Chapter 3

Malabsorption in Giardiasis

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Abstract

Giardia intestinalis is a flagellated parasite and is regarded as the most common cause of protozoan-associated diarrhoea worldwide. The organisms can be found in 80% of raw water supplies from lakes, streams and ponds and as many as 15% filtered water samples. *Giardia* intestinalis can be found worldwide including both temperate and tropical regions and can cause asymptomatic colonisation or acute or chronic diarrhoea illness. The symptoms vary from vague abdominal discomfort or severe abdominal pain, diarrhoea and weight loss. It is believed that these symptoms are a result of giardiasis-associated malabsorption syndrome, although the pathophysiology underlying intestinal disturbances remains incompletely understood. Interestingly, intestinal malabsorption is a result of epithelial dysfunction that shares similarities with those observed in other enteric disorders such as bacteria enteritis, Crohn's disease and celiac disease. Numerous other mechanisms of intestinal malabsorption have been postulated such as immunologic reactions, altered gut motility and fluid hypersecretion via adenylate cyclase activity. In this chapter, we will go through each mechanism of malabsorption associated with giardiasis and the consequences of this to the patients.

Keywords: intestinal malabsorption, giardiasis, epithelia, injury, growth retardation, chronic diarrhoea

1. Introduction

Giardia infection is a common intestinal infection worldwide [1, 2]. The worldwide incidence was estimated at 2.8×10^8 infection per year [3]. In the industrialised world, overall prevalence rates are 2–5%. In developing world, infection starts as early as in the infant year and is the major cause of childhood diarrhoea. Prevalence rates of 15–20% in children under 10 years are common [2, 4]. In Thailand, the prevalence of giardiasis ranges from 1.25 to 37.7% [5]. The incidence varies depending on age, living conditions, personal hygiene and environment sanitation. Despite the high prevalence of the infection, physicians often neglect to add giardiasis

as one of the differential diagnosis in patients present with chronic diarrhoea. This is due to the lack of expertise in many of our public hospitals.

Patients who are infected with *Giardia* intestinalis have symptoms ranging from asymptomatic to severe chronic diarrhoea. The pathogenesis of malabsorption syndrome–related chronic diarrhoea is not fully understood; however, many theories such as epithelial dysfunction, immunologic reactions, altered gut motility and fluid hypersecretion have been postulated.

Giardiasis can lead to grown retardation in children and severe malnutrition in adult patients. Patients can also present with protein energy malnutrition, vitamin A deficiency and iron deficiency anaemia. A cross sectional study in Malaysia including 281 children aged 2–15 years showed that 56.5% of the infected children have significantly underweight, while 61.3% have growth retardations [6].

2. Pathophysiology of malabsorption

2.1. Electrolyte transport abnormality

Giardiasis causes malabsorption of glucose, sodium and water and reduces disaccharidase activity due to loss of absorptive surface area [6]. Recent report also suggests that this parasite alters chloride secretory response in human colonic cells in vitro, as well as in murine models [7]. Moreover, study by Troeger et al. proved that in addition to malabsorption, chronic giardiasis may cause chloride hypersecretion in human [8]. Therefore, combinations of malabsorption and electrolyte transport abnormality are responsible for fluid accumulation in the intestinal lumen. The reasons behind these abnormalities remain poorly understood; however, multiple studies and reports suggest that parasite products may break the epithelial barrier. This activated T lymphocyte causing brush border to retract, which in turn leads to the disaccharidase deficiencies and epithelial malabsorption responsible for watery diarrhoea (**Figure 1**) [9, 10]. In fact, epithelial cells dysfunctions and disaccharide deficiencies are medicated by CD8+ T cells, whereas CD4+ T cells contribute to parasite clearance [11, 12]. Moreover, findings that athymic mice infected with *Giardia* do not exhibit microvillus injury and dysfunction despite the presence of live parasites refute the hypothesis that intestinal malfunction solely results from trophozoite attachment or parasite virulence factors [8, 11, 12].

