ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2022 July 9; 11(4): 321-384

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

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INDEXING/ABSTRACTING

The *WJCP* is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Toru Watanabe, Consolato M Sergi, Elena Daniela Serban, Surjit Singh

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PUBLICATION DATE
July 9, 2022

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World J Clin Pediatr 2022 July 9; 11(4): 321-329

DOI: 10.5409/wjcp.v11.i4.321

ISSN 2219-2808 (online)

MINIREVIEWS

Hereditary fructose intolerance: A comprehensive review

Sumit Kumar Singh, Moinak Sen Sarma

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Barone M, Italy
A-Editor: Wang JL, United States

Received: November 27, 2021
Peer-review started: November 27, 2021
First decision: April 13, 2022
Revised: May 8, 2022
Accepted: June 20, 2022
Article in press: June 20, 2022
Published online: July 9, 2022

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Abstract

Hereditary fructose intolerance (HFI) is a rare autosomal recessive inherited disorder that occurs due to the mutation of enzyme aldolase B located on chromosome 9q22.3. A fructose load leads to the rapid accumulation of fructose 1-phosphate and manifests with its downstream effects. Most commonly children are affected with gastrointestinal symptoms, feeding issues, aversion to sweets and hypoglycemia. Liver manifestations include an asymptomatic increase of transaminases, steatohepatitis and rarely liver failure. Renal involvement usually occurs in the form of proximal renal tubular acidosis and may lead to chronic renal insufficiency. For confirmation, a genetic test is favored over the measurement of aldolase B activity in the liver biopsy specimen. The crux of HFI management lies in the absolute avoidance of foods containing fructose, sucrose, and sorbitol (FSS). There are many dilemmas regarding tolerance, dietary restriction and occurrence of steatohepatitis. Patients with HFI who adhere strictly to FSS free diet have an excellent prognosis with a normal lifespan. This review attempts to increase awareness and provide a comprehensive review of this rare but treatable disorder.

Key Words: Hereditary; Fructose; Intolerance; Children; Liver; Steatohepatitis; Aldolase

Core Tip: Hereditary Fructose Intolerance is a rare autosomal recessive inherited disorder due to the mutation of enzyme aldolase B. Awareness regarding its diverse manifestations is required to clinically suspect and diagnose this condition. Genetic testing clinches the diagnosis. Treatment is simple and involves only the dietary exclusion of fructose, sucrose and sorbitol. The prognosis is favourable. This review provides a comprehensive understanding of the disease.

Citation: Singh SK, Sarma MS. Hereditary fructose intolerance: A comprehensive review. *World J Clin Pediatr* 2022; 11(4): 321-329
URL: https://www.wjgnet.com/2219-2808/full/v11/i4/321.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.321

INTRODUCTION

Fructose is a monosaccharide found in honey, fruits and many vegetables consumed daily. It is also the component of the main sweetening agent, sucrose in the majority of sweets and syrups. Small amounts of fructose are also produced in the human brain *via* the polyol pathway[1]. After ingestion, fructose is absorbed from the intestine through glucose transport proteins (GLUT) 5 and 2[2]. Subsequent metabolism is carried out predominantly in the liver, kidney and small intestine by the enzymes fructokinase, aldolase B, and triokinase[3]. Hereditary fructose intolerance (HFI) is a pathological condition that occurs due to a deficiency of enzyme aldolase B[3]. It is characterized by hypoglycemia, lactic acidosis, hypophosphatemia, hyperuricemia, hypermagnesemia and hyperalanemia due to dysregulation of gluconeogenesis, glycogenolysis and decreased inorganic phosphate[4].

EPIDEMIOLOGY AND GENETICS

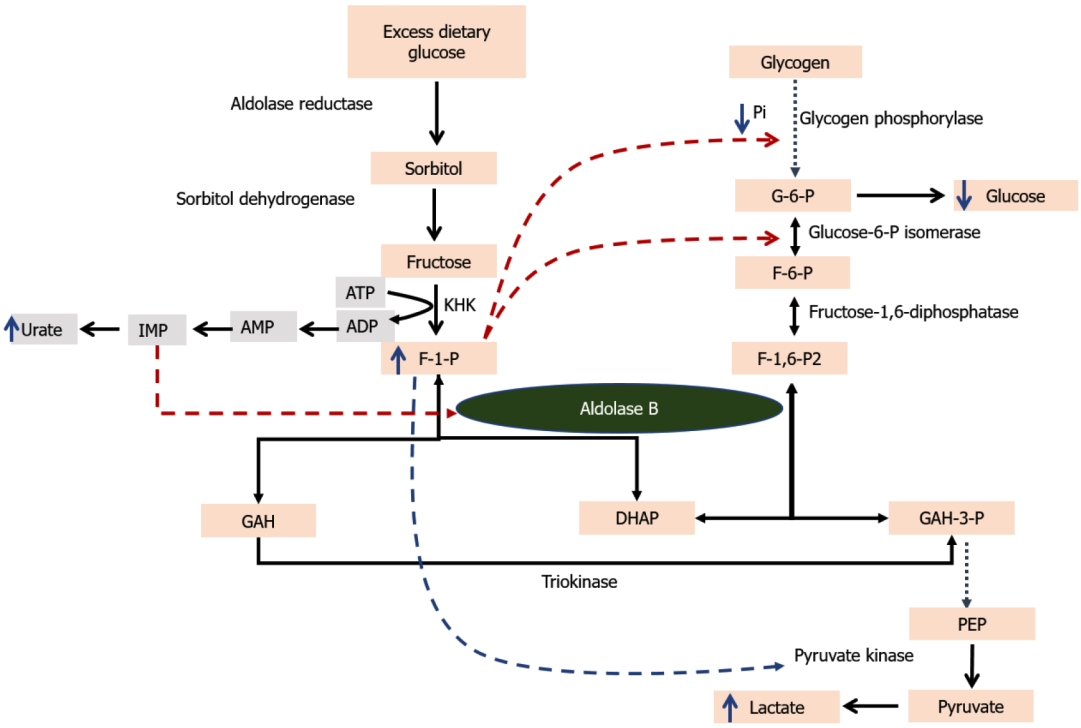
HFI is a rare autosomal recessive inherited disorder with an estimated population prevalence ranging from 1 in 20000 to 1 in 60000[5]. There is no sex predilection. The gene for the enzyme aldolase B (ALDOB) is located on chromosome 9q22.3. Mutational aberrations include simple missense mutations, deletions, frameshift mutations, and mutations at splicing sites. A systemic review was conducted to assess *ALDOB* gene variants among patients with HFI[6]. The prevalence of HFI was estimated from the carrier frequency of variants described in patients, as well as rare variants predicted as pathogenic by *in silico* tools. In silico predictive software allows assessing the effect of amino acid substitutions on the structure or function of a protein without conducting functional studies[7]. The application of in silico tools can significantly improve the detection of genes and variation[8]. The studies included in the systematic review described 1426 alleles involved in the pathogenesis of HFI, spread in 29 countries on four continents[6]. 68 variants in *ALDOB* were identified among patients with HFI distributed in different populations. These variants were detected in 85 different genotypic combinations. Most of the mutations described in patients with HFI are restricted to a single ethnic group. The commonest variants distributed worldwide that account for most of the identified cases are: NM_000035_3:c.178C>T, NP_000026.2:p.(Arg60Ter); NM_000035_3:c.360_363del, NP_000026.2:p.(Asn120LysfsTer32); NM_000035_3:c.448G>C, NP_000026.2:p.(Ala150Pro); NM_000035_3:c.524C>A, NP_000026.2:p.(Ala175Asp) and NM_000035_3:c.1005C>G, NP_000026.2:p.(Asn335Lys). The analyses showed that the variants p.(Ala150Pro) and p.(Ala175Asp) are the most frequent in patients, accounting for approximately 68% of the alleles. The p.(Ala150Pro) variant alone accounts for 53% of all alleles identified worldwide, and has a variable frequency between the different geographic regions.p.(Asn120LysfsTer32) variant is the third most frequent (4.6%)[9-11]. Five novel mutations, (c.324+1G>A, c.112+1delG, c.380-1G>A, c.677G>A, and c.689delA) have been reported from an Indian community[12].

PATHOGENESIS

It carries out the reversible conversion of fructose 1-phosphate (F-1P) to glyceraldehyde (GAH) and dihydroxyacetone phosphate (DHAP) as shown in (Figure 1). Aldolase B also plays a role in gluconeogenesis and glycolytic pathways as it catalyzes fructose 1,6-bisphosphate (F-1,6P2) conversion to DHAP and glyceraldehyde 3-phosphate (G3P) in a reversible manner (Figure 1). There are two other isoenzymes, aldolase A (predominantly expressed in skeletal muscle and red blood cells) and aldolase C (predominantly expressed in brain and smooth muscle) and both have a high affinity for F-1,6-P2 as a substrate[13]. The deficiency of aldolase A manifests mainly as recurrent rhabdomyolysis which may sometimes be accompanied by hemolysis and termed glycogen storage disorder type 12[14,15]. Aldolase C expression has been found to be associated with certain neuroendocrine tumors and is being studied as a marker of neuroendocrine tumors[16].

Metabolic consequences

In a patient with HFI, a fructose load leads to the rapid accumulation of F-1P which results in depletion of intracellular inorganic phosphate (Pi) and adenosine triphosphate (ATP). As a result, adenosine 5′-monophosphate (AMP) degradation is increased, and hence, inosine monophosphate (IMP) and urate



DOI: 10.5409/wjcp.v11.i4.321

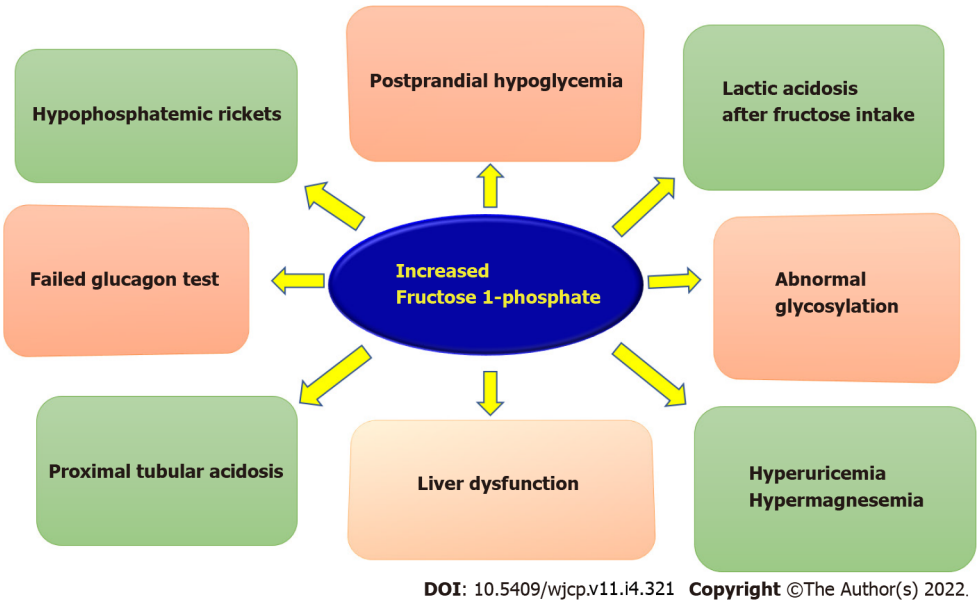
Figure 1 Illustrates the pathway of fructose metabolism. Fructose is converted by ketohexokinase to F-1P that acts as substrate for Aldolase B which forms dihydroxyacetone phosphate (DHAP) and glyceraldehyde (GAH) that enter the glycolytic/gluconeogenic pathways. Aldolase B also catalyzes the reversible conversion of F-1,6P2 to DHAP and GAH-3P. Accumulation of F-1P leads to inhibition of glucose -6 P isomerase and along with depletion of inorganic phosphate, inhibits glycogen phosphorylase (red broken line). Similarly, increased IMP inhibits any residual Aldolase B activity if present. F-1P also activated PK which promotes lactic acid production. ADP: Adenosine diphosphate; AMP: adenosine monophosphate; ATP: adenosine triphosphate; DHAP: dihydroxyacetone phosphate; F-6P: Fructose 6-phosphate; F-1P: Fructose 1-phosphate; F-1,6-P2: Fructose 1,6-biphosphate; G-6P: glucose 6-phosphate, GAH glyceraldehyde; GAH-3P: Glyceraldehyde 3-phosphate; IMP: inosine monophosphate; KHK: Ketohexokinase; PEP: Phosphoenolpyruvate; Pi: Inorganic phosphate; PK: Pyruvate kinase.

are generated rapidly resulting in hyperuricemia which is responsible for gout in patients with HFI (Figure 1). Increased IMP through specific inhibition of aldolase B creates a vicious cycle leading to a further increase in F-1P. Depletion of ATP also results in increased release of magnesium as well as impaired protein synthesis and ultrastructural lesions which are responsible for hepatic and renal dysfunction. The consequences of increased F-1P are shown in Figure 2.

