Original Article

Intestinal Parasitic Infection-Induced Intestinal Wall Cytoskeleton Dysfunction in Diabetes Mellitus

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Abstract

Background: The gastrointestinal tract (GIT) could harbor intestinal parasitic infections (IPIs) alongside a dense and diverse microbial community, termed GIT microbiome. We examined the role of IPI-related changes in intestinal echoanatomy in the pathophysiology of type 2 diabetes mellitus (T2DM). **Methods:** The study included 95 subjects (44 males and 51 females). The diagnosis was based on clinical presentation and laboratory tests, including serial stool microscopy for IPIs, and for diabetes, measurement of hemoglobin A_{1C}, fasting or random blood glucose level, or oral glucose tolerance testing. The B-mode ultrasound grayscale and color images using a high-frequency phased array transducer of 7.5 MHz of the duodenum and colon were obtained with and without water contrast. The duodenal wall thickness was used as measurement endpoint. **Results:** Eighty consecutive patients had at least one type of IPIs in serial stool microscopy, and 15 were healthy persons. Among the 80 IPI patients, 52 (65%) were diabetic, and 28 (35%) patients were nondiabetic. We demonstrated normal duodenum and colon echoanatomy in healthy persons. In patients with IPIs, the duodenal wall thickness (6.87 ± 2.09 mm) was greater than that in healthy persons (3.5 ± 1.07 mm) ($P < 0.001$). In diabetic patients, the duodenal wall thickness (7.23 ± 2.1 mm) was greater than that in nondiabetic patients (5.26 ± 2.07 mm) ($P < 0.001$). There were main effects of age and obesity but not sex. Antiparasitic treatment of IPIs alongside antidiabetic drugs improved control of fasting blood sugar. **Conclusion:** Ultrasound duodenography and colonography demonstrated IPI-induced intestinal wall thickening with rearrangement of the cytoskeleton, causing malfunction of the glucose transporter system which resulted in T2DM.

Keywords: Diabetes, gastrointestinal tract, parasites, tropical diseases, ultrasound

Introduction

There are approximately 100 trillion bacteria that occupy the gastrointestinal tract (GIT) mucosal surface, constantly interacting with metabolically and immunologically active cells. These microbes act as the first line of defense against foreign antigens by initiating a vast array of immunological activities that synergistically enhance mucosal and systemic immunity.[1] The GIT could harbor intestinal parasitic infections (IPIs) alongside a dense and diverse microbial community, which includes archaea, bacteria, protozoans, and viruses, collectively termed GIT microbiome. In 2017, the World Health Organization estimated that about 450 million people have IPIs.[2,3] IPIs constitute a global health burden causing clinical morbidity and mortality.[4] IPIs are caused by helminthic and protozoa parasites. Among helminthic parasites, *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm are the most prevalent and affect about one-sixth of the world population.[3,4] Protozoa parasites such as *Giardia lamblia* and *Entamoeba histolytica* are the most dominant cause of IPIs, infecting about 200 million and 500 million people, respectively,[5] especially in children in developing countries including Nigeria.[6]

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The GIT microbiome has been linked with systemic diseases including obesity, diabetes, hepatopathy, rheumatoid arthritis, cancer, and cardiovascular diseases.[7-12] In a 2015 survey, approximately 415 million people around the globe suffer from diabetes and, by 2040, we expect another 227 million patients with diabetes, as the seventh leading cause of human death.[13] The global prevalence rate of diabetes is 8.5%, and the estimated death toll for direct diabetes-caused morbidity for 2014 was 1.6 million.[13] Type 2 diabetes mellitus (T2DM) is characterized by raised fasting blood glucose. Although glucose is essential for energy production in the living body, excessive rise of fasting blood glucose could be an indication of poor metabolic regulation in various organs. The glucose transporters (GLUTs) play a critical role in maintaining normal glucose metabolism in various organs.[14]

The glucose transporter proteins are classified into two families: facilitative GLUTs and sodium-dependent GLUTs (SGLTs), through which glucose is transported by facilitated diffusion, and Na+/glucose is cotransported by an electrochemical gradient across the membrane, respectively.[15] In topology, all SGLT proteins have 14 transmembrane helices, including the SGLT1 and SGLT2 which function as a glucose/galactose transporter and a glucose transporter across the membrane, respectively. On the other hand, in humans, SGLT3 is not a transporter, rather it is thought to be a glucose sensor expressed in the enteric nervous system and muscle.[16] However, the functions of SGLT4, SGLT5, and SGLT6 are not known.