2.2. Role of parasite virulence factors

Stain-dependent activation of enterocyte apoptosis and epithelial dysfunction induced by *Giardia* may occur in the absence of any other cell types, and small intestinal permeability returns to baseline once *Giardia* is cleared [13]. Virulence factors in *Giardia* and its effect are currently under intensive research. Giardia is thought to express a certain surface glycoprotein able to induce fluid accumulation in the intestine. Moreover, this organism is known to produce variety of potentially toxic substances such as proteinase and lectins that maybe responsible for direct epithelia injury [14, 15]. Much genomic studies are still needed to identify *Giardia's* enterotoxin and ability of *Giardia*'s proteinase to activate host receptors; however, multiple studies have reported that proteinase along with *Giardia* enterotoxins are an important virulence

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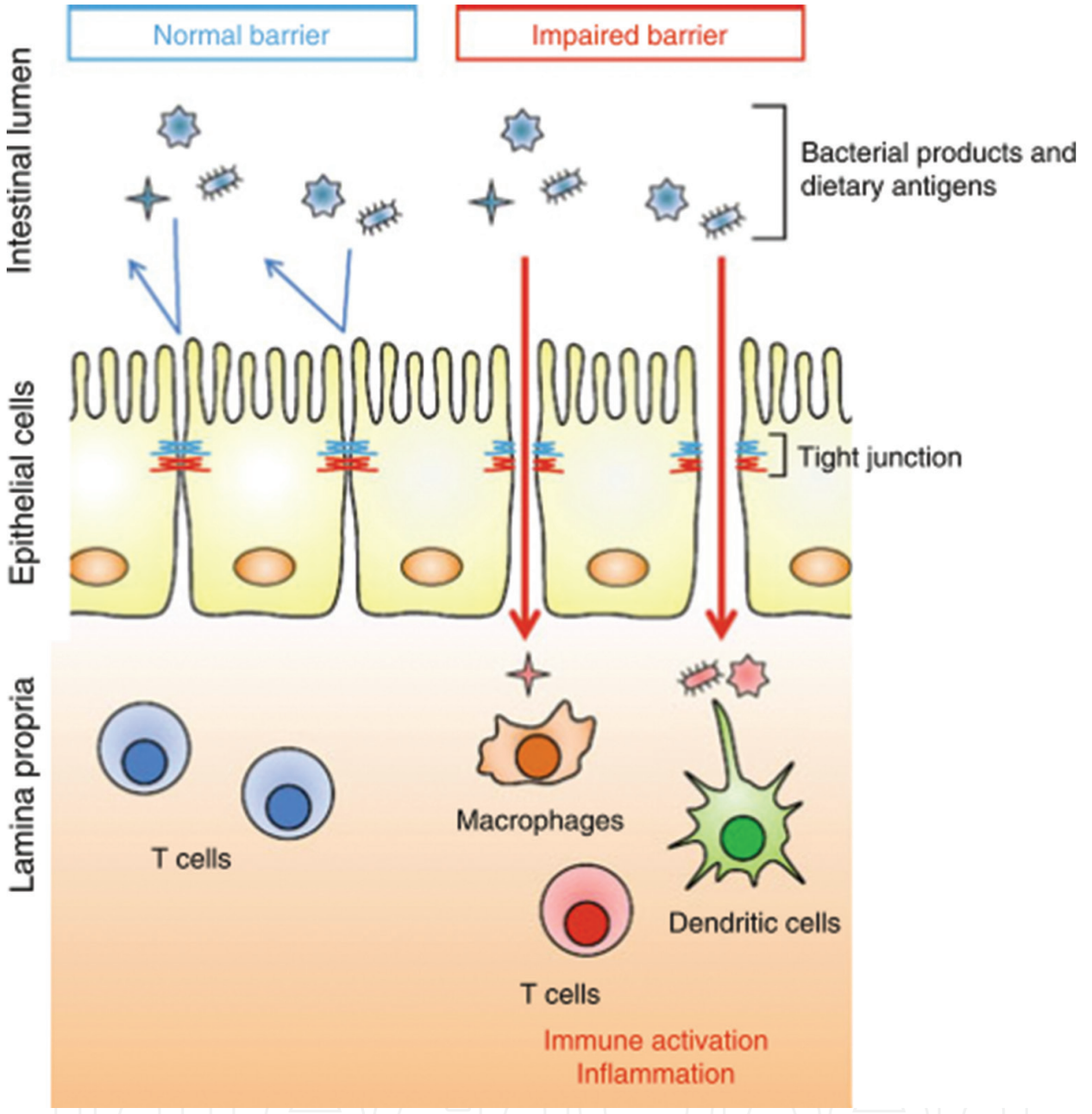