Increased F-1P along with reduced Pi is also responsible for inhibition of glycogenolysis through impairment of glycogen phosphorylase. This fructose-induced hypoglycemia in HFI is not corrected by the administration of exogenous glucagon which again emphasizes the impaired glycogenolysis pathway. Further, the accumulation of F-1P impedes gluconeogenesis by inhibition of glucose-6-phosphate isomerase (G6PI) (Figure 1). Overall, when a patient with HFI is given a fructose load, it leads to hypoglycemia due to deranged gluconeogenesis and glycogenolysis. In addition, lactic acidosis occurs due to activation of glycolytic pathway through increased activity of pyruvate kinase by F-1P and inability of aldolase B to convert DHAP and G3P to F-1,6P2. Notably, the metabolic consequences of fructose load also occur after ingestion of sorbitol found in various syrups and those with high glycemic foods such as rice. Sorbitol, through polyol pathways, is responsible for the endogenous production of fructose (Figure 1)[1].

CLINICAL FEATURES

The genotype-phenotype correlation has not been identified in patients with HFI. Patients with HFI develop symptoms only when exposed to dietary fructose directly or indirectly through sucrose or sorbitol. The classical presentation is described as an infant, otherwise healthy, presenting with nausea, protracted vomiting, poor feeding and lethargy and sometimes with seizures following the introduction of weaning foods containing sugar or starch[17]. Li *et al*[18] reported four cases of neonatal and early infantile acute liver failure associated with multi-organ failure induced by sucrose-containing common infant formula in patients with undiagnosed HFI. All patients were appropriately grown, born at term after uncomplicated pregnancies and deliveries, and discharged within the first week of life. There was no known consanguinity. One patient had a family history of an older brother who died on day 28 of life with a similar illness, though a specific diagnosis could not be ascertained. Another patient had a



DOI: 10.5409/wjcp.v11.i4.321

Figure 2 Illustrates the consequences of hereditary fructose intolerance.

maternal half-sister who required a liver transplant for an indeterminate liver failure. Careful dietary history was obtained in all infants, though fructose exposure was unclear in two of the 4 cases due to unreliable history or unclear ingredient labelling, which delayed diagnosis. In all four cases, the newborn screen was normal. The diagnosis was confirmed by ALDOB gene sequencing. All infants were homozygous for the common c.448G>C (p.A150P) pathogenic variant[19]. Sometimes, it may present late in childhood or adulthood owing to the self-imposed strict dietary restriction of fructose-containing food items[19,20]. The child shows a strong aversion to sweets.

An intermittent dietary restriction can have a subtle presentation in the form of isolated hepatomegaly or intermittent elevations in transaminases[21]. Thus, a dietary history of fructose intake and the presence of fatty liver are important clues to suspect an underlying HFI in infants. Chronic liver disease in form of fatty liver, steatohepatitis and even cirrhosis may occur in patients with HFI who are fed regularly on a fructose-rich diet. Examination typically shows growth failure and hepatomegaly with or without jaundice. Renal involvement usually occurs in the form of proximal renal tubular acidosis and may lead to chronic renal insufficiency. Metabolic derangements include hypoglycemia, lactic acidosis, hypophosphatemia, hyperuricemia and hypermagnesemia[6]. HFI presenting as relapsing acute axonal neuropathy has also been reported recently, which improves after dietary fructose omission[22].

In contrast to the classical presentation of the above acute symptoms, some patients with residual enzymatic activity may remain asymptomatic or require a larger burden of fructose to become symptomatic. HFI can also remain masked in the presence of concomitant diseases. Aldag *et al*[23] reported an infant developing unexplained liver failure and metabolic dysfunction soon after a successful pyloromyotomy for hypertrophic pyloric stenosis and the diagnosis was confirmed by genetic testing. Similarly, Bobrus-Chociej reported that elevated transaminases and fatty liver may continue to prevail despite a compliant gluten-free diet in patients with celiac disease. In such a situation, a strong degree of suspicion for HFI is required[24].

Heterozygotes with HFI do not present with classical manifestations of HFI. It has been shown that there are significant but occult metabolic derangements in HFI heterozygous carriers. Randomized cross-over trials show that a high fructose diet (1.4 g/kg/d) increased postprandial plasma uric acid, insulin and hepatic insulin resistance index as compared to those on a low fructose diet (< 10 g/d). This analysis provides insight as to the extent of metabolic damages that can take place in homozygotes in whom these trials are deemed unethical[25]. There are several reports of gouty arthritis due to hyperuricemia in children with heterozygous mutation for HFI[26].

EVALUATION

A meticulous history revealing a clear correlation between exposure to dietary fructose and the onset of symptoms is the key to suspecting the possibility of underlying HFI. There are various pitfalls in the diagnosis of HFI. Kim *et al*[27] in their case series of 5 patients with subtle symptoms and aversion to sweets. They make a pertinent point that emphasis of classic teaching on infantile acute liver failure and biochemical derangements, such as hypoglycemia and hypophosphatemia, after the first exposure to

fructose may inadvertently increase the likelihood of missing cases of HFI characterized by other manifestations. Hence index of suspicion must be high and wide screening must be employed. HFI should be looked for in any patient with unexplained reasons for failing to thrive. HFI is also often misdiagnosed with other nongenetic and genetic conditions, including an eating disorder, recurrent hepatitis, and glycogen storage disease. Moreover, fructose intolerance may not be pathognomonic for HFI alone, given the description of rare patients with fruit-induced, food protein-induced enterocolitis syndrome. Furthermore, the lack of a specific and practical biomarker for HFI means that neither newborn screening nor biochemical testing can be used to establish the diagnosis. Compliance, discrimination and psychosocial issues may be specific problems in adolescence[28].

Detection of non-glucose-reducing substances in the urine sample while on a fructose-containing diet is a bedside screening test. The presence of reducing sugars (glucose/fructose/Lactose) in urine can be detected by Benedict's test[29]. While glucose can be detected in urine by glucose dipsticks, a positive Benedict's test in urine with a negative glucose dipstick test points to the presence of other reducing sugars like fructose/Lactose. Provocative fructose tolerance tests in young children are cumbersome and fraught with the dangers of hypoglycemia. Are there simpler biochemical ways to screen for HFI? Untreated HFI patients present abnormal transferrin (Tf) glycosylation patterns due to the inhibition of mannose-6-phosphate isomerase by fructose-1-phosphate. Hence, elevated serum carbohydrate-deficient Tf (CDT) may allow the prompt detection of HFI. The CDT values improve when an FSS-restrictive diet is followed. Cano *et al*[30] showed that by capillary zone electrophoresis method, asialoTf correlated with dietary intake of sucrose and that pentasialoTf + hexasialoTf negatively correlated with dietary intake of fructose in patients with HFI. Moreover, the tetrasialoTf/disialoTf ratio also differentiated treated HFI patients from healthy controls. However some patients with HFI have been initially misdiagnosed with type 1 congenital disorders of glycosylation[31].

Liver biopsy in patients with HFI shows macro vesicular steatosis with or without changes in inflammation and fibrosis[32]. For confirmation, a genetic test is favoured over the measurement of aldolase B activity in liver biopsy specimens as later is invasive and not widely available. Genetic testing has high sensitivity and specificity and includes single gene sequencing, multi-gene panels, and genomic testing [33].

DIFFERENTIAL DIAGNOSIS

Acute presentation of HFI mimics sepsis, acute infectious hepatitis, hemophagocytic lymphohistiocytosis and other metabolic diseases such as galactosemia, tyrosinemia, organic academia and urea cycle defect. In children presenting with hepatomegaly, fatty liver and raised transaminases, possibilities of Wilson disease, glycogen storage disorder, alpha-1 antitrypsin deficiency should be considered. Presentation as hypoglycemia, acidosis and hepatomegaly mimic fructose 1,6 bisphosphate deficiency, beta-ketothiolase deficiency, pyruvate carboxylase deficiency, congenital disorder of glycosylation, fatty acid oxidation defects and milder variants of respiratory chain defects. Predominant gastrointestinal symptoms and aversion to sweets distinguish HFI from the rest of the differential diagnoses.

TREATMENT

Being a complex metabolic disorder, management of HFI needs a multidisciplinary approach with the involvement of a pediatrician, clinical geneticist, dietician with experience in metabolic disorders, hepatologist and nephrologist. The crux of HFI management lies in the absolute avoidance of foods containing fructose, sucrose, and sorbitol (FSS). Patients presenting with an acute metabolic crisis should be admitted to an intensive care setting and initiated intravenous glucose (dextrose), treatment of metabolic acidosis, (if present) and supportive treatment. Strict avoidance of FSS in the diet along with supplementation of other sources of carbohydrate (glucose, corn-starch) results in rapid reversal of symptoms. At length repetitive counselling, clear instructions on dietary restrictions and continuous reinforcement are required to maintain long-term dietary compliance and precipitations of breakthrough events. Table 1 enlists the food items which should be avoided and which are permitted in patients with HFI. Patients with HFI on a strict FSS elimination diet can develop several nutritional deficiencies, especially vitamins mainly Vitamin C found predominantly in fruits and vitamin B complex. Thus, it is recommended to add multivitamin supplements to prevent the consequences of these deficiencies[34].