SGLT1 is expressed mainly in the intestine and kidney.[15,16] More specifically, SGLT1 is expressed in the brush-border membrane (BBM) of the intestine, and glucose absorption across the BBM disappeared in SGLT1-deficient mice, which indicates that intestinal glucose absorption in the intestine is mediated predominantly by SGLT1.[14,15] Others have suggested that SGLT1 is expressed in incretin-secreting cells and is involved in incretin secretion.[16,17] The SGLT inhibitor, phlorizin, reduces incretin secretion, the intestinal hormone that is secreted on meal ingestion.[17] SGLT2 is expressed highly in the kidney.

The absorption of glucose is electrogenic in the small intestinal epithelium. The major route for the transport of dietary glucose from the intestinal lumen into enterocytes is the Na^+/glucose cotransporter (SGLT1) and also through the action of glucose transporter type 2 (GLUT2).[18] The activity of SGLT1 is regulated by the membrane potential of small intestinal epithelial cells (IECs). The complex carbohydrates reaching the small intestine are hydrolyzed to monosaccharides such as glucose or galactose before they are transported across the intestinal mucosa. The passive move out of the basolateral surface of enterocytes contains a facilitated-diffusion GLUT2 which allows glucose to move from the IEC into the extracellular medium near the blood capillaries.[18] This absorption of glucose may be adjusted by GLUT2.[18-20] The translocation of GLUT2 from cytoplasmic vesicles into the apical membrane markedly increases the capacity of glucose uptake by the enterocyte.[20-23]

Some IPIs have been associated with T2DM. The frequency of giardiasis was significantly higher in diabetic patients (15%) compared to dyspeptic patients (7%) and healthy controls.[24] Giardial infections cause significant duodenal wall thickening with cytoskeletal rearrangement as demonstrated using high-frequency ultrasound duodenography.[25-27] It was demonstrated that the presence of the IPIs alters the cytoskeleton of the cells of the intestinal epithelium. The various components assembly undergo dynamic rearrangement. The beautifully precise structure of the intestinal brush border undergoes a rapid reorganization in response to a variety of extrinsic pathogens. Moreover, the ordered appearance of the constituent cells of the intestinal epithelium is in constant motion, from their formation in the crypt to their ultimate extrusion from the monolayer.

In the present work, we hypothesize that the changes in the GIT microbiome due to the presence of IPIs breach the integrity of the intestinal mucosa, causing a rearrangement of the intestinal cytoskeleton, which alters the transport activities of SGLT1 and GLUT2, leading to malabsorption of glucose and its abnormal metabolism in T2DM. The inflammatory processes caused by IPIs lead to increased intestinal wall thickness, which could be measured using high-frequency ultrasound duodenography and colonography.[25-27] Moreover, others have suggested that pathogenic bacteria including enteropathogenic *Escherichia coli* and enterohemorrhagic *E. coli* cause profound cytoskeletal rearrangement in IECs during attachment or invasion. The rearrangement of cytoskeletal proteins could be a signal to upregulate host defense response.[28]

