Chronic diarrhea in children: Part I. physiology, pathophysiology, etiology

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Abstract

Chronic diarrhea is an important cause of morbidity and mortality in children. Although the pattern of the problem is well established in Western countries, limited data are available from Saudi Arabia. The purpose of this review is to provide an updated overview of the physiology of digestion, pathophysiology and etiology of diarrhea with particular emphasis on patterns prevalent in Saudi Arabia.

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Definition

The term diarrhea is derived from the Greek language (dia = through, rhein = to flow), denoting increased fluidity and frequency of fecal discharges. Chronicity is defined by more than two weeks duration in infants and four weeks for older children. Other authors recommend three weeks duration as a definition of chronicity for all age groups.

The term intractable diarrhea of infancy is defined as diarrhea of more than two weeks duration, occurring in the first three months of life, and resistant to standard treatment resulting in a severe life threatening condition. However, advances in nutritional support, and parenteral nutrition in particular, have improved survival and resulted in the replacement of the word intractable by the terms prolonged, protracted, or persistent diarrhea of infancy. In addition, the syndrome of intractable diarrhea of infancy is caused by many disorders that are heterogeneous and not specific for infants less than three months, making such designation rather controversial.
Nevertheless, the syndrome of protracted diarrhea in infancy may be primary (idiopathic) also called non-specific enterocolitis which is not to be confused with the term chronic nonspecific diarrhea (irritable bowel syndrome), a clearly more benign condition. On the other hand the syndrome may be secondary to any disease causing chronic diarrhea.

Chronic diarrhea in any age group, however, should be regarded and approached as a symptom and not a disease entity. The term "parenteral diarrhea" implies that the cause of the symptoms is outside the gastrointestinal tract. Chronic otitis media and urinary tract infections especially in infants are some of the conditions that may present with chronic diarrhea.

**Physiology of Digestion and Absorption**

The normal alimentary tract receives, digests and absorbs large amounts of nutrients, water, and electrolytes. In adults and older children, about two liters of liquid are ingested and six to seven liters of salivary, gastric, biliary, and intestinal fluids are secreted daily. Since only 100 to 200 ml of water is present in stool each day, more than 95% of fluids is efficiently absorbed, mostly by the small intestine (at a rate of 200 to 400 ml/hour).

The colon, however, is capable of increasing this process so that the rate of water absorption by both small and large intestine may reach 500 ml/hour. Fluid load (over feeding, secretory diarrhea) is excreted in the stool resulting in diarrhea.

Digestion of nutrients is essential for their absorption. Therefore, understanding the process of digestion is necessary for the clinical approach of patients with chronic diarrhea associated with malabsorption.

**Carbohydrates**

The type of carbohydrates in infants diet (human breast milk and/or cow's milk formula) is lactose. Other formulas derived from cow's milk may contain variable amounts of dextrins, whereas table sugar and soy bean based formulas contain sucrose. Lactose and sucrose are disaccharides normally hydrolysed by brush border disaccharidases. The resulting monosaccharides (glucose, galactose, fructose..) are absorbed mostly by transport systems into the capillaries. In addition to oligo-and disaccharides, the diet of older infants and children contains starch, which is a polymer of glucose molecules, requiring hydrolysis mostly by the pancreatic alpha-amylase into maltose (1-4 bonds) and dextrins (1-4, 1-6 bonds). [Table - 1] and [Figure - 1] summarize the digestion and maldigestion/malabsorption of disaccharides respectively.

**Proteins**

The gastric digestion of proteins starts with the conversion of pepsinogens I and II (secreted by the principal cells) to pepsin. This conversion is catalysed by hydrochloric acid (secreted by the parietal cells). Pepsin acts on polypeptides breaking
bonds with terminal NH2 resulting in the production of aminoacid radicals.