CONTROVERSIES IN MANAGEMENT

Diet

Although a strict FSS diet is recommended while treating HFI, there is no clarity as to whether small

Table 1 Food items to be avoided and permitted in hereditary fructose intolerance

Food category	Foods to be avoided	Foods permitted
Fruits	All fruits, fruit juices, fruit extracts, shakes, squashes	None
Cereals	Sweetened/sugar-coated cereals	All except sweetened/sugar coated cerelas
Vegetables	Sweet potatoes, peas, Zucchini	All others including potatos and onions
Breads	Any breads prepared with fructose/sucrose/sugar/sorbitol	Breads prepared without fructose, sucrose, sugar, or sorbitol
Deserts and sweeteners	All desserts/sweets prepared with sugar (cake, pie, ice cream, sherbet, sweetened lime soda)	Dietetic ice cream, dietetic puddings; natural yogurt
Poultry	Milk products added with sugar (sweetened curd/yogurt, fruit yogurt, milkshake, chocolate milk)	Milk without sugar, chicken, Turkey
Meat	Ham, bacon, hot dogs, processed meats; any other meat where sugar is used in processing	Beef, veal, lamb, pork; All Fish
Miscellaneous	Ketchup and other sauces/ condiments containing sugar, Honey, Jam, jelly, Candy, Cookies, Chocolates, , Carbonated beverages, medicinal syrups	Vegetable juices, coffee, tea, salt, pepper, broths/soups from permitted vegetables, eggs, nuts

amounts of fructose can be tolerated in the diet. At what permissible limit of fructose will liver and kidney damage not occur? Restriction of FSS may lead to growth failure even in clinically asymptomatic HFI patients. There is insufficient information about the long-term outcomes of minimal fructose ingestion. A recent study from Italy reported the ten years of follow-up of patients with HFI. Fatty liver (on sonography) persisted in 93.8% of patients despite being on FSS restricted diet of < 1.5 g/d (35). The authors also found that a significant proportion of patients continued to have raised transaminases (37.5%) even when dietary compliant. There are two reasons for the persisting liver abnormalities in patients with HFI. Firstly, fructose may be endogenously produced by the sorbitol-aldose reductase pathway, which can be activated after a glucose-enriched meal, nephrotoxic drugs or stressful conditions like sepsis and major surgery. Secondly, the permissible limits of fructose ingestion may not be safe in asymptomatic patients of HFI. The latter is supported by the determination of CDT by isoelectric focusing among the patients with HFI on an FSS-free diet by Di Dato *et al*[35]. They showed a significant correlation between the amount of fructose consumed and the percentage of disialoTf and tetrasialoTf/disialoTf ratio. The authors suggested that serum CDT profile could be considered a good tool to monitor FSS intake. In addition, CDT determination could be used to identify the maximum daily fructose tolerability of each HFI patient. However, the lack of widespread availability and high cost are the main barriers to the application of this tool.

Non-alcoholic fatty liver disease and HFI

As evident from the study by Di Dato *et al*[35], the majority of the patients with HFI despite being on an FSS-free diet continued to have fatty liver. In another cross-sectional study of 16 patients, non-alcoholic fatty liver disease (NAFLD) was found in 9 (56%) patients[32]. The importance lies in the fact that fatty liver may progress to steatohepatitis, hepatic fibrosis and cirrhosis. Moreover, there is an increased risk of type 2 diabetes and cardiovascular diseases[36,37]. The studies in ALDOB-KO mice as well as in patients with HFI have demonstrated that NAFLD may not be the result of direct lipogenic effects of fructose[38,39]. In addition, when ALDOB-KO mice were chronically exposed to small amounts of fructose in the chow (approximately 0.3%), they showed an increased accumulation of hepatic triglycerides, hepatic inflammation and signs of periportal fibrosis[38,40]. Notably, these ALDOB-KO mice also had increased intrahepatic F-1P concentrations[38]. Lanaspa *et al*[38] also showed the increased hepatic expression of enzymes was seen in de novo lipogenesis with an abundance of cytosolic glucokinase in ALDOB-KO mice. Thus, it can be speculated that the accumulation of F-1P in ALDOB-KO mice may stimulate hepatic glucose uptake, thereby enhancing the storage of glycogen and fat.

In the experimental model, almost all the metabolic abnormalities in the ALDOB-KO mice were ameliorated when supplemented with ketohexokinase (KHK), an enzyme involved in the phosphorylation of fructose[38]. Treatment with osthole, a natural KHK inhibitor also showed the same results[41]. Additionally, osthole treatment inhibited de novo lipogenesis in ALDOB KO mice. In humans, a loss of KHK results in essential fructosuria (OMIM #229800) which is a benign condition[42]. Hence, KHK inhibition may serve as a potential therapeutic target for the treatment of NAFLD in patients with HFI. Ghannem *et al*[43] have unusually reported epithelioid granulomas in association with liver adenomatosis and macrovesicular steatosis in an adult with HFI that yielded negative workup for tuberculosis, sarcoidosis and other infectious diseases. They postulated that the granulomas in the non-tumour liver sections may have developed from the inflammatory stress due to inflammatory hepatocellular adenomas.

Vaccines

There are considerable controversies about the safety concerns of vaccines that contain fructose, sucrose or sorbitol in HFI. Saborido-Fiaño *et al*[44,45] argue that the safe threshold of fructose was 2.4 mg/kg/dose and various oral rotavirus vaccines would not qualify for that category. This requires the need to revisit the vaccine content. The authors also cautioned against the use of Sars-Cov-2 vaccines in children affected with HFI. Urru *et al*[46] demonstrated the safety of these vaccines in adults.

PROGNOSIS

The data on long-term follow-up of patients with HFI is not available in the literature. However, In a recent study of HFI children with a mean follow-up of 10.3 ± 5.6 years, all of them were asymptomatic but had evidence of fatty liver in the majority and raised transaminases in some of them[26]. Interestingly, fructose intake in these children did not correlate with either of the two findings. The two case reports of HFI being diagnosed in adulthood because of self-imposed restriction to fructose in the diet since infancy may signify that the patients with HFI who adhere strictly to an FSS-free diet may have a good prognosis and normal lifespan[19,20]. On the other hand, when compliance is poor, renal and liver-related complications in the form of chronic renal insufficiency and hepatic fibrosis may ensue.

FUTURE RESEARCH

There is a need for data on the long-term outcome of HFI patients on an FSS-restricted diet to provide more insights into the consequences of NAFLD, cardiovascular disease and type 2 diabetes. Recent studies emphasized the role of F-1P in the hepatic fat accumulation of ALDOB-KO mice and the development of NAFLD. However, the exact role of endogenous fructose production (*via* the polyol pathway) in the accumulation of intrahepatic F-1P remains to be determined in animals as well as humans. Finally, clinical trials are required to show the benefit of KHK inhibition in the treatment of NAFLD in HFI patients.

CONCLUSION

HFI has diverse manifestations involving gastrointestinal, liver and renal issues. It mimics many metabolic conditions which present similarly. Other than genetics, there are no reliable laboratory markers that effectively diagnose this condition. A straight-forward FSS-free diet generally leads to a good long-term prognosis. There are however considerable controversies on the effect of dietary therapy on the liver, biochemistry, coexistence of steatosis and permissible levels of fructose in vaccines. Future research should be directed to basic sciences and long-term outcomes of this disease.

FOOTNOTES

Author contributions: Sarma MS conception, final drafting of the manuscript; Singh SK conception, primary drafting of the manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Country/Territory of origin: India

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 July 9; 11(4): 330-340

DOI: 10.5409/wjcp.v11.i4.330

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Case Control Study

Effects of adherence to the Mediterranean diet in children and adolescents with irritable bowel syndrome

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Soares RLS, Brazil; Ulasoglu C, Turkey

Received: December 13, 2021
Peer-review started: December 13, 2021
First decision: March 24, 2022
Revised: March 24, 2022
Accepted: April 28, 2022
Article in press: April 28, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Irritable bowel syndrome (IBS) is a highly prevalent gastrointestinal disorder in children and adults, which increased over the past twenty years. The Mediterranean diet is a well-known diet full of antioxidants and anti-inflammatory ingredients.

AIM

To evaluate the safety, tolerability, and effects of adherence to the Mediterranean diet on disease patterns in children and adolescents with IBS.

METHODS

This prospective, cross-sectional case-controlled study included 100 consecutive IBS patients diagnosed according to Rome IV criteria, aged 12-18 years. Patients

were subdivided into two groups (50 patients each); Group I received a Mediterranean diet, and Group II on their regular diet for six months. Besides IBS scores (IBS-SSS, IBS-QoL, and total score), different clinical and laboratory parameters were evaluated at the start and end of the study.

RESULTS

The Mediterranean diet was safe and well-tolerated in IBS patients. IBS children and adolescents with good adherence to the Mediterranean diet (KIDMED Score ≥ 8 points); group I showed significant improvement in IBS scores. IBS-SSS in the Mediterranean diet group was 237.2 ± 65 at the beginning of the study and decreased to 163.2 ± 33.8 at the end of the study ($P < 0.001$). It did not show a significant improvement in the group with a regular diet (248.3 ± 71.1 at the beginning of the study compared to 228.5 ± 54.3 at the study end with $P < 0.05$). The mean IBS-SSS in the Mediterranean diet group significantly improved compared with the group with a regular diet. Mean IBS-QoL in group I improved from 57.3 ± 12.9 at the start of the study to 72.4 ± 11.2 at the study end ($P < 0.001$) and significantly improved when compared to its level in group II at the study end (59.2 ± 12.7 with $P < 0.001$), while group II showed no significant improvement in IBS-QoL at the study end when compared to the beginning of the study (59.2 ± 11.7 with $P > 0.05$). The mean total IBS score in group I became 28.8 ± 11.2 at the end of our study compared to 24.1 ± 10.4 at the start ($P < 0.05$) and significantly improved when compared to its level in group II at the end of the study (22.1 ± 12.5 with $P < 0.05$), while in group II, non-significant improvement in the total score at the end of our study compared to its mean level at the start of the study (22.8 ± 13.5 with $P > 0.05$).

CONCLUSION

The Mediterranean diet was safe and associated with significant improvement in IBS scores in children and adolescent patients with IBS.

Key Words: Mediterranean diet; Irritable bowel syndrome; Children and adolescents; Safety; Tolerability

Core Tip: Diet is an essential factor in the pathogenesis and management of irritable bowel syndrome (IBS) patients. Studies involving different modalities of diets in IBS are lacking with contradictory results. The Mediterranean diet is a well-known balanced diet with anti-inflammatory properties. We prospectively studied 100 pediatric and adolescent patients with IBS, divided into two equal groups: group I received a Mediterranean diet, and group II had a regular diet for six months. Different clinical and laboratory parameters besides IBS scores were evaluated at the start and end of the study. The current study showed that the Mediterranean diet is a safe and effective low-cost new strategy in pediatric and adolescent patients with IBS.

Citation: Al-Biltagi M, El Amrousy D, El Ashry H, Maher S, Mohammed MA, Hasan S. Effects of adherence to the Mediterranean diet in children and adolescents with irritable bowel syndrome. *World J Clin Pediatr* 2022; 11(4): 330-340

URL: https://www.wjgnet.com/2219-2808/full/v11/i4/330.htm

DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.330

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the highly prevalent gastrointestinal disorders in children and adults, which increased over the past twenty years. It has a significant effect on the lives of affected children and their families and poses a substantial burden on healthcare systems[1]. It is classified as one of the functional gastrointestinal disorders; characterized by varying degrees of abdominal pain or discomfort, abdominal distension, altered bowel habits, and flatulence, and can be divided into four subtypes; IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), IBS with mixed bowel habits (IBS-M) and IBS unsubtyped (IBS-U)[2].

IBS pathogenesis is a poorly recognized disorder. Many theories were proposed to explain its pathogenesis[3]. It could be related to low-grade inflammation of the bowel mucosa. Dysbiosis with dysregulation of brain-gut axis function and bacterial overgrowth are commonly seen in IBS and are accepted theories that can explain the occurrence of IBS. Immune activation and visceral hypersens-

itivity are possible pathogenetic mechanisms associated with disturbed gastrointestinal motility[4,5]. A possible mechanism is dysregulated neurotransmitters such as cholecystokinin, vasoactive intestinal peptides, and serotonin with the abnormal gut-brain axis[6]. Moreover, food allergy or vitamin deficiency may play a role[7,8].

A few potential therapeutic modalities are available to treat children with IBS, and fewer of them have shown some benefits. Additionally, most of the described pathophysiological mechanisms and treatment choices are adult studies. These have surfaced as challenges when dealing with pediatric IBS, and they need to be overcome for the effective management of children with IBS[9].