Figure 1. Impaired epithelial tight junctions as a result from attachment of *Giardia*'s trophozoite causing activations of immune response by influx of bacterial products leading to activation of T cells causing injury to brush boarder leading to malabsorption and diarrhoea.

factors in many organisms including *Giardia*. Proteinase-activated receptors are member of class G-protein coupled signalling receptors that can modulate enterocyte apoptosis and increase intestinal permeability [16]. **Table 1** shows example of *Giardia* major virulence factor [17].

2.3. Other possible pathophysiology of giardiasis

As in the case with other enteropathogens, induction of apoptosis in enterocytes by *Giardia* is the key components of the pathophysiology of giardiasis [18, 19]. Enterocytes apoptosis in giardiasis

Function	Virulence factor
Attachment	Colonisation and attachment to intestinal endothelium is by the ventral adhesive disc and surface lecithin
Circumvention of the natural factors of the intestinal lumen	Re-localization by flagellar motility allows further colonisation. Protective factors such as variant-specific surface protein (VSP) protect *Giardia* from luminal proteases
Antigenic variation	*Giardia* is cleared from the body by IgA directed clearance. This is protected by VSP
Alteration of host innate defences	Down regulate epithelial production of nitric oxide by releasing arginine deaminase
Anti-inflammatory modifications	Unknown trophozoite products have anti-inflammatory roles
Survival in stomach acid and the external environment	Differentiation into cysts

IgA, immunoglobulin A; VSP, variant-specific surface protein.

Table 1. The major virulence factors of *Giardia* spp. *Giardia* is a complex organism; they produce complex enterotoxin and proteinase causing epithelial cell damage.

is Caspase 3, Caspase 9 dependent [20]. The reasons behind the activations of these proteins, which play crucial roles in apoptosis, still have not been fully understood. However, it is believed that both host and parasite factors modulate the activation of these proteins, although the exact mechanism is still not known. Interestingly, Giardia's trophozoites may halt enterocytes cell-cycle progression by consumption of arginine and upregulation of cell-cycle inhibitory genes [21].

Other possible key pathophysiology of giardiasis is *Giardia*-induced epithelial bush boarder microvilli shortening. This leads to symptoms of maldigestion and malabsorption such as diarrhoea. The factor contribute to microvilli shortening is still not fully validated; however, it was postulated that parasite's toxins may play a key role in the development of this abnormality. This is very similar to "protease" which was released in patients with bacterial overgrowth causing villi shortening and malabsorption syndrome [22].

Giardia infections tend to be self-limiting in immune-competent patient. A recent study in Brazilian children suggests that symptoms are less severe during re-infection. This supports the previous hypothesis that, during the primary infection, the immunity develops leading to less severe symptoms [23]. Patients who are immunodeficiency or have common variable immune deficiency such as Bruton's X-linked agammaglobulinema are prone to chronic giardiasis. This finding confirms the importance of immune system in giardiasis [24].

3. Symptoms and sign of chronic infection with giardiasis

Chronic infection is particularly important in children as it may cause malabsorption leading to growth retardation. There are reports of small intestinal villous atrophy especially in

children. It is important at this stage to exclude coeliac sprue on gastrointestinal immunodeficiency syndrome for the correct diagnosis to be made [25].

Other symptoms include:

3.1. Chronic diarrhoea

A small number of people develop acute explosive watery diarrhoea, foul flatus, abdominal cramps and vomiting. These symptoms usually last 3–4 days before subacute symptoms develop. Symptoms of chronic infection including chronic diarrhoea, anorexia and weight loss occur as much as 66% of the infected individuals [1]. Chronic sporadic diarrhoea may continue for months, and post-infected lactase deficiency also presented in 5–40% of cases [1].

Stools of the infected individuals become more mushy, malodourous and greasy. Watery diarrhoea may alternate with soft stools or even constipation. Steatorrhea is a common finding in patients who have malabsorption syndrome.