Methods

Subjects

There were 95 subjects (male = 44; female = 51; male mean ± standard deviation [SD] age = 45.3 ± 16.9 years; female mean ± SD age = 46.5 ± 19.1 years) recruited for this study. The study group included 80 consecutive patients who had symptomatic and laboratory-confirmed IPIs. For comparison, sonograms obtained from 15 healthy persons (male = 6; female = 9; mean ± SD age = 26 ± 13 years) who had no history of diabetes or parasites in stool were recruited. The clinical symptoms, history of disease onset, and duration were collected using a standardized questionnaire designed to determine the qualitative and quantitative characteristics of symptoms of the illness. The questionnaire noted the reported intensity and periodicity of abdominal pain. The body mass index (BMI), fasting blood sugar (FBS), hemoglobin A_{1C} (HbA_{1C}), random blood sugar, and glucose tolerance tests were monitored. A fasting plasma glucose level of 126 mg/dL (6.99 mmol/L) or greater, an HbA_{1C} level of 6.5% or greater, or a 2-h postload glucose level of 200 mg/dL (11.1 mmol/L) or greater was considered consistent with the diagnosis of T2DM. A fasting plasma glucose level of 100–125 mg/dL (5.55–6.94 mmol/L), a

HbA_{1C} level of 5.7% to 6.4%, or a 2-h postload glucose level of 140 mg/dL to 199 mg/dL (7.777–11.04 mmol/L) is consistent with prediabetes.[29] According to onset and duration of illness at presentation, the patient population was categorized as (1) acute – within 1 month or less, (2) subacute – within the past 12 months or less, and (3) chronic – after 12 months. The epidemiological exposure to contaminated food or water was noted for each subject. The exclusion criteria included patients with a history of alcoholism, ulcerative lesions, major gastrointestinal diseases such as polyposis, collagen vascular diseases, pancreatic diseases, liver diseases, Crohn's disease, tropical sprue, colon cancer, and diverticulitis. The protocol was approved by the institutional human research ethics review board.

Stool analysis

Laboratory diagnosis was based on microscopic detection of IPIs in fecal smears of three pooled individual specimens or duodenal aspirates. *G. lamblia* and other parasites were examined by direct microscopy of wet preparations of a stool sample.[30] At least two parasitologists examined the stool samples and discrepancies resolved by repeated tests examined by a third parasitologist not involved in the initial evaluation. The quantitative estimation of IPIs in stool samples was based on count per high field (phf) of view. In control follow-up studies, there was a negative stool test or reduced count of trophozoites phf.

Ultrasound examination

A detailed description of the ultrasound examination protocol has been given elsewhere.[25-27] Briefly, abdominal ultrasound examinations were performed using B-mode and color flow Doppler ultrasonography with 2.5 MHz and 7.5 MHz phased array transducer (S4 probe) of a duplex color flow Doppler ultrasound system (Agilent HP/Philips SONOS 5500, Philips Medical Systems, Cambridge, MA, USA). The sonographic examination preceded the result of stool analysis. All ultrasound examinations were performed with and without water contrast after overnight fasting (for at least 16 h) using a standard scanning procedure.[25-27] Water contrast imaging was performed by having adult subjects take at least 1 L of water before the examination. Scan examination was performed in the supine horizontal, left posterior oblique, and left lateral decubitus positions using the intercostal and subcostal approaches. Abdominal scan of the internal organs including the liver, gallbladder, spleen, pancreas, duodenum, colon, and kidneys was routinely evaluated in all subjects. Color flow Doppler ultrasonography was used to examine the localization of lesions in relation to vessels. All ultrasound studies including measurements and grading of echogenicity were performed by a single-trained sonographer using built-in software. Measurements were taken between peristaltic waves. The measurement endpoints of the duodenal wall thickness (with water contrast) (DUOTHICK) were measured between two mucosal folds of Kerckring,[25-27] from the surface of the moderately echogenic mucosa, through the hyperechoic submucosa and hypoechoic muscularis to the hyperechoic serosa layer. Similarly, the ascending colon wall thickness (ASCTHICK) and descending colon wall thickness (DSCTHICK) were measured between two haustra to examine the effect of chronic IPIs on the colon in 40 cases. The IPI lesions were characterized by location, wall thickness, echogenicity of intestinal wall tissue, presence or absence of flattening or loss of duodenal folds and/or colonic haustration, presence or absence of hyperechoic floating foci (HFF) demonstrating chaotic and/or bulk motility, presence or absence of perilesional tissue echogenicity, and type of colonic peristalsis. The helminthic parasites were characterized as hyperechoic curvilinear foci (HCF) with serpentine motility. Chaotic motility was defined as sonographically observed rapid floatation movements in all directions by HFF, between peristaltic waves. Bulk motility was defined as sonographically observed slow floatation movements of HFF in mainly one direction, between peristaltic waves.