The Mediterranean diet is characterized by many vegetables, fruits, bread, and other forms of cereal, rice, beans, and nuts. It also includes virgin olive oil as the principal source of fat, moderate amounts of dairy products (basically cheese and yogurt), moderate amounts of fish, and red meat in low quantities. The value of this dietary model is related to being a balanced and diverse diet that can provide most of the recommended macronutrients in proper proportions. It is characterized by a low content of saturated fatty acids, high monounsaturated fatty acids, high amounts of fiber, complex carbohydrates, and essential antioxidants[10]. They play a crucial role in preventing cardiovascular and cerebrovascular diseases, diabetes, obesity, neurodegenerative illnesses, and cancer[11,12].

Data suggests that the Mediterranean diet might be beneficial in alleviating the functional gastrointestinal symptoms through increased fiber and antioxidant consumption and a low intake of saturated fats and oligosaccharides[13,14]. However, information about the compliance and efficacy of the Mediterranean diet in children and adolescents with IBS is lacking. We aimed to study the effects of the Mediterranean diet on the symptoms of IBS in children and adolescents.

MATERIALS AND METHODS

We designed the study to evaluate the Mediterranean diet's tolerability, safety, and potential efficacy in children and adolescent patients with IBS. After explaining the study design, goals, and rights, all patients/caregivers provided written consent or permission. We conducted the study according to the Helsinki Declaration of 1975. This prospective randomized, case-controlled study was carried out in the Pediatric and Gastroenterology departments, Tanta University Hospital, Egypt, between September 2020 and July 2021. We included one hundred consecutive children and adolescents with IBS diagnosed according to Rome IV criteria[15], aged 12-18 years old. We divided the patients into two groups (50 patients each); the group I received a Mediterranean diet with good adherence (KIDMED Score ≥ 8 points), and Group II received a regular diet. Allocation to the groups was done using simple randomization. The study was not blind as we need to do patient and family education about the Mediterranean diet.

Inclusion criteria

Patients aged 12–18 years were diagnosed with childhood irritable bowel syndrome according to ROME IV criteria[15].

Exclusion criteria

Exclusion criteria include recent changes in IBS therapy, gastrointestinal infection, history of gut surgery or radiation, celiac disease, overweight or underweight according to the centile curve[16], chronic diseases such as renal failure or diabetes mellitus, and patients not adherent to the dietary protocol.

Study intervention: During the study period (6 mo), the patients in group I had the Mediterranean diet as a sole intervention besides their regular treatment. Patients (and their caregivers) received one-to-one education and counseling by a dietitian trained in the Mediterranean diet during each visit. Before each visit, patients and their families completed a three-day food intake record to help assure compliance with the diet. We closely followed up with the patients with the study team, including the dietitian, research pediatrician, and research gastroenterologist, for questions and problem intervention during the study period.

All participants had complete history taking, including dietetic history, thorough clinical examination, and anthropometric measurements such as height, weight, and body mass index (BMI). All participants with IBS filled out the IBS symptoms severity score (IBSSSS) questionnaire[17]. IBSSSS consists of 5 items (severity and frequency of abdominal pain, bloating, satisfaction with bowel habits, and quality of life) collected by direct interview using the visual analog scale (VAS). We scored each item on a scale from 0–to 100. A score below 75 means that the patient is in remission. The mild, moderate, and severe boundary scores are 75–175, 175–300, and above 300. A decrease in the score of 50 or more was considered a significant improvement. The patients also had an IBS quality of life (IBSQoL) questionnaire[18]. Effectiveness, reliability, and sensitivity of IBSSSS to treatment are verified by IBSQoL, which has 34 items, using a 5-choice scale (0–4). We transformed the summed total score to a 100-scale ranging from 0 (lowest) to 100 (highest). A total score of IBS measured by a VAS of 100 scales is used to evaluate the real IBS symptoms' impact on the quality of life, which was done at the same

frequency as IBSSSS and IBSQoL scores.

The patients also had routine laboratory investigations such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), serum calcium, random blood sugar, renal and hepatic functions, serum proteins, urine, and stool analysis. Fecal calprotectin was measured, and fecal blood in the stool was done in all included patients to exclude patients with inflammatory bowel disease. Follow-up visits were done at one, three, and six months. All IBS scores, laboratory parameters, and growth parameters (body weight, height, and BMI) were repeated at the end of our study.

KIDMED test: The Mediterranean diet quality index for children and teenagers (KIDMED test) is an instrument developed and validated by Serra-Majem *et al*[19]. It is used to evaluate the adherence of children and youths to the Mediterranean diet. The index ranges from 0 to 12. It is based on a 16-questions test that can be self-administered or conducted by interview (pediatrician, dietitian, *etc*.). Questions indicating a negative association concerning the Mediterranean diet are assigned a value of -1, and those with a positive aspect are given a value of +1. The total values from the processed test are categorized into three degrees: (1) ≥ 8, optimal adherence to the Mediterranean diet; (2) 4–7, adherence improvement is needed to adjust intake to Mediterranean patterns; and (3) ≤ 3, poor adherence to the Mediterranean diet[20].

The primary outcome of the current study was to assess the effects of adherence to the Mediterranean diet for six months on the IBS symptoms and severity score. The secondary outcome was to evaluate the safety and tolerability of the Mediterranean diet in children and adolescents with IBS.

Ethical considerations

This clinical study was conducted following the principles of the Declaration of Helsinki. At the beginning of the study, all subjects (and caregivers) were fully informed about the study objectives and their rights. They signed a written informed consent to participate in the study. The local Ethical Committee approved the study. The study is registered with the registration number PACTR-202008711997928. All authors had access to the study data and have reviewed and approved this final manuscript.

Statistical analysis

A sample size of 45 IBS patients in each group was required to achieve a power of more than 80 to detect a difference of 60 in the mean of the primary outcome point (IBSSSS) based on a previous study [21]. We recruited more than the estimated sample size, expecting a possible lack of adherence to the Mediterranean diet or withdrawal from the study, undermining our results. We collected and analyzed the data using SPSS version 17 (SPSS Inc., Chicago, IL, United States). We expressed the continuous data as mean ± SD. We used the paired *t*-test to compare the same group before and after treatment. An independent *t*-test was used for comparison between group 1 and group 2. We expressed the categorical variables as numbers and percentages and analyzed them using the Chi-square test. We used the Pearson correlation to evaluate the correlation between the Mediterranean diet with IBS scores. The statistical significance was defined as $P < 0.05$.

RESULTS

This study included 100 children and adolescent patients with IBS aged 12-18 years; divided into two groups included 50 patients. Group-I had 27 males and 23 females with a mean age of 15.5 ± 1.8 years, and group II had 26 males and 24 females with a mean age of 15.2 ± 1.5 years. Before the study, the average duration of IBS symptoms was 34.4 ± 9.1 mo in group I and 35.3 ± 9.8 mo in group II. We illustrated the demographic, growth parameters, clinical subtypes, IBS severity, treatment drugs, and IBS scores in both groups in Table 1. We found no significant differences between the two groups in all measured parameters at the start of our study.

Basic laboratory data in all patients done at start of our study (Table 2) with non-significant differences between both groups regarding serum albumin(4.1 ± 0.9 g/dL in Group-I and 4.3 ± 0.88 in Group-II with $P = 0.93$) ,serum triglycerides(120.7 ± 45.6 mg/dL in Group I and 112.9 ± 49.4 in Group-II with $P = 0.44$), serum cholesterol (154.0 ± 36.6 mg/dL in Group I and 163.6 ± 44.1 in Group II with $P = 0.35$),random blood glucose level (86.20 ± 20.20 mg/dL in Group I and 85.7 ± 9.70 in Group II with $P = 0.91$), hemoglobin level (13.10 ± 1.60 g/dL in Group-I and 13.6 ± 1.80 in Group II with $P = 0.47$). Fecal calprotectin was normal in both groups (12 ± 9.10 μg/g in group I and 11 ± 8.80 in Group II with p 0.52), and it was done to exclude patients with inflammatory bowel disease.

The Mediterranean diet was well tolerated in IBS patients. Only three patients could not tolerate it and were withdrawn from the study (one after one month and two patients after three months, replaced by other patients; Figure 1). No adverse events regarding the Mediterranean diet were reported as reflected by non-significant changes in growth parameters (height, weight, and BMI), laboratory parameters (serum albumin, triglycerides, cholesterol, glucose, and hemoglobin levels) at the end of our study when compared to the same parameters at the start of the research and when compared to group-

Table 1 Demographic data and clinical characteristics in irritable bowel syndrome patients' groups before the start of the Mediterranean diet

Variable	Group I (Mediterranean diet) (*n* = 50)	Group II (*n* = 50)	*P* value
Age (yr)	15.50 ± 1.80	15.2 ± 1.5	0.88[1]
Sex (M: F)	27:23	26:24	0.90[2]
Height (z-score)	0.04 ± 1	0.04 ± 1.00	0.66[1]
Weight (z-score)	0.14 ± 0.99	0.12 ± 0.89	0.83[1]
BMI (z-score)	0.18 ± 0.88	0.17 ± 1.02	0.77[1]
IBS subtypes			0.47[2]
IBS-C	22 (44 %)	21 (42 %)	
IBS-D	20 (40 %)	21 (42 %)	
IBS-M	4 (8 %)	5 (10 %)	
IBS-U	2 (4 %)	3 (6 %)	
IBS severity			0.55[2]
Mild	12 (24%)	14 (28 %)	
Moderate	33 (66%)	31 (62 %)	
Severe	5 (10%)	5 (10 %)	
Duration of IBS symptoms (mo)	34.40 ± 9.10	35.30 ± 9.80	0.58[1]
Treatment drugs[3]			0.66[1]
Gastroprokinetic	50	50	
Antidepressants	11	12	
Antacids	18	20	
Antibioticsprobiotics	924	723	
IBS-SSS	237.20 ± 65	248.30 ± 71.10	0.68[1]
IBS-QoL	57.30 ± 12.90	59.10 ± 11.70	0.71[1]
Total score	24.10 ± 10.40	22.80 ± 13.50	0.82[1]

[1]Independent *t*-test.
[2]Chi-square test.
[3]Treatment drugs for one month before starting the study and during the whole study period.
BMI: Body mass index; IBS: Irritable bowel syndrome; IBS-C: IBS constipation; IBS-D: IBS diarrhea; IBS-M: IBS mixed; IBS-U: IBS unsubtyped; IBS-SSS: IBS symptoms severity score questionnaire; IBS-QoL: IBS quality of life questionnaire.