3.2. Function gastrointestinal disorder

FGID represents a group of disorders characterised by recurring gastrointestinal symptoms. IBS and functional dyspepsia are best describing FGID. There are multiple reports of post-infectious IBS following salmonella, campylobacter infections. These usually follow episodes of acute gastroenteritis. Interestingly, recent reports suggest that individuals who are infected with *Giardia duodenalis* develop post-infectious IBS symptoms without parasitic load [26]. Irritable bowel syndrome (IBS) characterised by abdominal discomfort associated with altered bowel habit with no abnormality in routine diagnostic test. One common theory that has been postulated is that these symptoms develop following episodes of acute gastroenteritis. This explains the persisting symptoms of chronic diarrhoea and abdominal pain despite parasite clearance [27]. The risk of developing IBS increases six-fold after gastrointestinal infection as shown from multiple recent meta-analyses. This is interesting because these risks could remain elevated for at least 2–3 years post-infection. Moreover, it is estimated that 7–31% of patients with gastroenteritis go on to develop post-infectious IBS [27, 28]. Risk factors of developing IBS in this situation include longer duration of symptoms, younger age and female gender. The exact mechanisms of post-infectious IBS is still not known; however, there are reports that suggest that it associates with increase intestinal permeability, increase gut motility and increase number of enterochromaffin cells leading to persistent intestinal inflammation, which is characterised by increase T lymphocytes, mask cells and inflammatory cytokines [29, 30].

3.3. Other gastrointestinal symptoms

Report suggests that symptoms of lactase intolerance such as excessive flatus, abdominal bloating and diarrhoea can occur as a consequence of giardiasis. These patients will not be able to take milk, cheese or any products that contain lactose. It may take up to 1 month following the clearance of the parasite until the body return to normal state.

4. Extraintestinal manifestation of giardiasis and long-term consequences

4.1. Nutritional consequences

In combination with diarrhoea, giardiasis leads to iron deficiency anaemia, micronutrient deficiencies, protein-energy malnutrition, growth and cognitive retardation and malabsorption [31]. Studies from Peru and Brazil found that diarrhoea disease occurring in the first 2 years of life negatively correlates with verbal fluency, cognitive function and may lead to long-term growth failure [32]. Growth failure is assessed by anthropometric indices such as height for weight, height for age and weight for age. Interestingly, the prevalence of giardiasis is higher among children between 6 months and 5 years in developing country as compare to industrialised country [33]. Therefore, it has long been linked optimum health of children, socio-economic status, socio-cultural and environmental factors (**Table 2**).

4.2. Failure to thrive

Failure to thrive (FTT) is the term used when a child present with a rate of weight gain that is significantly below the expected weight from children of the same age, sex and ethnicity [34]. Common causes of FTT are inadequate food intake, inadequate food absorption, or maldigestion of nutrients and excessive loss of nutrient [34]. There is a strong association between *Giardia* infection and malnutrition, wasting and stunting [31–33]. Malabsorption, maldigestion and malnutrition due to giardiasis have been shown to affect anthropomorphic factors as well as calories intake during childhood especially in the second year of life [31]. Researchers now

Post-infectious consequence	Speculated mechanism involved
Ocular pathologies	Speculated involvement of toxic metabolite produced by the parasite.
Arthritis	Increase intestinal permeability leads to increase bacteria in synovial fluid joint.
Allergy	Alteration of antigen uptake due to dysfunction of the intestinal barrier.
Hypokalemic myopathy	Loss of potassium related to diarrhoea, impaired nutrient and electrolyte absorption
Failure to thrive	Inadequate food intake, reduced nutrients absorption, excessive utilisation of energy, steatorrhea, maldigestion, malabsorption
Stunting	Nutritional status, sanitary, socio-economic conditions, loss of intestinal surface area, maldigestion, malabsorption
Impaired cognitive function	Chronic malnutrition and stunting following G. duodenalis
Post infectious irritable bowel syndrome	Microscopic duodenal inflammation. Interaction host-gastrointestinal microbiota. Increased T-cells and Mast-cells
Cancer	Still need further research

Table 2. Extraintestinal and long-term complication of giardiasis.

develop key predictors of FTT and growth disturbance such as severity of diarrhoea diseases and duration of infection episodes [35]. Of note, vitamin deficiencies such as vitamin A, B1, B3, B6 and B12 are common reasons behind grown stunt in children infected with giardiasis.