Treatment regimen

The treatment regimen for protozoal infections involved the use of metronidazole intravenous infusion (500 mg in 100 mL) or one tablet (500 mg) or two tablets (250 mg) three times daily for 10 days.[31] In addition, helminthiasis was treated using albendazole (400 mg) twice daily for 3 days.[32] The treatment regimen could be extended or repeated after control studies. The treatment of T2DM followed the recommendations of the American Diabetes Association 2021.[33]

Statistical analysis

Statistical analysis was performed using *t*-test statistic and analysis of variance (ANOVA) for group comparison with the software package IBM SPSS Statistics for Windows, version 28.0.1.1. (15) (IBM Corp., Armonk, N. Y., USA). Mean values were reported as mean ± SD. The level of statistical significance was set at $P < 0.05$.

Results

Patients with IPIs complained about abdominal pain, particularly in the right upper quadrant, flatulence, nausea, vomiting, rumbling, perceived weight loss, occasional constipation, or diarrhea. The healthy persons presented no symptoms. Measurements of dimensions of the duodenum and colon were taken at maximal dilation between peristalsis using images taken with water contrast. The stool analysis yielded IPIs, mainly a mixture of microorganisms including *E. histolytica*, *E. coli*, *G. lamblia*, *A. lumbricoides*, hookworm, *T. trichiura*, and *Taenia* species.

General effects

A one-way ANOVA was performed to examine the effects of parasites on the dependent variables: age, BMI, FBS, and DUOTHICK. A one-way ANOVA revealed that there was a statistically significant difference in age, between the patients with parasites (age = 49.66 ± 16.4 years) and the control group (age = 26 ± 13 years), $F(1,93) = 27.66$, $P < 0.001$. There was a statistically significant difference in BMI, between

patients with parasites (BMI = 26.46 ± 6.74) and the control group (BMI = 20.8 ± 6.2), F (1,86) =8.97, P < 0.005. There was a statistically significant difference in FBS, between patients with parasites (FBS = 156.73 ± 84.3 mg/dL) and the control group (FBS = 78.5 ± 9.3), F (1,93) =12.77, P < 0.001. Furthermore, there was a statistically significant difference in DUOTHICK, between patients with parasites (DUOTHICK = 6.87 ± 2.1 mm) and the control group (DUOTHICK = 3.51 ± 1.1 mm), F (1,93) =36.35, P < 0.001.

Another one-way ANOVA was performed to examine the effects of diabetes on the dependent variables: age, BMI, FBS, and DUOTHICK. There were 52 (54.7%) diabetic patients and 43 (45.3%) nondiabetic patients. The one-way ANOVA revealed that there was a statistically significant difference in age, between the diabetic patients (age = 54.27 ± 13.7 years) and the nondiabetic group (age = 35 ± 17.7 years), F (1,93) =32.6, P < 0.001. There was a statistically significant difference in BMI, between diabetic patients (BMI = 27.8 ± 7.3) and nondiabetic group (BMI = 22.8 ± 5.4), F (1,86) =12.8, P < 0.001. There was a statistically significant difference in FBS, between diabetic patients (FBS = 197.2 ± 78.4 mg/dL) and nondiabetic group (FBS = 80.5 ± 12), F (1,93) =93.4, P < 0.001. Furthermore, there was a statistically significant difference in DUOTHICK, between diabetic patients (DUOTHICK = 7.2 ± 2.1 mm) and nondiabetic group (DUOTHICK = 5.2 ± 2 mm), F (1,93) =20.4, P < 0.001.