Table 2 Laboratory data of all patients at the start of the study

Variable	Group I (Mediterranean diet) (*n* = 50)	Group II (*n* = 50)	*P* value
Albumin (g/dL)	4.10 ± 0.90	4.30 ± 0.88	0.93
Triglycerides (mg/dL)	120.70 ± 45.60	112.90 ± 49.40	0.44
Cholesterol (mg/dL)	154.00 ± 36.60	163.60 ± 44.10	0.35
Glucose (mg/dL)	86.20 ± 20.20	85.70 ± 9.70	0.91
Hemoglobin (g/dL)	13.10 ± 1.60	13.60 ± 1.80	0.47
Fecal calprotectin (μg/g) *n* < 50	12 ± 9.10	11 ± 8.80	0.52

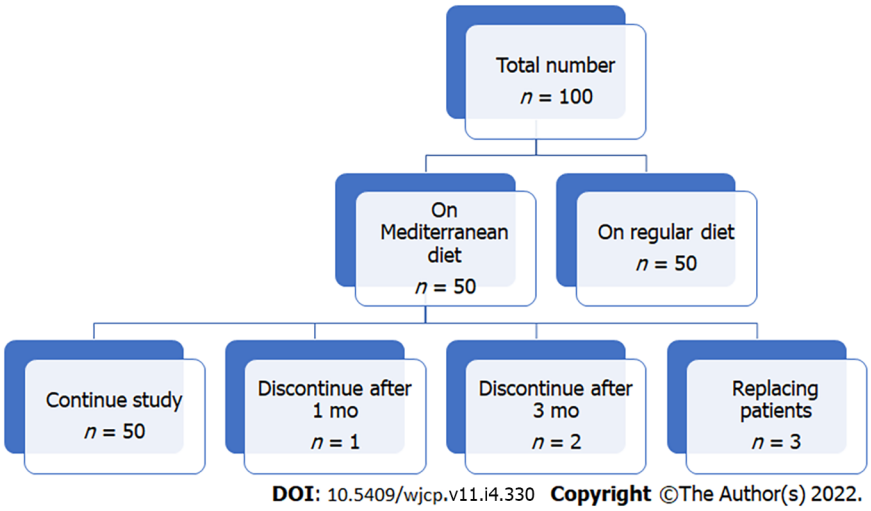
II at the end of our study (Table 3). At the end of our research, there was a significant improvement in all IBS scores in IBS patients who received a Mediterranean diet (group I) compared to such scores at the start of the study and when compared to group II at the end of the study (Table 3). The mean IBS-SSS in group-I became 163.20 ± 33.80 at the study end compared to 237.20 ± 65 at the start ($P < 0.001$), with

Table 3 Growth parameters, laboratory data, and irritable bowel syndrome scores in all patients at the start versus at the end of the study

Variables		Group I (Mediterranean diet) (n = 50)			Group II (n = 50)			P value[1]
		Start	End	P value	Start	End	P value	
Growthparameters	Height (z-score)	0.04 ± 1	0.04 ± 0.92	0.88	0.04 ± 1.00	0.04 ± 0.99	0.63	0.18
	Weight (z-score)	0.14 ± 0.99	0.13 ± 1.0	0.54	0.12 ± 0.89	0.12 ± 0.55	0.61	0.36
	BMI (z-score)	0.18 ± 0.88	0.17 ± 0.69	0.6	0.17 ± 1.02	0.16 ± 1.08	0.80	0.55
Laboratory data	Albumin (g/dL)	4.10 ± 0.90	4.3 ± 0.94	0.77	4.30 ± 0.88	4.50 ± 0.91	0.49	0.54
	Triglycerides (mg/dL)	120.7 0 ± 45.60	118.50 ± 47.10	0.90	112.90 ± 49.40	115.20 ± 50.40	0.51	0.65
	Cholesterol (mg/dL)	154 ± 36.60	155.80 ± 32.20	0.56	163.60 ± 44.1	168.10 ± 42.90	0.63	0.28
	Glucose (mg/dL)	86.2 ± 20.20	81.90 ± 24.50	0.27	85.7 ± 9.7	87.30 ± 11.20	0.28	0.73
	Hemoglobin (g/dL)	13.1 ± 1.60	14.00 ± 1.10	0.66	13.60 ± 1.80	13.20 ± 1.50	0.71	0.33
	Fecal calprotectin (μg/g) n < 50	12 ± 9.10	11.30 ± 9.90	0.81	11 ± 8.80	10.80 ± 9.20	0.88	0.62
IBS scores	IBS-SSS	237.20 ± 65	163.20 ± 33.80	0.001[1]	248.3 ± 71.1	228.50 ± 54.30	0.29	< 0.001[1]
	IBS-QoL	57.30 ± 12.9	72.40 ± 11.2	<0.001[1]	59.1 ± 11.7	59.20 ± 12.70	0.77	< 0.001[1]
	Total score	24.10 ± 10.4	28.80 ± 11.20	0.02[1]	22.8 ± 13.50	22.10 ± 12.50	0.94	0.03[1]

[1]P value is for group I *vs* group II at the end of the study.

BMI: Body mass index; IBS: Irritable bowel syndrome; IBS-SSS: IBS symptoms severity score questionnaire; IBS-QoL: IBS quality of life questionnaire.



DOI: 10.5409/wjcp.v11.i4.330

Figure 1 The flow chart of the study.

significant improvement when compared to group-II at the study end (228.50 ± 54.30) with P < 0.001, while in group-II, there was no substantial improvement in IBS-SSS at the study end compared to its mean level at the start of the study (228.50 ± 54.30 *vs*. 248.30 ± 71.10 with P = 0.29). Mean IBS-QoL in group-I became 72.40 ± 11.20 at the end of our study compared to 57.30 ± 12.90 at the start (P < 0.001) and significantly improved when compared to its level in group II at the end of the study (59.20 ± 12.70 with P < 0.001), while in group II, non-significant improvement in IBS-QoL at the end of our study compared to its mean level at the start of the study (59.20 ± 12.70 *vs* 59.10 ± 11.70 with P = 0.77). The mean total score in group I became 28.80 ± 11.20 at the end of our study compared to 24.10 ± 10.40 at the start (P = 0.02) and significantly improved when compared to its level in group II at the end of the study (22.10 ± 12.50) with P = 0.03, while in group II, non-significant improvement in the total score at the end of our study compared to its mean level at the start of the study (22.10 ± 12.50 *vs*. 22.80 ± 13.50 with P = 0.94). These changes reflect the Mediterranean diet's positive impact on the symptoms and lifestyle of IBS children and adolescents.

DISCUSSION

What should we eat? This question is one of the most frequently asked questions by patients with IBS and their caregivers. Many patients also seek dietary guidelines because the diet is considered safer than medical therapies. Treating IBS symptoms by modifying the patient's diet has been one of the most desirable therapeutic strategies for a long time. Unfortunately, the scarcity of high-quality evidence supporting a specific dietary intervention resulted in the unnecessary exclusion of diets despite lacking evidence of efficacy and safety, especially in pediatric age groups[22]. The current study found that the Mediterranean diet was safe and well-tolerated in IBS patients. Compared to the control group, good adherence to the Mediterranean diet resulted in significant improvement in IBS scores and IBS-QoL and total IBS scores. Many previous studies on children and adolescents showed a negative correlation between compliance with the Mediterranean diet and the development of various diverse pathological conditions, such as obesity, asthma, and recurrent cold[23,24].

Considering the potential association of adherence to the Mediterranean diet with the development of functional gastrointestinal disorders (FGIDs), much data from the adult population supports the beneficial effect of the Mediterranean diet on preventing the development of or lessening the gastrointestinal (GI) symptoms in patients with GI disorders, both functional (IBS, functional dyspepsia, gastroesophageal reflux) or organic (inflammatory bowel disease)[25]. Elmaliklis *et al*[26] showed that adherence to the Mediterranean diet (including functional foods containing probiotics, prebiotics, antioxidants, fiber, vitamins, minerals) was significantly lower in adult patients with various gastrointestinal disorders such as IBS, Crohn's disease, ulcerative colitis, and gastroesophageal reflux than in controls.

Another Southern Italian study by Zito *et al*[27] investigated the association between adherence to the Mediterranean diet and the onset of symptoms in adults with functional dyspepsia or IBS. They demonstrated a negative correlation between compliance with the Mediterranean diet and the development of gastrointestinal symptoms. They concluded that good adherence to the Mediterranean diet could prevent the development of gastrointestinal symptoms in adults. Moreover, they showed that patients with functional dyspepsia and IBS between 17 and 24 years had significantly poorer Mediterranean diet adherence than the age-matched controls. Interestingly, Strisciuglio *et al*[28] studied the adherence to the Mediterranean diet in children and adolescents suffering from inflammatory bowel disease with an age-matched population with FGIDs (gastroesophageal reflux and functional constipation). It was found that children/adolescents with inflammatory bowel syndrome had poorer adherence to the Mediterranean diet than those with FGIDs. However, there is no data on the association of Mediterranean diet adherence with the prevalence of FGIDs in children and adolescents.

In the current study, the Mediterranean diet was well tolerated in IBS patients; only three patients could not tolerate it and were withdrawn from the study (one after one month, two patients after three months, and replaced by other patients). No adverse events regarding the Mediterranean diet were reported as reflected by non-significant changes in growth parameters (height, weight, and BMI), laboratory parameters (serum albumin, triglycerides, cholesterol, glucose, and hemoglobin levels) at the end of our study when compared to the same parameters at the start of the research and when compared to group II at the end of our study.

Our study found positive effects of the Mediterranean diet in children and adolescents with IBS, with significant improvements in all IBS scores compared to the patients on the regular diet. These effects may be due to the specific components of the Mediterranean diet, which is characterized by a high intake of plant-based foods (vegetables, legumes, fruits, nuts, whole grain cereals), olive oil as the primary fat source, moderate amounts of dairy products (yogurt and cheese), and low or moderate cuts of fish and meat, with well-known antioxidant and anti-inflammatory properties[10]. Regular consumption of such products induces an accumulation of nitrate/nitrite/NO, polyunsaturated fatty acids (PUFA), and polyphenolic compounds, such as resveratrol, in the human body[12]. The most important dietary sources of NO_3^- for the human body include green vegetables such as spinach, lettuce, collard greens and radishes, beets, and meat. At the organ level, NO_2^--dependent vasorelaxation plays a role in hypoxic blood flow regulation and improves tissue microcirculation[29,30].

The Mediterranean diet traditionally includes an abundance of vegetables and fish; both contain a substantial amount of diverse PUFA (ω-3, 6, 9). Briefly, PUFAs are divided into three classes based on the position of the first double bond from the methyl carbon, labeled "ω": ω-3 (DHA-docosahexaenoic, EPA-eicosapentaenoic, and ALA-α-linolenic), ω-6 (LA-linoleic, GLA-γ-linolenic, and AA-arachidonic); and ω-9 (OA-oleic). Extensive studies have revealed that the protective effects of EPA and DHA could be mediated by forming reactive lipid molecules called Resolvins[31]. Resolvins (E1 and D1) have a well-known anti-inflammatory property by preventing polymorphonuclear neutrophil (PMN) activation and translocation into the tissue[32,33]. Resolvin E1 regulates cytokine/chemokine production[34] and inhibits TNFα-induced nuclear translocation of NF-kB[35]. Freeman *et al*[36] characterized several electrophilic oxo-derivatives of DHA and EPA, synthesized in activated macrophages *via* the cyclooxygenase-2 dependent pathway. Like Resolvins, these also possess strong anti-inflammatory properties.

Regular consumption of grape wine is an integral element of the Mediterranean diet. The anti-inflammatory benefits of grape wine could be attributed to its phenolic components. Polyphenolic compounds such as quercetin, resveratrol, or catechins are potent antioxidants; thus, one of the mechanisms of protection they provide might be the inhibition of oxidative stress[37]. Moreover, the effect of the Mediterranean diet on gut microbiota may be an additional factor. Previous studies demonstrated that good adherence to the Mediterranean diet was associated with lower *Escherichia coli* (*E. coli*) counts and a higher *Bifidobacteria* to *E. coli* ratio[38].

The strength of the current study is that it is the first report on the association between adherence to the Mediterranean diet and IBS symptoms in children and adolescents. The main limitation is the cross-sectional design, which allows the assessment of good associations but not conclusions on causality. The study was also from a single center, so the data cannot be generalized.

CONCLUSION

Results of the current study indicate that good adherence to the Mediterranean diet is safe and associated with significant improvement in IBS-score in children and adolescents. The mechanisms underlying this association and the causality between the Mediterranean diet and IBS need further clarification. If other studies with extensive metabolomic analysis and microbiome assessments confirm the current study's findings, this will complete the picture of the diet–health interaction and relationship. Until then, we should encourage children and adolescents to follow the Mediterranean diet to have a place among other measures in minimizing the symptoms.

