathic symptoms Cardio-myopathy Growth impediment
Includes type IIIa [~1/85,000] and IIIb [~1/15,000] which are symptomatic variants and IIIc (glucosidase activity deficiency) and IIId (transferase activity deficiency)				IIIb Liver disease only

(*continued on next page*)

Table 5 (*continued*)

Code for specific disorder and incidence	Defect enzyme	Tissue	Conversion	Deficiency symptoms
IV (Andersen) [~1/600,000 to 1/800,000]	*Glycogen branching enzyme*	Liver	Catalyses the transfer of α-(1−4) glucosyl units from the exterior of a developing linear glycogen chain to an α-(1−6) location on the same or a local chain	Liver disease early in life (classic form, death usually by age 5, some hypoglycaemia) whilst the non-progressive form is less invasive Hepatomegaly Cirrhosis Some neuromuscular forms (four presentations)
V (McArdle) [~1/100,000]	*Myophosphorylase* (Muscle form of glycogen phosphorylase)	Muscle	$Glycogen_n$ α-(1−4) chain + P_i → $Glycogen_{n-1}$ + Glucose-1-phosphate	Myalgia Weakness Exercise intolerance
VI (Hers) [~11 cases reported probably more unreported]	*Liver phosphorylase*	Liver	$Glycogen_n$ α-(1−4) chain + Pi → Glycogenn-1 + Glucose-1-phosphate	Hepatomegaly Growth deficiency Hypoglycaemia
VII (Tarui) [>100 cases]	*Phospho-fructokinase*	Muscle Erythrocytes	Fructose-6-phosphate + ATP ↔ Fructose-1,6 bisphosphate + ADP	Myopathy Haemolytic anaemia Weakness (muscle) throughout the body
No attributed Roman numeric [~30 families]	*Phospho-glycerate kinase*	Muscle Erythrocytes	1,3- Biphosphoglycerate + ADP ↔ 3-phosphoglycerate + ATP	Exercise intolerance Haemolytic anaemia Cramps Convulsions Central nervous system − seizures and stroke
IX [~1/100,000]	*Phosphorylase kinase*	Liver Muscle	Phosphorylates *glycogen phosphorylase b* to more active *phosphorylase a*	Hepatomegaly Growth problems Myopathy Hypoglycaemia
X [~15 cases]	*Phosphoglycerate mutase*	Muscle	3-phosphoglycerate ↔ 2-phosphoglycerate	Exercise intolerance Cramp
XI [~1/million]	*Lactate dehydrogenase*	Muscle	Pyruvate + NADH ↔ Lactate + NAD	Exercise intolerance Cramp Skin lesions Dystocia
XII [~1/20,000]	*Aldolase A*	Muscle	Fructose 1,6-bisphosphate ↔ Dihydroxyacetone phosphate + glyceraldehyde-3-phosphate	Exercise intolerance Cramp
XIII [~<1 million, 1 case recorded]	*β-Enolase*	Muscle	Phosphoglycerate ↔ Phosphoenol pyruvate + H_20	Exercise intolerance Cramp

Adapted from Smit et al. [68]; Mayatepek et al. [69]; Bhattacharya [58,70]; Kishnani and Chen [71]; Weinstein et al. [72].

4.3.5. Glycogen storage disease/disorders

The condition describes a number of enzyme deficiencies related to glycogen metabolism (synthesis/deposition and hydrolysis) and glycolysis (Table 5). The specific enzyme deficiencies can be prevalent in different tissues and most especially muscle and the liver. Some of the forms are very rare (which may be associated with fatality during development) as reported in Table 5. Patients with glycogen storage disease are treated commonly with oral nature maize starch or physically modified maize starch - to allow for the slow and controlled release of glucose [56–60]. This prevents hypoglycaemia and related disorders - especially nocturnal hypoglycaemia which is especially life threatening.

5. Monosaccharides interplay in disease

Recent research [61] has indicated that the small intestine (of mice) has the capacity to metabolise dietary fructose into glucose and organic acids. Ketohexokinase presence in the small intestine is key to this conversion. This mechanism 'shields' the liver from the potential toxicity of the fructose. Excess fructose can overload this system, however, whereupon the fructose goes to the liver. This biochemistry provides one example of how sugar utilisation and metabolism is regulated with care by the body-using a range of mechanisms.

Another example of monosaccharide interplay in disease is the role of the polyol pathway in diabetic retinopathy as diseased by Lorenzi [62]. In this pathway, glucose is converted into sorbitol and then fructose. According to the author, it is an attractive mechanism by which to explain in part at least cellular toxicity associated with diabetic hypoglycaemia.

6. Conclusions

The body metabolises the three common dietary monosaccharides fructose, galactose and glucose differently although they all provide calories in health. In view of the critical nature of these molecules - and most especially glucose - for energy transport around the body there are severe implications if there are congenital problems with absorption or metabolism. Many examples of genetically transferred metabolic enzyme defects occur in man - where some are more deleterious to health than others.

Author contribution

Xin Qi - prepared and approved the manuscript.
Richard Tester - prepared and approved the manuscript.

Conflict of interest

Authors declare no conflicts of interest.

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