A one-way ANOVA was performed to examine the combined effects of parasites and diabetes compared to parasites alone and controls, on FBS and DUOTHICK. Of the 80 patients with IPIs, 52 (65%) were diabetic, whereas 28 (35%) were nondiabetic. There was a statistically significant difference in FBS, between diabetic patients with parasites (FBS = 197.2 ± 78.36 mg/dL), compared to patients with parasites alone (FBS = 81.56 ± 13.3 mg/dL) and controls (FBS = 78.5 ± 9.3 mg/dL), F (2,92) =46.2, P < 0.001. Similarly, there was a statistically significant difference in DUOTHICK, between diabetic patients with parasites (DUOTHICK = 7.2 ± 2.15 mg/dL), compared to patients with parasites alone (DUOTHICK = 6.2 ± 1.86 mg/dL) and controls (DUOTHICK = 3.5 ± 1.07 mg/dL), F (2,92) =21.55, P < 0.001.

To examine the effect of duration of illness in patients with chronic IPIs on colonic wall thickness, a one-way ANOVA was performed to compare the effect of chronic parasites on the dependent variables ASCTHICK and DSCTHICK, respectively. There was a statistically significant difference in ASCTHICK, between patients with chronic parasites (ASCTHICK = 8.7 ± 2.9 mm) and control group (ASCTHICK = 3.33 ± 1.1 mm), F (1,53) =48.9, P < 0.001. Similarly, there was a statistically significant difference in DSCTHICK, between patients with chronic parasites (DSCTHICK = 9.3 ± 3.7 mm) and control group (DSCTHICK = 3.33 ± 0.9 mm), F (1,53) =38.7, P < 0.001.

To examine the effects of the independent variable sex (male, female), on the dependent variables: age, BMI, FBS, and DUOTHICK, a one-way ANOVA was performed. There was no statistically significant difference (p = *NS*), between male and female subjects, for any of the dependent variables.

Sonographic findings in normal duodenum

In healthy persons, the wall thickness of the duodenum was 3.5 ± 1.07 mm.

Figure 1a shows ultrasound duodenography demonstrating the normal tri-layer echoanatomy in a healthy person. There are undulating folds of Kerckring (white arrowheads) of the moderately echogenic mucosa and hyperechoic submucosa layer (white arrow), the middle hypoechoic muscularis layer (double white arrowheads), and the outer hyperechoic serosa layer (black arrowhead). The wall thickness of the duodenum is measured across all three layers between two folds of Kerckring (double black arrowheads). There were no HFF or HCF in the lumen of the duodenum in healthy persons. Figure 1b shows the colonic echoanatomy in a healthy person. The colonic wall comprises alternate hypoechoic and hyperechoic bands corresponding to the histological layers. The latter comprises a moderately echogenic mucosa and hyperechoic core submucosa (black arrow), a hypoechoic muscularis layer (double gray arrowheads), and an outer hyperechoic serosa (black arrowhead). The outer layer of longitudinal muscle in the colon demonstrated a relatively hyperechoic taenia coli libera (gray arrow). The colon displayed segmentations, where local movements of the colonic segments aid the absorption of water and help to form feces by providing a kneading action. The peristaltic movements are brought about by contractions of segments of circular muscles and the adjacent portions of the taenia coli; they produce folds of the wall known as haustra (white arrowhead). The ascending colon wall thickness was 3.33 ± 1.09 mm and descending colon wall thickness was 3.33 ± 0.9 mm. Further details of the description of the colonic echoanatomy have been given elsewhere.[25-27]

Sonography of intestinal parasitic infections in symptomatic patients

In patients with IPIs, the duodenal wall thickness (6.87 ± 2.1 mm) was greater than that in healthy persons (3.5 ± 1.1 mm) (P < 0.05). All patients had duodenal inclusions of HFF [Figure 2a; white arrow head]. The echoanatomy was characterized by flattened duodenal folds, increased wall echogenicity, loss of typical tri-layer structure, and increased wall thickness [Figure 2a, double black arrowheads]. The HCF [Figure 2b, white arrow] with serpentine motility fills a significant space in the duodenum with increased duodenal wall thickness [Figure 2b, double white arrowheads]. There are macroscopic changes in the echoanatomy of the duodenal wall which suggests rearrangement of the intestinal wall cytoskeleton.