ARTICLE HIGHLIGHTS

Research background

Irritable bowel syndrome (IBS) has a significant effect on the lives of affected children and their families and poses a substantial burden on healthcare systems. A few potential therapeutic modalities are available to treat children with IBS, and fewer of them have shown some benefits.

Research motivation

A few potential therapeutic modalities are available to treat children with IBS, and fewer of them have shown some benefits. The authors need to conduct more studies to help patients with IBS alleviate their symptoms.

Research objectives

The authors aimed to study the effects of the Mediterranean diet on the symptoms of IBS in children and adolescents.

Research methods

The authors studied one hundred consecutive IBS patients diagnosed according to Rome IV criteria, aged 12-18 years old. The authors divided the patients into two groups (50 patients each), the group I received a Mediterranean diet with good adherence (KIDMED Score ≥ 8 points), and Group II received a regular diet.

Research results

IBS children and adolescents with good adherence to the Mediterranean diet (KIDMED Score ≥ 8 points); group I showed significant improvement in IBS scores. IBS-SSS in the Mediterranean diet group was 237.2 ± 65 at the beginning of the study and decreased to 163.2 ± 33.8 at the end of the study ($P < 0.001$). It did not show a significant improvement in the group with a regular diet (248.3 ± 71.1 at the beginning of the study compared to 228.5 ± 54.3 at the study end with $P < 0.05$). The mean IBS-SSS in the Mediterranean diet group significantly improved compared with the group with a regular diet. Mean IBS-QoL in group I improved from 57.3 ± 12.9 at the start of the study to 72.4 ± 11.2 at the study end ($P < 0.001$) and significantly improved when compared to its level in group II at the study end (59.2 ± 12.7) with $P < 0.001$, while group II showed no significant improvement in IBS-QoL at the study end when compared to the beginning of the study (59.2 ± 11.7 with $P > 0.05$). The mean total IBS score in group I became 28.8 ± 11.2 at the end of our study compared to 24.1 ± 10.4 at the start ($P < 0.05$) and significantly improved when compared to its level in group II at the end of the study (22.1 ± 12.5) with $P < 0.05$, while in group II, non-significant improvement in the total score at the end of our study compared to its mean level at the start of the study (22.8 ± 13.5) with $P > 0.05$.

Research conclusions

Mediterranean diet was safe and associated with significant improvement in IBS scores in children and adolescent patients with IBS.

Research perspectives

The authors need to extend our study for a longer duration. We also need to investigate the effects of the Mediterranean diet on the various GIT functions, including bowel movement, stool consistency, and the impact on the gut microbiota.

ACKNOWLEDGEMENTS

We thank the anonymous referees and editors for their valuable suggestions.

FOOTNOTES

Author contributions: Hasan S, El-Amrousy D, and El-Ashry H performed the clinical part and collected the data; Maher S performed the laboratory part; Mohammed MA did the statistical analysis; Al-Biltagi M analyzed the data and wrote the manuscript; and All the authors revised and agreed on the final version of the manuscript.

Institutional review board statement: We performed to study according to the latest version of Helsinki's Declaration. The Research and Ethics Committee at the Ministry of Health, Kingdom of Bahrain, approved the study.

Informed consent statement: An informed written consent was signed by all subjects (and their caregivers).

Conflict-of-interest statement: None of the authors had potential undisclosed conflicts of interest.

Data sharing statement: Data are available upon reasonable request.

STROBE statement: The authors have read the STROBE statement, and the manuscript was prepared and revised according to the STROBE statement.

Country/Territory of origin: Egypt

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 July 9; 11(4): 341-350

DOI: 10.5409/wjcp.v11.i4.341

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Study

Prevalence, phenotype and medication for the pediatric inflammatory bowel disease population of a state in Southeastern Brazil

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Day AS, New Zealand; Wen XL, China; Xiao Y, China
A-Editor: Elpek GO, Turkey

Received: January 7, 2022
Peer-review started: January 7, 2022
First decision: March 9, 2022
Revised: March 23, 2022
Accepted: June 3, 2022
Article in press: June 3, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Inflammatory bowel disease (IBD) can lead to social and economic impacts worldwide. In Brazil, where its adult prevalence is increasing, the epidemiology of the pediatric population is not well known, although there is a documented increase in pediatric IBD incidence worldwide. Brazil has continental dimensions, and Espírito Santo is a state of southeastern Brazil, the region with the highest demographic densities and is the economically most important in the country.

AIM

To assess the prevalence, incidence, phenotype and medications in a Southeastern Brazilian pediatric population.

METHODS

Data were retrieved from the Public Medication-Dispensing System of the Department of Health in Espírito Santo state from documentation required to have access to highly expensive medication from August 1, 2012 to July 31, 2014. There were 1048 registered patients with IBD of all ages, and of these patients, the cases ≤ 17 years were selected. The data were obtained through the analysis of administrative requests for these medications and included medical reports, endoscopy exams, histopathology and imaging tests, which followed the Clinical Protocols and Therapeutic Guidelines of the Brazilian Government. Only confirmed cases of IBD were included in the study.

RESULTS

There were 55 pediatric patients/1048 registered patients (5.34%), with Crohn's disease (CD) representing 30/55 (55%), ulcerative colitis (UC) 24/55 (43.6%) and 1 unclassified IBD, a significant difference from adult patients (P = 0.004). The prevalence of IBD in pediatric patients was 5.02 cases/100.000 inhabitants; the incidence in 2014 was 1.36 cases/100.000 inhabitants. The mean age at diagnosis was 12.2 years (± 4.2). There were 7 children diagnosed up to 6 years old, 7 between 7 to 10 years old and 41 between 11 and ≤ 17 years old. There was no difference in the distribution of UC and CD between these age categories (P = 0.743). There was no difference in gender distribution in relation to adults. Children and adolescents with UC had a predominance of pancolitis, unlike adults (P = 0.001), and used aminosalicylates and immunomodulators for their treatment. Pediatric patients with CD did not present a difference in disease location but had a higher frequency of fistulizing behavior (P = 0.03) and perianal disease phenotype (P = 0.007) than adult patients. Patients with CD used more immunomodulators and biological therapy. Treatment with biological therapy was more frequently used in pediatric patients than in adults (P < 0.001).

CONCLUSION

Although the data from this study demonstrate that incidence and prevalence rates are low in southeastern Brazil, these data demonstrate the severity of IBD in pediatric patients, with the need for early diagnosis and therapy, avoiding serious damage.

Key Words: Inflammatory bowel disease; Pediatric; Prevalence; Phenotype; Brazil

Core Tip: In Brazil, where the prevalence of inflammatory bowel disease (IBD) in adults is increasing, the epidemiology of the pediatric population is not well known, although there is a documented increase in pediatric IBD incidence worldwide. Espírito Santo is a state of southeastern Brazil, the region with the highest demographic densities and that is the economically most important in the country. Our epidemiological data, including behavior and medication, evaluate the comparison between the pediatric and adult age groups. Therefore, this study has the potential to reinforce the need for adequate care of pediatric patients with IBD, with the potential to influence public health policies.

Citation: Martins AL, Fróes RSB, Zago-Gomes MP. Prevalence, phenotype and medication for the pediatric inflammatory bowel disease population of a state in Southeastern Brazil. *World J Clin Pediatr* 2022; 11(4): 341-350

URL: https://www.wjgnet.com/2219-2808/full/v11/i4/341.htm

DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.341

INTRODUCTION

Inflammatory bowel disease (IBD) can lead to social and economic impacts worldwide. In Brazil, where its prevalence is increasing, the epidemiology of the pediatric population is not well known, although there is a documented increase in pediatric IBD incidence worldwide[1,2]. Represented by ulcerative colitis (UC), Crohn's disease (CD) and unclassified inflammatory bowel disease (U-IBD), these diseases have a chronic evolution, with more severe clinical manifestations and complex treatment when started in the pediatric age group[3,4]. IBD initiation in childhood and adolescence is described in up to 25% of patients[3,5].

The main signs and symptoms of IBD in the pediatric age range are diarrhea, abdominal pain and stunting, which can be confused with other diseases, causing a delay in diagnosis and inappropriate therapies. Considering the more aggressive phenotypes and worse therapeutic response in this age group, early recognition of the disease becomes extremely important[4-6].

There are still few epidemiological studies in the pediatric age group; however, this information is relevant as it can define characteristics specific to each region and provide improvements to the health system with programming of costs related to propaedeutics and treatment. In addition, early diagnosis and adequate therapy could provide better results, that is, deep remission, with better physical, social and school health quality[4].

Some epidemiological studies of IBD have been carried out in Brazil[7,8]; however, the majority were in reference centers for adult care, and other recent studies used the database of records of the "Sistema Único de Saúde (SUS)" which is Brazilian Health System[9,10]. Brazil has continental dimensions, but

there is no obligation to notify a case of IBD in the country, and there is no unified registry, although the Brazilian government provides medication for the treatment of IBD through the sector of the supply of high-cost drugs for chronic diseases, which all citizens are entitled to access. The aim of this study is to evaluate the epidemiology, phenotype and treatment of IBD in pediatric patients in the state of Espírito Santo, a state of Southeastern Brazil, the region with the highest demographic densities and most economic importance in the country, to contribute to possible improvements, both in the assistance and administrative areas of the health service.

MATERIALS AND METHODS

Study location and data collection

The study was conducted between August 1, 2012, and July 31, 2014, in the Public Medication Dispensing System of the Department of Health of Espírito Santo, sector for Pharmaceutical Assistance, which is responsible for dispensing medications for patients with IBD in the whole state.

This study evaluated patients with a confirmed diagnosis of IBD aged ≤ 17 years old from a total sample containing 1048 patients of all ages, with phenotype and treatment available, who received medications through the Federal Government and for whom the incidence and prevalence of IBD was determined in a previous study[9].

In medication-dispensing services, the evaluation is conducted by a gastroenterologist doctor, in this case, the author of the research, who was responsible for dispensing the medication for IBD. The data analyzed were obtained through the analysis of administrative requests of these medications and included personal identification documents, medical reports, endoscopy exams, histopathology and imaging tests, which followed the Clinical Protocols and Therapeutic Guidelines of the Brazilian Government[11,12].

As the study included patients aged 17 years, we chose to use the Montreal classification to establish the phenotype of IBD for CD and UC[13]. For the patients whose endoscopic examination, imaging, and histopathological and laboratory examinations associated with medical reports had difficulty in defining CD and UC, the terminology "unclassified inflammatory bowel disease" (U-IBD) was applied.

Dependent variables included the diagnosis, IBD classification, medications, new cases (diagnosis made less than 12 months before the time of the process of evaluation at the Pharmaceutical Assistance) and old cases (diagnosis older than 12 mo), distributed in assessment year 1 (August 1, 2012 to July 31, 2013) and year 2 (August 1, 2013 to July 31, 2014). Independent variables included age and sex.

Study limitations

The study was conducted with secondary data, and some information may not be complete. Not all patients with CD included in the study had an upper gastrointestinal endoscopy/biopsy, and magnetic resonance. Medical reports and few older documents have been damaged due to time, making it impossible to define the localization of the disease in some cases.

In Brazil, medications for IBD are expensive and provided by the Public Health care System for patients treated in the public and private systems. However, it is possible that some patients in the private system obtained their oral medications directly from drugstores without utilizing the public system.

Ethical considerations

This study was approved by the Ethics and Research Committee of the Nossa Senhora da Gloria Children's Hospital (CAAE 19602813.8.0000.5069) after obtaining authorization from the State Office for Pharmaceutical Assistance. The terms clarification and consent were waived because the data used were secondary data.