4.3. Cancer

Multiple reports have described pancreatic cancer with pancreatic giardiasis. However, the relationship of these remains unknown. The coexistence of these two diseases may prompt further research into mechanism of carcinogenesis in giardiasis [36]. Interestingly, *Giardia's* trophozoite is usually found in proximal small intestine, but they can be identified in stomach, distal small bowel, and caecum, and there are reports of pancreatic infection with giardiasis [37].

4.4. Impair cognitive function

Cognitive functions are important especially in the first 2 years of life, as there is rapid brain growth and maturation. Nutrition, infection and other environmental factors have been found to affect neuroplasticity and have long-lasting effect in developing children [38]. One of the most important causes of brain development abnormality is malnutrition. Micronutrients deficiencies (such as iodine) and iron deficiency have been found to cause impairment in cognitive function in children [38]. The complex interaction among malnutrition, diarrheal disease and environmental factors such as low socioeconomic status and education makes it extremely difficult to determine the exact reason for cognitive impairment [39, 40]. However, chronic malnutrition and stunting during infancy secondary to giardiasis have been associated with poor cognitive functions [39–41]. Furthermore, diarrheal disease during early childhood was found to impair visual-motor co-ordination, auditory, short-term memory and cortical cognitive functions [40].

There are studies that associate *Giardia* with poor language cognition and impair psychomotor development [31]. These studies also demonstrate a role for nutrient malabsorption and micronutrient deficiencies such as zinc, iron, or vitamin (A and B12) in human and in animals [40–42]. It was widely known that significantly lower serum ferritin and iron affect psychomotor development, and this has been detected in patients with giardiasis [38]. Similarly, diarrheal disease due to giardiasis was linked to poor cognitive function by causing zinc and iron micronutrient deficiency, as well as defects in anti-oxidant system which can affect neuroplasticity [38]. Zinc supplements were found to decrease the rate of diarrhoea caused by giardiasis [43]. This issue remains complicated, and further investigation is needed to the reversal of cognitive impairment following micronutrient supplement or *giardia* clearance.

4.5. Muscular complications

Hypokalaemia myopathy has long been associated with coeliac disease, radiation enteritis and infections. Several cases of myopathy following hypokalaemia induced by giardiasis have been reported with both immunocompromised and immunocompetent patients [44]. This suggests that *giardia* can trigger muscular manifestations independently to the immune status of the host. During infection, potassium loss is related to number of bout of diarrhoea per day [44]. Hypokalaemia following bouts of diarrhoea is the trigger of transient myopathy.

In fact, after the resolve of diarrhoea, myopathy also improves. Main symptoms of these patients are proximal myopathy which is transient, but patients may have other co-morbid symptoms associated with hypokalaemia.

5. Diagnosis

5.1. History

To diagnose giardiasis, an expert microbiologist is required to identify giardia trophozoite in stool samples. Initial steps to diagnose malabsorption require extensive history and physical examinations. Duration of diarrhoea, stool characteristic and presentation of other symptoms such as poor night vision (vitamin A deficiency), pin and needles in both arms and legs (vitamin B6, B12 deficiency), poor cognitive functions, muscle wasting and significant weight lost suggest present of malabsorption. However, extensive history is still needed to exclude other differential diagnosis of chronic diarrhoea [45] (**Table 3**). History of travel especially to the endemic area of *giardia* helps increase suspicion for this infection.

Effective ways in history taking is to know the differential diagnosis of diarrhoea.

Other information that should be obtained is

1. Onset: gradual, sudden, congenital. Diarrhoea caused from malabsorption usually progressive in term of frequency and consistency.
2. Pattern: continuous or intermittent.
3. Iatrogenic factors such as drugs, radiation, tube feeding.
4. Systematic diseases such as endocrine (hypothyroidism, hypothyroidism), immunological diseases, and neoplasm.
5. Other associated symptoms such as abdominal pain (location, precipitating, aggravating, relieving factors).