Ascending and descending colons in intestinal parasitic infections

In symptomatic patients with IPIs, there are increased colonic wall dimensions. The wall thickness (8.7 ± 2.89 mm) of the ascending colon was greater than that in healthy

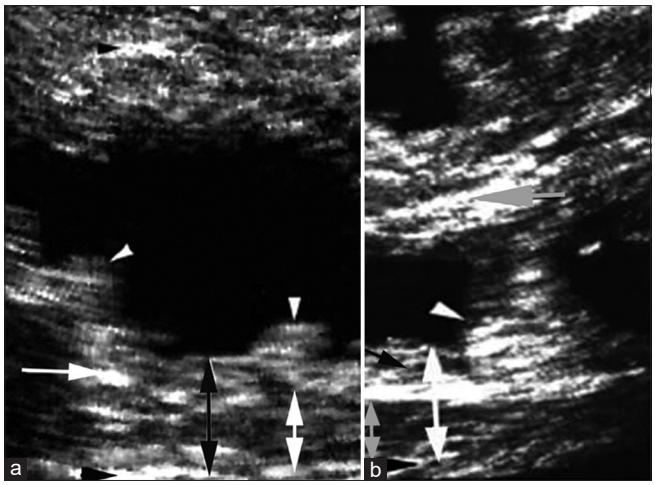

Figure 1: (a) Duodenal and (b) colonic echoanatomy in a healthy person

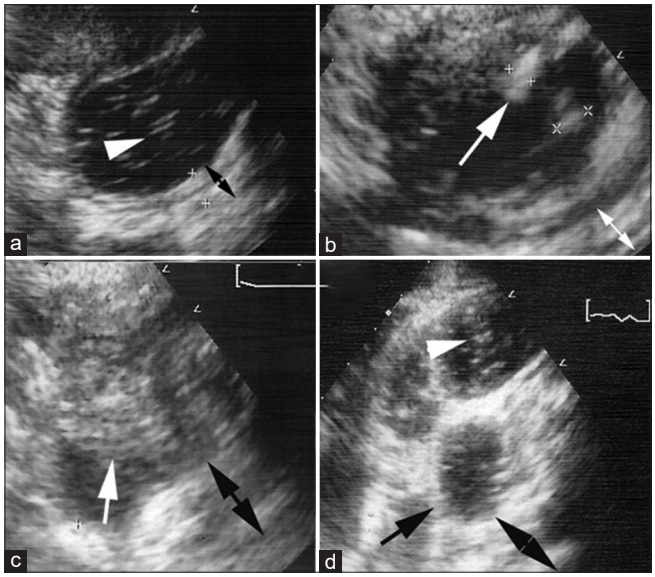

Figure 2: (a-d) Sonographic appearance of intestinal parasitic infections in the duodenum (a-b) and colon (c-d) in symptomatic patients

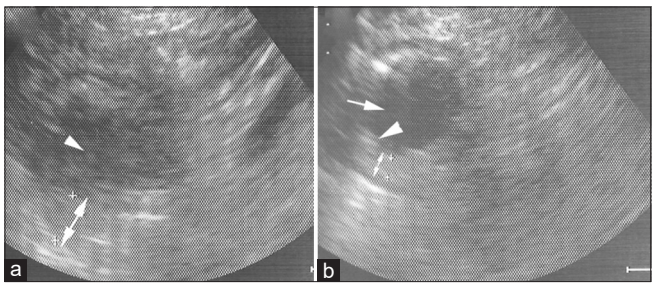

Figure 3: (a-b): Sonographic appearance in a diabetic patient (a) and follow-up (b)

persons (3.33 ± 1.1 mm) ($P < 0.05$). Similarly, the wall thickness (9.32 ± 3.67 mm) of the descending colon was greater than that in healthy persons (3.33 ± 1 mm) ($P < 0.05$). In IPIs, some patients displayed HFF with bulk motility in the ascending colon [Figure 2c; white arrow, with water contrast], others showed HFF with chaotic motility in the descending colon [Figure 2d, white arrow head], and some displayed mixed motility. There was increased wall thickening of the ascending colon [Figure 2c, double black arrowheads] and descending colon [Figure 2d, double black arrowheads], increased wall echogenicity, and loss of haustration in both the ascending and descending colons. There was occasional flattening or thinning of the colonic haustra in different segments of the colon [Figure 2d, black arrow]. There are macroscopic changes in the echoanatomy of the colonic walls which suggests rearrangement of the cytoskeleton in the wall of the colon.