Statistical analysis

An Excel spreadsheet was used to collect all the data, and all patients aged ≤ 17 years of age when diagnosed were selected, building a new Excel table that was analyzed using SPSS Statistics 20.0 software. Data were tabulated and analyzed through descriptive analysis of frequencies, percentages, averages, and standard deviations (SD). To determine associations between categorical variables, a chi-square test was used, and Fisher's exact test was also used when appropriate. A P value of < 0.05 was considered statistically significant.

Data from the Brazilian Institute of Geography and Statistics (IBGE) were used to calculate prevalence and incidence based on the estimated census of 2014, in which the total estimated population of Espírito Santo was 3.885.049 inhabitants[14] and the population ≤ 17 years old was 1.095.669 inhabitants[15]. To calculate incidence, new cases arising in the second year of the study were used (August 1, 2013, to July 31, 2014), and prevalence was calculated as the number of children (≤ 17 years) who received dispensed IBD-related drug prescriptions during the study period that ended on July 31, 2014.

RESULTS

Incidence and prevalence

Out of a total sample of 1048 patients analyzed in medication-dispensing services at the Pharmaceutical Assistance in Espírito Santo who were diagnosed with IBD, 55 (5.24%) were diagnosed at ≤ 17 years old. There were predominance of CD 30/55 (54.5%), with UC 24/55 (43.6%) and 1 had a diagnosis of U-IBD, different from the sample of adult patients (P = 0.004).

In 2013, 33 patients were registered, and in 2014, 22 patients were registered, for a total of 55 cases. Of the 22 cases registered in 2014, 14 were new cases: 7 were CD and 7 were UC. The calculated prevalence and incidence are based on the estimated census of 2014[14,15]. The prevalence of IBD in pediatric patients in the state of Espírito Santo, Brazil, was 5.02 cases/100.000 inhabitants/year, while the incidence in 2014 (year) was 1.27 cases/100.000 inhabitants/year. The prevalence of CD was 2.73/100.000 inhabitants, and the incidence was 0.63 cases/100.000 inhabitants/year. The prevalence of UC was 2.19/100.000 inhabitants, and the incidence was the same as that of CD (0.63 cases/100.000 inhabitants).

Demographic characteristics

Seven children were diagnosed up to 6 years old, 7 were diagnosed between 7 to 10 years of age and 41 were diagnosed between 11 and 17 years of age, and there was no difference in the distribution of UC and CD between these age categories (P = 0.743), as summarized in Table 1. The distribution of sex is shown in Figure 1, but the difference was not significant (P = 0.357).

Disease Phenotype and Medication

The distribution of UC and CD phenotypes was compared with that in the adult group, and we observed the highest frequency of pancolitis in UC and perianal disease in CD in the group ≤ 17 years, as shown in Table 2. Perianal disease is more associated with fistulizing disease in CD, as shown in Figure 2. The distribution of biologics used in this group was compared with that in the adult group, and no significant difference was observed, as shown in Table 3.

Oral aminosalicylates (mesalazine/sulfasalazine) were the drugs most used in UC, and in CD, we observed a greater use of the immunomodulators than aminosalicylates, as shown in Figure 3.

DISCUSSION

This is the first epidemiological study of the incidence and regional prevalence of IBD in a pediatric/adolescent population in a state of our country based on searches at the National Center in Biotechnology Information. There is a documented increase in the incidence and prevalence of pediatric IBD worldwide, and although this information is of great value for the planning of the health system, the few existing studies present different methodologies, which makes a more reliable analysis difficult [3,16-20].

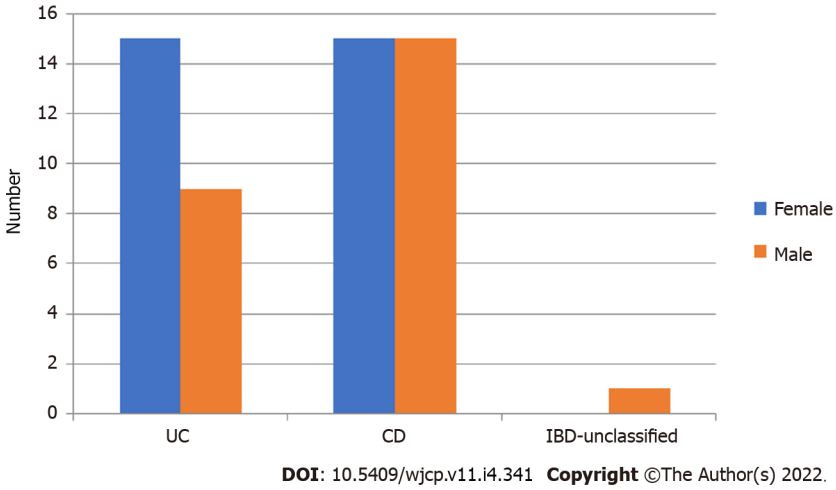
In this study, we observed that the prevalence of IBD ≤ 17 years in the state of Espírito Santo, southeastern Brazil, in 2014 was 5.02 cases/100.000 inhabitants/year (CD: 2.73/100.000 and UC: 2.19/100.000), higher than the prevalence of IBD in Mexico[18] in Central America in patients < 18 years old, with 0.18 cases/100.000 inhabitants, but much lower than other regions, as in the 2017 study by Ludvigsson *et al*[3], in Sweden that analyzed data between 1993 to 2010 and reported 75 cases/100.000 inhabitants (CD 29/100.000 and UC: 25/100.000) and the 2019 study by Jones *et al*[21] in Scotland that analyzed data from 2009 to 2018 and found prevalence in children under 17 of 106 cases/100.000 inhabitants. Roberts *et al*[22], 2020, in a systematic review of pediatric IBD in Europe, found few prevalence studies using national and regional data. The highest prevalence rates of CD were approximately 60/100.000 in Hungary from 2011 to 2013. Regarding UC, the highest prevalence was approximately 30/100.000 in 3 regions: Hungary, Sweden and Denmark[22]. In North America, in Canada (Manitoba), 1978-2007 study showed an increase in prevalence from 3.1 to 18.9/100.000 in CD and UC from 0.7 to 12.7/100.000 inhabitants in UC[23].

The incidence of pediatric IBD in this study was 1.36 cases/100000 inhabitants/year, with equivalent CD and UC values of 0.63/100,000. Our incidence was higher than that observed in Argentina (0.4/100.000)[17] and Mexico (0.04/100.000)[18] but lower than that in other areas of the world, as noted in the 2018 systematic review of the incidence of IBD in children/adolescents from Sýkora *et al*[16], from 1985 to 2018, which found that the highest annual pediatric incidences of IBD were 23/100.000 person/years in Europe (Finland), 15.2/100.000 in North America (Canada) and 11.4/100.000 in Asia/Middle East and Oceania. However, the highest pediatric CD incidence was 13.9/100.000 in North America (Canada), followed by 12.3/100000 in Europe (France). Regarding UC, the highest annual incidence was 15.0/100.000 in Europe (Finland) and 10.6/100.000 in North America (Canada)[16]. In the analysis of incidence and prevalence, we can conclude that we still have low rates.

Table 1 Demographic data from pediatric and adult patients diagnosed with inflammatory bowel disease in the state of Espírito Santo, from August 2012 to July 2014

Characteristics	Total amount		Age at diagnosis ≤ 17 yr		Age at diagnosis ≥ 18 yr		*P* value
	n	%	*n*	%	*n*	%	
	1.048	(100)	55	(5.24)	993	(94.76)	
Mean age at diagnosis (yr)	39.2	± 16.1	12,2	± 4.2	40,7	± 15.1	NA
Mean actual age (yr)	42.0	± 16.1	15,3	± 4.6	43,5	± 15.0	NA
Sex							
Male	433	(41.3)	25	(44.6)	408	(41.1)	0.522
Female	615	(58.7)	30	(55.4)	585	(58.9)	
IBD							
Crohn's disease	357	(34.1)	30	(54.5)	327	(32.9)	**0.004**
Ulcerative colitis	669	(63.2)	24	(43.7)	645	(65)	
Unclassified IBD	22	(2.1)	1	(1.8)	21	(2.1)	

Continuous values are expressed as mean ± SD and analyzed. Proportions are expressed in *n* (%) and analyzed by the chi-square test. NA: Not available; IBD: Inflammatory bowel disease..



DOI: 10.5409/wjcp.v11.i4.341

Figure 1 Distribution of inflammatory bowel diseases in the pediatric population regarding gender. UC: Ulcerative colitis; CD: Crohn's disease; IBD: Inflammatory bowel disease.

The frequency of IBD in the pediatric range in our region was 5.34%, below the global values (10% to 25%)[2,6]. Despite different methodologies, this study had a higher frequency than the West-Eastern European study in 2014 of children under 15 years of age, which presented a frequency of 3% (45/1560 patients)[19], and less than a study in Mexico in 2015, which showed that the frequency in pediatric patients under 18 years was 7.1% (32/479)[18].

In the distribution of IBDs, there was a slight predominance of CD (54.5%) compared to UC. Worldwide data are quite variable. A 2014 study by Burisch of West-Eastern Europe[19] found that Western Europe has an equivalent distribution between CD/UC, while Eastern Europe had a predominance of UC[19]. In Argentina[17], equivalence between CD and UC was observed. The study by Van Limbergem in the United Kingdom, 2008[6] observed a predominance of CD (66%) *vs*. UC (23.7%) in 416 pediatric patients < 17 years old. Buderus *et al*[20], 2015, found a predominance of CD (64%) in relation to UC (29%) in Germany, and Chaparro, 2018[24] also found a predominance of CD (61.5%) in Spain (2007-2017). In Mexico, the Yamamoto-Furusho study[18] observed a predominance of UC in 2015 (85%). We still have much diversity in the distribution of the disease.

In the study of the UC phenotype, pancolitis prevailed, similar to other pediatric studies worldwide [16-18,21,24]. In addition, our study showed a significant difference in relation to the adult group, with a higher frequency of extensive disease (pancolitis) in younger people.

Table 2 Phenotype data of pediatric and adult inflammatory bowel disease patients, in the state of Espírito Santo, from August 2012 to July 2014

Characteristics	Total amount		Age at diagnosis ≤ 17 yr old		Age at diagnosis ≥ 18 yr old		*P* value
	n	%	*n*	%	*n*	%	
	1.048	(100)	56	(5.34)	992	(94.66)	
Ulcerative Colitis	669	(63.2)	24	(42.9)	645	(65.0)	
Extension							
E1	198	(30.3)	3	(12.5)	195	(31.0)	**0.037**[1]
E2	247	(37.9)	6	(25.0)	241	(38.4)	0.183
E3	209	(32.0)	15	(62.5)	194	(30.8)	**0.001**
Crohn's disease	352	(34.1)	30	(55.4)	322	(32.9)	
Localization							
L1	11	(31.4)	5	(16.1)	408	(41.1)	0.194
L2	102	(28.9)	10	(32.3)	584	(58.9)	0.861
L3	109	(30.4)	11	(35.5)	92	(28.6)	0.698
L4	11	(30.4)	1	(1.8)	10	(1)	
L1+L4	8	(2.3)	1	(3.2)	7	(2.2)	
L3+L4	12	(3.4)	2	(6.5)	10	(3.1)	
Behavior							
B1	200	(56.5)	18	(60.0)	182	(56.3)	0.686
B2	76	(21.5)	1	(3.3)	75	(23.3)	**0.005**[1]
B3	75	(21.2)	11	(36.7)	64	(19.5)	**0.030**
Perianal disease	92	(25.9)	14	(46.6)	78	(24.1)	**0.007**

[1]Proportions are expressed in *n* (%) and analyzed using the Chi-square test and Fisher's exact test. L1: Ileal; L2: Colonic; L3: Ileocolonic; L4: Upper gastrointestinal; B1: Inflammatory; B2: Stricturing; B3: Fistulizing; NA: Not available.