Type of diarrhoea	Causes	Example
Secretory	Exogenous secretagogues	Enterotoxins (e.g., cholera)
	Endogenous secretagogues	Neuroendocrine tumours (e.g, carcinoid syndrome)
	Absence of ion transporter	Congenital chloridorrhea
	Loss of intestinal surface area	Intestinal resection, diffuse intestinal mucosal disease
	Intestinal ischemia	Diffuse mesenteric atherosclerosis
	Rapid intestinal transit	Intestinal hurry following vagotomy
Osmotic	Ingestion of poorly absorbed agent	Magnesium ingestion
	Reduced nutrient transport	Lactase deficiency

Table 3. Differential diagnosis of chronic diarrhoea [45].

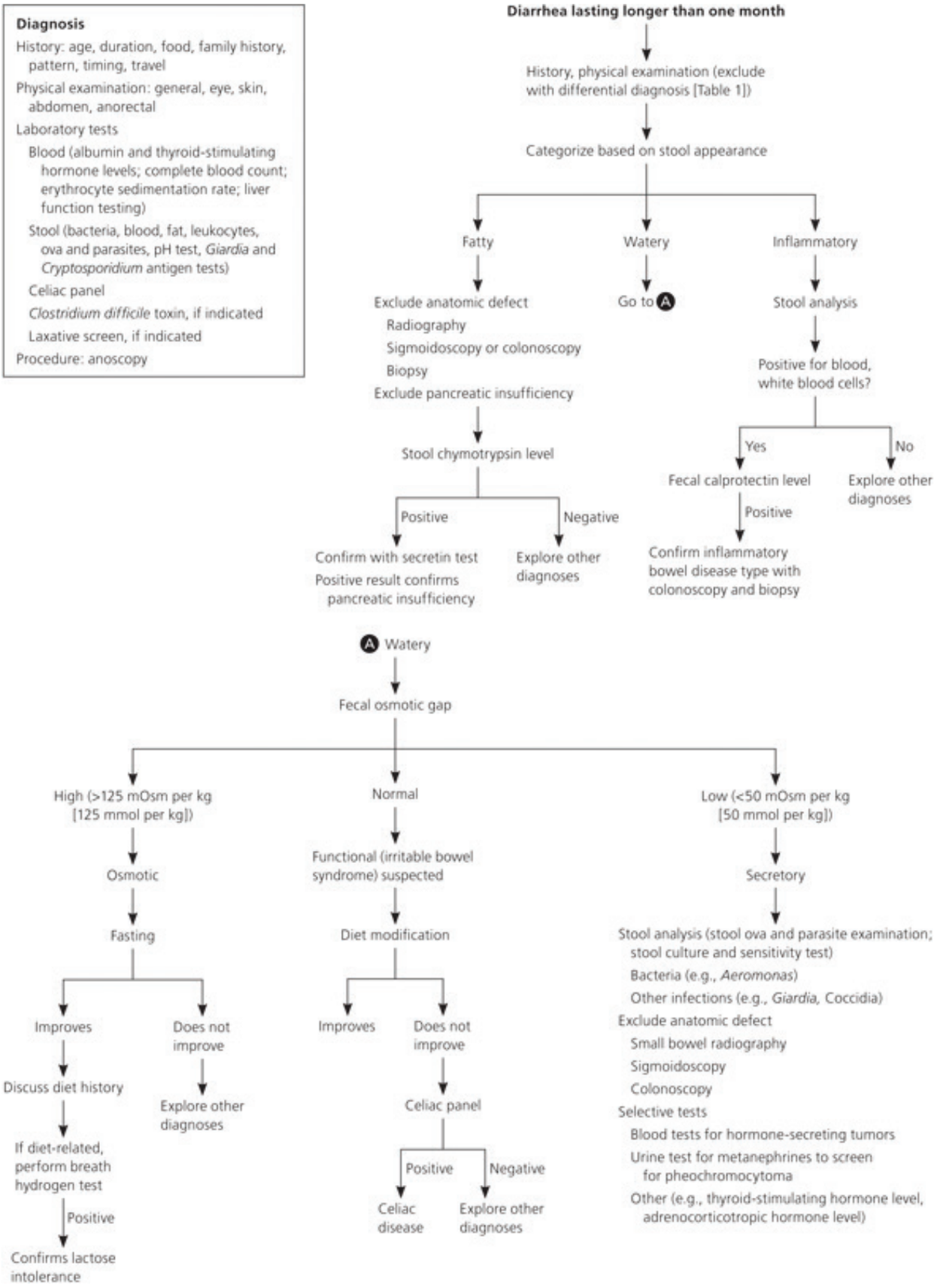

Figure 2. Diagnosis algorithm for chronic diarrhoea.