Sonographic appearance in diabetic patients and follow-up

In a typical case, the pretreatment (HbA_{1C} = 8.7%) ultrasound image [Figure 3a] was characterized by changes in echoanatomy demonstrating increased duodenal wall thickness (DUOTHICK = 11.1 mm) [Figure 3a, double white arrowheads], increased wall echogenicity, rearrangement of the tri-layer wall structure, loss of duodenal folds of Kerckring, and HFF [Figure 3a, white arrowhead] in the lumen of the duodenum. The patient was treated for IPIs with intravenous metronidazole and tablets of albendazole.[31,32] The patient had cardiovascular disease risk factors including moderate hypertriglyceridemia (218 mg/dL). The T2DM was managed with Synjardy, a combination of empagliflozin (12.5 mg) and metformin hydrochloride (1000 mg), one tablet twice daily, along with diet and exercise. The drugs, empagliflozin, and metformin hydrochloride belong to the class of antidiabetics: SGLT2 inhibitors and biguanides, respectively.[33] The SGLT2 transporter is expressed highly in the kidney. The hypertriglyceridemia was managed with statin therapy. The posttreatment (HbA_{1C} = 7.2%) ultrasound image [Figure 3b] taken 3 months later shows remarkable transformational macroscopic changes in echoanatomy demonstrating reduced duodenal wall thickness (DUOTHICK = 4.89 mm) [Figure 3b, double white arrow heads], reduced wall echogenicity, recovery of the normal arrangement of the tri-layer wall structure, the appearance of duodenal folds of Kerckring [Figure 3b, white arrow head], and no HFF in the duodenal lumen. The 6th month follow-up test (HbA1C = 6.3%) on August 2, 2022, attained primary endpoint (HbA_{1C} < 6.5%). Treatment of diabetic patients with IPIs using metronidazole and albendazole alongside antidiabetic drugs improved the control of FBS in all patients.

Discussion

The findings demonstrated that many patients with IPIs were obese and diabetic and had increased intestinal wall thickness. Among the 80 consecutive patients with IPIs, 65% developed T2DM. The latter suggests that patients with IPIs are at increased risk of developing T2DM. Furthermore, in diabetic patients, pretreatment ultrasound scans showed

increased HFF in the lumen, increased wall echogenicity, loss of duodenal folds of Kerckring, increased duodenal wall thickness, and rearrangement of the intestinal wall structure. However, in posttreatment ultrasound scans, there were remarkable transformational changes demonstrating the absence of HFF in the lumen, reduced wall echogenicity, the appearance of duodenal folds of Kerckring, reduced duodenal wall thickness, and recovery of the normal arrangement of the tri-layer wall structure. The effects of chronic IPIs also caused increased colonic wall thickness in both the ascending and descending colons. Treatment of diabetic patients with IPIs using metronidazole and albendazole alongside antidiabetic drugs improved the control of FBS in all patients. The ultrasound scans demonstrated the effectiveness of the treatment of IPIs on intestinal echoanatomy, possibly restoring regulation of the glucose transporter system in the intestine and facilitating better control of FBS with antidiabetic drugs.

We propose a mechanism for the association of IPIs and T2DM. The repeated cases of IPIs in childhood and adulthood caused rearrangement of the intestinal cytoskeleton resulting in malfunction of the glucose transporter system. The normal absorption of glucose implicates an electrogenic mechanism in the well-ordered small intestinal epithelium. The main mechanism of transport of dietary glucose from the intestinal lumen into enterocytes is the SGLT1 and also through the action of GLUT2.[18-20] We demonstrated the macroscopic echoanatomy of the intestinal wall depicting rearrangement of the cytoskeleton. The latter compromises the membrane potential of IEC and hence the regulation of the activity of SGLT1. The disturbance in the regulation of the activity of SGLT1 would mean that the complex carbohydrates reaching the small intestine after hydrolysis to monosaccharides such as glucose or galactose are nonselectively transported across the intestinal mucosa. Similarly, the activity of GLUT2,[18] which allows glucose to move from the IEC into the extracellular medium near the blood capillaries, is impaired. The cumulative effects of the IPI-induced rearrangement of the duodenal wall cytoskeleton would lead to raised FBS. Of course, these effects of IPIs work synergistically with other factors such as age and obesity to lead to T2DM.