The pancreatic digestion of proteins is the most important step. Pancreatic enzymes, secreted in the form of inactive zymogens, are activated "in cascade". The first step is the activation of trypsinogen to trypsin by the action of enterokinase (enteropeptidase, synthetised by the enterocytes). Other pancreatic zymogens (Chymotrypsinogen, proelastase, procarboxypeptidases A and B) are activated by the trypsin. The end products of pancreatic enzymes proteolysis consists of peptides and free aminoacids. Peptides are further hydrolysed by the intestinal peptidases to form aminoacids, which are absorbed directly into the blood.

In human disease, gastric atrophy has little effect on nitrogen excretion. Intestinal enterokinase deficiency (Primary or Secondary) may have profound effects on protein digestion similar to those of exocrine pancreatic insufficiency that occurs in cystic fibrosis or other chronic pancreatic diseases.

**Lipids**

The average diet contains about 30% fat, of which 98% are triglycerides. Fat constitute a major source of energy, essential fatty acids, and fat soluble vitamins. Dietary long chain triglycerides (> 12C) require hydrolysis by intra luminal lipase (Lingual, gastric, pancreatic) to form free fatty acids, mono-and diglycerides. These products are mixed with bile acids to form micelles, a process of solubilization and emulsification necessary for fat absorption by the enterocytes. Inside the enterocytes, mono- and diglyceride are resterified to form triglyceride which are mixed with phospholipids and cholesterol to form chylomicrons. This process (Chylomicron formation) requires the presence of Apoprotein. Chylomicrons are absorbed into lymphatics and then in the blood. Medium chain triglycerides, relatively more water soluble than long chains triglycerides, are directly absorbed into the blood after hydrolysis by lingual and gastric lipases.

The major steps of digestion and absorption of fat are illustrated in [Figure - 2]. Malabsorption of fat, causing steatorrhea, may occur from level 1 through 5. Disorders of step 1, are represented by pancreatic exocrine insufficiency (Cystic fibrosis, chronic pancreatitis .. etc). Step 2 disorders include bile acid deficiency (congenital or acquired). Step 3, may be affected by mucosal diseases (Celiac disease, severe chronic gastroenteritis ... etc). Step 4, the formation of chylomicrons, is disturbed in apoprotein deficiency (A-beta lipo proteinemia). Finally step 5, exci of fat into the lymphatics, may not be possible in cases of acquired or congenital lymphatic obstruction (Intestinal lymphangiectasia).

**Water and Electrolytes**

Intestinal water absorption is a passive process occurring in response to osmotic and hydrostatic pressure gradients across the intestine. Osmoses may be generated by active transport of electrolyte or non-electrolytes (Carbohydrates, aminoacids). Water and electrolytes cross the intestinal mucosa either passively by passing through the paracellular pathway (tight junction) or actively through the apical and basolateral pathways. Sodium is absorbed by at least three mechanisms. The sodium pump (Na-K- ATP ase), located in the baso lateral membrane of the cell, drives sodium out of
the cell to the interstitial space (three sodium ions are exchanged for two potassium ions entering the cell). This process creates a low intracellular sodium concentration which drives more sodium into the cell. Similarly, the exchange of three sodium ions for two potassium ions results in intracellular electronegativity which drives more sodium from the intestinal lumen into the cell. The other mechanism of sodium absorption is neutral and occurs when sodium is in the form of sodium chloride or with sodium exchanged for hydrogen ions and parallel exchange of chloride in the cell and bicarbonate in the intestinal lumen. This mechanism is lacking in congenital chloridorrhea. The last mechanism of sodium absorption occurs through transport proteins. In this Co-transport mechanism, sodium is linked to D-glucose, D-galactose, amino acids, dipeptides or tripeptides.

Sodium is efficiently absorbed by the colon primarily by an electrogenic mechanism through selective sodium pores. This process is regulated by aldosterone which stimulates sodium absorption and potassium excretion.