As **Table 3**, the initial step in the evaluation of chronic diarrhoea is to send stool off for assessment of stool osmotic gap. This allows the differentiation of chronic watery diarrhoea into secretory (faecal osmotic gap <50 mOsm per kg) and osmotic (faecal osmotic gap >125 mOsm per kg). Watery diarrhoea is likely osmotic because the symptoms caused by malabsorption and maldigestion.

5.2. Physical examinations

Physical examination is important and provide important clue into the diagnosis of chronic diarrhoea [45]. Recent weight loss and lymphadenopathy could result from chronic infection or malignancy. Eye finding such as episcleritis or exophthalmia suggests that the diarrhoea is caused by inflammatory bowel disease (IBD) and hyperthyroidism, respectively. The signs that are directly attributed to giardiasis are limited; in fact, there are no specific signs that direct the clinician to suspect giardiasis. However, signs such as anaemia (iron deficiency anaemia), nail pallor, glossitis and koilonychias suggest that there is malabsorption of iron, and cause such as *giardia*, especially in region such as Thailand, should be identified.

5.3. Laboratory diagnosis

Stool microscopy is an important initial test to identify *giardia* trophozoite, blood and faecal leukocyte. Faecal pH test can be done quickly in most centre along with faecal electrolyse to help distinguish secretory diarrhoea from osmotic diarrhoea. A complete blood count, albumin level, erythrocyte sedimentation rate, liver function testing, thyroid-stimulating hormone level and electrolyte levels are important and help exclude other diagnosis such as hyperthyroidism, inflammatory bowel disease, chronic pancreatitis as well as chronic hepatitis [45]. **Figure 2** shows the diagnosis algorithm in managing patients with chronic diarrhoea [45].

6. Conclusion

Giardia is one of the most common water-borne diseases in Thailand and in the world. The finding is particularly more in the area with poor sanitation and unsafe water. In Thailand, the parasites are found in lake and canal but also in water supplies, swimming pool and well. *Giardia* can be transmitted through food and person-person contact. *Giardia* infection usually will be cleared within a few weeks; however, patients might still have intestinal symptoms even after the infection is cleared.

The mechanisms of malabsorption in giardiasis are still obscured. The mechanism such as epithelial dysfunction, villi malformation and immunological disordered has been postulated to be an important cause of malabsorption and maldigestion in giardiasis. It is important to recognise symptoms of chronic giardiasis because this may lead to long-term disability.

Infection with *Giardia* duodenalis may remain asymptomatic or cause acute or chronic diarrhoea. In addition to the intestinal presentation, patient may also develop extra-intestinal complication such as impairment of cognitive function, muscular complications and nutritional

deficiencies. Moreover, giardiasis is now recognised as important cause of failure to thrive, stunting and growth retardation in children of the developing countries. In Thailand, giardiasis is considered as public health importance. Although, the long-term consequences of giardiasis is variable, school health program and health education are available for parents and children aimed at reducing the prevalence of parasitic infection and, as a consequence, have a beneficial effect on child growth and development [39].

The diagnosis of giardiasis can be very difficult in asymptomatic individuals. However, the initial steps should include history taking and physical examinations. There are many differential diagnosis of chronic diarrhoea in both adult and children; therefore, good approach in to diagnosis of giardiasis can help reduce hospital health care cost for the patients. Stools sample should be obtained as are sent for microscopy to identify giardia's trophozoite. Serum iron, ferritin, B12 and sign of complications of giardiasis should be investigated.

Treatment aimed directly at clearing the parasite. The antibiotic that is most frequently used is metronidazole. Nutrition supplements, improved health hygiene and sanitation are important aspect into management of giardiasis. Symptoms such as diarrhoea may persist long after the parasites have been cleared.

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