Chronic diabetes is an impairment in the way the body regulates and uses glucose as fuel for energy. T2DM results from the body's ineffective use of insulin. It is well established that age and obesity play important roles. In addition, we suggest an important role for IPIs which cause intestinal wall thickening and malabsorption of glucose from the GIT, leading to an excessive rise in blood sugar. Although our study cohort is very small and is a pilot study, the conclusions are very important and for the first time in the literature demonstrate that noninvasive ultrasound measured intestinal wall thickness is an important measurement endpoint and could be a surrogate marker for use in clinical trial studies to monitor the effects of IPIs in the etiopathogenesis of T2DM. Furthermore, the findings suggest a role for noninvasive high-frequency ultrasound duodenography and colonography in the diagnosis and follow-up of patients with IPIs and T2DM.

The public health implications of our findings are enormous. It has been estimated that over 1 billion people in the world, majority of children were infected with IPIs caused by helminths and protozoa.[34] The findings in the present study suggest a close association of IPIs with T2DM in adults, which could have started in childhood. This would imply that over half of the patients with IPIs may develop T2DM later in life. Given the rising cases of IPIs, especially in developing countries, there would be an expected increase in cases of T2DM. The latter calls for a renewed global initiative to detect and treat IPIs as a preventive strategy toward reduction of the overall burden of disease including T2DM. We humbly suggest that the Global Fund Strategic Initiatives for 2024 and beyond include means to incentivize increased program quality and efficacy focused on IPIs in populations in developing countries with the greatest need, particularly in the childhood populations with the highest global burden of disease. Such a global initiative should address the specific barriers to diagnosis and treatment of IPIs in the adult and most vulnerable childhood population. There is a need to scale up treatment, especially in children under five who bear the most burden of IPIs and other diarrheal diseases. The global initiative could scale up the implementation of innovative approaches toward community prevention of food and water-borne infections as well as promote the use of techniques such as diagnostic noninvasive ultrasound among family practice physicians in developing countries.

Some have suggested that metabolic surgery is more effective than conventional medical therapy in the long-term control of T2DM.[35] The hypothesis we have proffered here could be applied to explain the efficacy of Roux-en-Y gastric bypass and the biliopancreatic diversion surgeries in the control of T2DM. We suggest that the metabolic surgical procedures divert food from areas of the duodenum with rearrangement of the wall cytoskeleton and compromised regulation of the activity of SGLT1, to regions of the intestine with normal walls. Future studies could explore the use of high-frequency ultrasound duodenography and colonography in randomized controlled trials of metabolic surgery for T2DM. Perhaps, the ultrasound technique may help improve patient selection and define more specifically anatomic areas of the intestine that require to be bypassed in metabolic surgery for T2DM. Furthermore, we have demonstrated that treatment of IPIs may restore the integrity of the intestinal wall and the patient could attain a primary endpoint within a short time. It remains to be explored in randomized clinical trials if this approach is comparable to the results of metabolic surgery for T2DM.

Noninvasive ultrasound imaging is widely available in most developing countries including Nigeria. The imaging technique for high-frequency ultrasound duodenography and

colonography has been described in detail elsewhere.[25-27] In combination with serial stool analysis, the family practice physician is well equipped to diagnose and treat these patients that form a large segment of their patient population.

Conclusion

Ultrasound duodenography and colonography demonstrated IPI-induced intestinal wall thickening with rearrangement of the cytoskeleton resulting in malfunction of the glucose transporter system, which facilitated the development of T2DM.

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Conflicts of interest

There are no conflicts of interest.

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