Chloride (Cl−), is the major ion that is actively secreted. This process is coupled with the Na-KATPase pump, which accumulate Cl− in the cell. Cyclic AMP or increase in intracellular calcium stimulates Cl− secretion in the intestinal lumen. Similarly, certain enterotoxins, bile acids, fatty acids, laxatives and hormones are capable of stimulating Cl− secretion. Potassium transport is primarily passive but active absorption and secretion have been demonstrated. Bicarbonate is usually absorbed in the jejunum and secreted by the duodenum, ileum, and colon.

Vitamins

Fat soluble vitamins (A, D, E, K) are absorbed with fat. Therefore, disorders of fat digestion and absorption may be associated with fat soluble vitamin deficiency. Folic acid is not synthetised by the body. Therefore, normal absorption is necessary. Folate compounds are absorbed most probably passively in the duodenum and jejunum, hydrolysed by brush border specific peptidases. The products of hydrolysis are then metabolised by lysosomes. Vitamin B12 is attached to a dietary protein from which it is freed by gastric pepsin. Free B12 binds to two molecules of intrinsic factor to form a complex that protects vitamin B12 from digestion by bacteria during passage through the small bowel. In the ileum, the complex binds to receptor sites, the intrinsic factor remains bound to the receptor after facilitating B12 entry in the enterocytes.

Calcium

Calcium is absorbed primarily in the duodenum but also throughout the small intestine by an active process. Vitamin D increases the absorption of calcium. The presence of large amount of fatty acids in the intestine markedly reduces calcium absorption by forming insoluble calcium soaps.

Iron

It is absorbed mostly in the duodenum and jejunum. At the acid pH of the stomach, ferric and ferrous iron are rendered soluble by chelation with ascorbic acid, carbohydrates, or amino acids. The process of Iron transport is highly regulated by
mucosal cell transferrin, which closely reflects iron body stores. Absorption of iron is carrier mediated as transferrin binds iron in the intestinal lumen and transports it across the brush border.

**Magnesium and Zinc**

Magnesium is absorbed in the jejunum and ileum by a separate transport mechanism. As is the case of calcium, magnesium forms complexes with phosphates, citrates, sulfates, and proteins. Muscle cramps and tetany may reflect hypomagnesemia in patients with malabsorption. Zinc is absorbed also by a transport system in the small bowel. A zinc-binding ligand transports zinc across the enterocytes to the serosal surface. Absorbed zinc, bound to albumin, is transported in the circulation. \[7\]

Deficiency in the amount or function of the zinc-binding ligand causes atrodermatitis enteropathica.

**Pathophysiology of Diarrhea**

There are at least four processes that may result in diarrhea. Osmotic, secretory, dysmotility, and exudative mechanism occur singly or more commonly in combination.

**Osmotic Diarrhea**

The presence of poorly absorbed solutes in the intestinal lumen causes water and electrolytes shift from the plasma to the intestine. These solutes may be magnesium (laxatives, antacids), phosphates or citrates. Carbohydrate accumulation, however, is the commonest cause of osmotic diarrhea in children. Carbohydrates such as lactose, sucrose, isomaltose, glucose, and galactose may be present in the intestine in large quantity as a result of congenital or acquired enzyme or transport defects. The disappearance of diarrhea upon fasting or elimination of the involved solute is characteristic of osmotic diarrhea. An osmotic gap is present in the stool (stool osmolality - stool (Na + K) x 2 = > 50 mOsm).

**Secretory Diarrhea**

This type of diarrhea is caused by active secretion of electrolytes, with concomitants water drag. The stool may be isotonic to plasma and the cause may be in or outside the intestine. Excess secretion may be generalised or localised. Increased intestinal secretion may be mediated by hormones (Vasoactive intestinal polypeptide - VIP), bacterial toxins (E coli, cholera), and drugs. These substances, as well as bile acids, fatty acids, and prostaglandins, act by stimulation of adenylcyclase resulting in elevated levels of cyclic AMP in the intestinal mucosa, causing increased secretion of crypt cells and diarrhea. Secretory diarrhea is usually of large volume, persists during fasting, and has an isotonic electrolyte composition.

A rare, but interesting cause of secretory diarrhea was described by Verner and Morrison in 1958. These authors described two patients with profuse watery diarrhea, hypokalemia, and nonbeta islet cell adenoma of the pancreas. This pancreatic cholera
syndrome is also known as Verner-Morrison syndrome, WDHA syndrome (watery diarrhea, hypokalemia, achlorhydria). A similar syndrome with excessive VIP production has been reported in patients with nonpancreatic tumors (ganglieneuroma, neurofibroma, ganglioneuroblastoma). On the other hand, hormones such as prostaglandins, calcitonin, pancreatic polypeptide, gastric polypeptide, substance P, secretin, glucagon, neurotensin, and enkephalins have been isolated from these patients but the significance of this finding is uncertain.

**Intestinal Motility Disorders**

Abnormal motor activity of the small and large bowel may cause diarrhea. Increased activity (rapid transit) results in diarrhea because of reduced exposure time of the chyme to the absorptive surface. Reduced activity (delayed transit) favors bacterial overgrowth and diarrhea. Patients with pyloroplasty, carcinoid syndrome, and irritable bowel syndrome usually have rapid transit dysmotility, and patients with intestinal pseudo obstruction syndrome, scleroderma and strictures usually have delayed or slow transit dysmotility. However, in some patients, other factors play a role in mediating diarrhea. For example, in the carcinoid syndrome, where diarrhea is believed to be caused by hypermotility, other factors such as hypersecretion induced by serotonin may be operative.

**Exudative Disorders**

Inflammation and ulceration of the bowel may cause losses of blood or blood products in the stools. Inflammatory bowel diseases and allergic (eosinophilic) gastroenteropathy are the major examples, but the mechanism of diarrhea is usually more complex in patients with protein-losing gastroenteropathies.

**Etiology of Chronic Diarrhea**

The differential diagnosis of chronic diarrhea is extensive. If one excludes chronic infections outside the intestine (Urinary tract infection, otitis media) and the irritable bowel syndrome (toddler's diarrhea chronic non-specific diarrhea), which is a common and benign condition, gastrointestinal disorders causing chronic diarrhea are associated with malabsorption and failure to thrive [Table - 2]. It is worth noting that the pattern of chronic diarrhea in developing countries is quite different from descriptions in the west. In Saudi Arabia, for example, although many types of diarrhea have been reported, [8][9][10][11] frequency of certain causes is quite interesting. In two studies from Riyadh over five years [12] and Alkhobar over seven years (unpublished data), the post enteritis syndrome was the commonest cause of chronic diarrhea in children. These findings are consistent, with patterns from other developing countries, but different from those in the west, where cystic fibrosis and celiac disease are the commonest causes of chronic diarrhea. The distribution of other diagnoses is presented in [Table - 3], to emphasize the existence, in our area of diseases such as cystic fibrosis, celiac disease and other inherited disorders. In view of the fact that these data come from two referral university hospitals, no incidence or prevalence conclusion could be made. Nevertheless, since patients are referred from almost all parts of the country, these data are fairly representative of the general
pattern of causes of pediatric chronic diarrhea in Saudi Arabia.

References


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Figure 1. Pathophysiology of disorders of digestion and absorption of carbohydrates.

CARBOHYDRATE MALDIGESTION/ MALABSORPTION
(Pancreatic insufficiency, intestinal mucosal injury, disaccharidases deficiency, monosaccharides malabsorption)

Accumulation of carbohydrate in intestinal lumen

- Osmotic diarrhea
  - Watery/Bulky

- Positive Reducing Substances (>0.5%)

- Fermentation by colonic bacteria

↑ Production H₂O/CO₂

- Increased H₂/CO₂ in breath

- Accumulation of organic acids

- Low stool pH (<5.5)
Figure 2. Digestion and absorption of fat: LCTG and MCTG = Long and Medium Chain Triglycerides. Phl = phospholipids. Chole = Cholesterol. FFA = Free fatty acids. 1-5: levels of fat maldigestion and malabsorption.