Table 3 Data on the use of biological therapy in patients with inflammatory bowel disease pediatric and adults, in the state of Espírito Santo, August 2012 to July 2014

Biological	Total amount		Age at diagnosis ≤ 17 yr old		Age at diagnosis > 18 yr old		*P* value
	n	%	*n*	%	*n*	%	
	1.048	(100)	55	(5.24)	993	(94.76)	
IBD	187	(17.8)	19	(34.5)	168	(16.9)	***P* = 0.001**
CD	155	(43.5)	17	(56.7)	138	(42.2)	*P* = 0.126
UC	30	(4.5)	2	(8.3)	28	(4.3)	*P* = 0.353

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease.

In pediatric DC, the ileocolonic form predominated, as in other studies from Germany[20], Italy[25], Spain[24], Argentina[18] and Mexico[18]. Four patients had involvement of the upper intestinal tract (16%), similar to a study in Spain (15.4%)[24] but different from the results in Germany (53.6%)[20]. These differences may have occurred due to the limitations of the current study, as they were based on secondary data, and possibly, a smaller study of the upper gastrointestinal tract using imaging methods was performed.

Our study showed no significant difference in the location of CD in relation to adult patients.

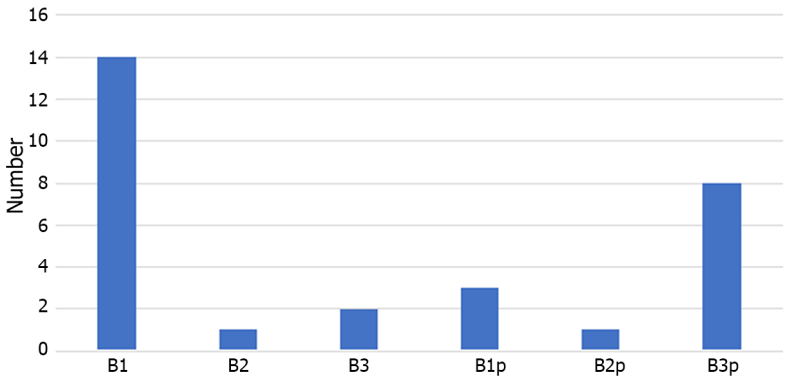


Figure 2 Distribution of the phenotype regarding the behavior of pediatric Crohn's disease patients in the state of Espírito Santo, from August 2012 to July 2014. B1: Inflammatory; B2: Stricturing; B3: Fistulizing; p: Perianal disease.

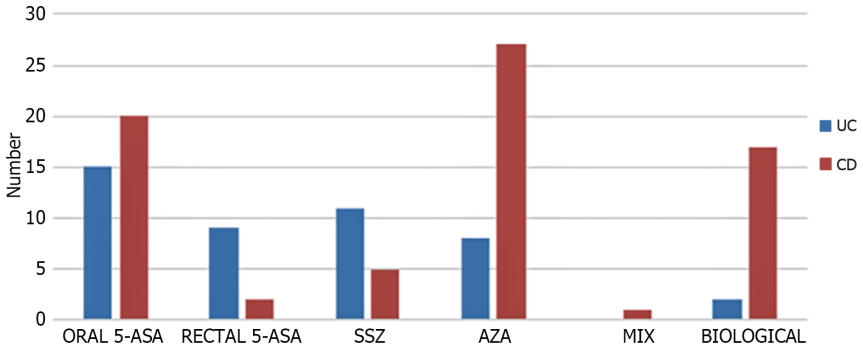


Figure 3 Distribution of medicines for pediatric age inflammatory bowel disease patients in the state of Espírito Santo, from August 2012 to July 2014. SSZ: Sulfasalazine; ASA: Mesalazine; AZA: Azathioprine; MTX: Methotrexate; BIOLOGICAL: Infliximab or adalimumab; UC: Ulcerative colitis; CD: Crohn's disease.

We observed a high frequency of perianal disease ("p") with 46.6% of pediatric/adolescent CD, which demonstrates the most serious behavior in this age group. Our data were higher than those of a Germany study[20] with 11.5% perianal disease, of a Canadian study[26] with 16% perianal disease in 2019, and of a Spanish study[24] with 16.4% perianal disease in 2018. When compared to the adult group, we observed the highest frequency of fistulizing behavior (B3) and perianal disease (p) in the pediatric age group, that is, more severe behavior in the youngest.

In the treatment of UC, oral aminosalicylates (mesalazine/sulfasalazine) were the most commonly used drugs, compatible with current therapeutic recommendations[27]. The use of corticoids was not evaluated in this study, as they are not dispensed by this state health care sector, and at the time of this study, biologics were not approved in our country for pediatric patients[11].

On the other hand, in CD, we observed a greater use of the immunomodulators when compared to aminosalicylates, according to guidelines[28]. Biological therapy was used in 56.7% (17/30) of pediatric patients with CD, compared with 42.2% of adult patients, but no significant difference was found (P = 0.126). We observed a higher use of biologic therapy in pediatric patients with Crohn's disease when compared to the 15% of the Hungarian study (2011-2013)[29] and 7.7% in the study from Poland (2012-2014)[30] We were able to observe that the use of medication in our region is consistent with the data from the literature recommendations[27,28], but we can see that pediatric patients with Crohn's disease used more frequent biologic therapy than those in another study.

CONCLUSION

In Brazil, where the incidence and prevalence of IBD are increasing in adults, it was observed that the prevalence and incidence in pediatric age are higher than those in other regions in Latin America, lower than those in Europe and North America, and in relation to the data worldwide, our pediatric IBD prevalence and incidence are still low. Children and adolescents with UC had a more extensive form (pancolitis) than adults, as in CD, and fistulizing forms (B3) and perianal diseases ("p") were more prevalent, which led to the high frequency of biological therapy in these patients with IBD before the age ≤ 17 years. These data, added to other epidemiological studies, demonstrate the severity of IBD in

the pediatric age group, with the need for early diagnosis and early intervention and correct use of specific therapy, avoiding serious secondary damage during the disease´s evolution.

Although we recognize the limitations of this study, as not all patients included had a complete imaging study (magnetic resonance imaging, an upper gastrointestinal endoscopy/biopsy) and secondary data based on documentation of the Public Health System was used, it is the first epidemiological pediatric IBD data published in the country. Although more studies are needed, this reports includes real-world data that can contribute to the planning of public health actions.

ARTICLE HIGHLIGHTS

Research background

Pediatric inflammatory bowel disease in a region of Brazil.

Research motivation

The pediatric inflammatory bowel disease data are practically unknown in Brazil and South America.

Research objectives

To determine the epidemiology of pediatric inflammatory bowel disease and its characteristics in Brazil and South America.

Research methods

The data were retrieved from the Public Medication-Dispensing System of the Department of Health in Espírito Santo state of Brazil.

Research results

The prevalence and incidence in pediatric ages are higher than those in other regions in Latin America. More severe disease was observed in the youngest patients. Pancolitis is more frequent in ulcerative colitis, and fistulizing and perianal disease are more frequent in Crohn's disease. Use of biological therapy was compared in the pediatric and adult groups.

Research conclusions

We have little data on inflammatory bowel disease in Latin America. We need to better understand the epidemiology, phenotype and medication used for the treatment of inflammatory bowel disease in each region.

Research perspectives

Obtain better therapeutic approaches and contribute to the planning of public health actions.

FOOTNOTES

Author contributions: Martins AL contributed to concept, design of the research, collection of the data, analysis, interpretation, and writing; Fróes RSB contributed to interpretation, writing and review; Zago-Gomes MP contributed to analyses study, statistical analysis, interpretation, and writing.

Institutional review board statement: This study was approved by the Ethics and Research Committee of the Nossa Senhora da Gloria Children's Hospital (CAAE 19602813.8.0000.5069) after obtaining authorization from the State Office for Pharmaceutical Assistance. The term of clarification and consent was waived because the data used is secondary data.

Informed consent statement: The terms of clarification and responsibility were not necessary because the information used were secondary data from Espírito Santo's State Health Department documents.

Conflict-of-interest statement: All the authors have no conflicts of interest to disclose related to the manuscript.

Data sharing statement: No additional data are available.

Country/Territory of origin: Brazil

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2022 July 9; 11(4): 351-359

DOI: 10.5409/wjcp.v11.i4.351

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Study

Frequency of celiac disease and distribution of HLA-DQ2/DQ8 haplotypes among siblings of children with celiac disease

Yasin Sahin, Serdar Mermer

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D, D
Grade E (Poor): E

P-Reviewer: Alkhayyat M, United States; JAIN S, India
A-Editor: Nardi PD, Italy

Received: January 10, 2022
Peer-review started: January 10, 2022
First decision: March 8, 2022
Revised: March 18, 2022
Accepted: June 3, 2022
Article in press: June 3, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Celiac disease (CD) is a multifactorial disease, but genetic factors play a major role in its etiology. It has been known that human leucocyte antigen (HLA)-DQ2/DQ8 haplotypes are one of the most important predisposing genetic factors. The risk of developing CD in first-degree relatives and especially siblings of celiac patients is quite high because of having the same HLA haplotypes.

AIM

To evaluate the frequency of CD and the distribution of the HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

METHODS

Patients with biopsy-proven CD and their siblings were included in the study; those who did not have HLA genotyping were excluded from the study. All siblings were on a gluten-containing diet. The HLA genotyping, tissue transglutaminase antibody IgA antibody test, and total IgA test were performed in all participants.

RESULTS

A total of 57 celiac patients and their 112 siblings were included in the study. The mean age of celiac patients and siblings were 10.30 ± 3.87 years and 9.90 ± 6.11 years, respectively. HLA-DQ2/DQ8 alleles were detected in 98.2% of patients with CD and 90.2% of siblings of celiac patients. HLA-DQ genotypes were present in all siblings diagnosed with CD. Tissue transglutaminase antibody IgA test was found to be positive in 16 siblings. CD was diagnosed in 12 siblings (10.7%) by intestinal biopsy.

CONCLUSION

The prevalence of CD was found to be 10.7% in siblings of celiac patients in our study. One-third of the siblings diagnosed with CD were asymptomatic. We detected HLA-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. In addition, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later. Therefore, we suggest that siblings of celiac patients should be followed up with clinical findings as well as HLA analysis and serological examination. Since the risk of developing CD is much higher in asymptomatic siblings, we recommend that siblings should be screened for CD even if they are asymptomatic.

Key Words: Celiac disease; Frequency; Genetic; HLA haplotypes; Intestinal biopsy; Siblings

Core Tip: Celiac disease (CD) is a multifactorial disease, but genetic factors play a major role in its etiology. Human leucocyte antigen-DQ2/DQ8 haplotypes are one of the most important predisposing genetic factors. We detected human leucocyte antigen-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. Also, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later. Siblings of celiac patients should be followed up with clinical findings and human leucocyte antigen analysis and serological examination. We recommend that siblings should be screened for CD even if they are asymptomatic.

Citation: Sahin Y, Mermer S. Frequency of celiac disease and distribution of HLA-DQ2/DQ8 haplotypes among siblings of children with celiac disease. *World J Clin Pediatr* 2022; 11(4): 351-359
URL: https://www.wjgnet.com/2219-2808/full/v11/i4/351.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.351

INTRODUCTION

Celiac disease (CD) is a systemic autoimmune disease triggered by gluten intake in genetically susceptible individuals characterized by various degrees of small intestinal damage[1]. It is a multifactorial disease, but genetic factors play a major role in its etiology. It has been known that human leucocyte antigen (HLA)-DQ2/DQ8 genotypes are one of the most important predisposing genetic factors[2-4].

The risk of developing CD in first-degree relatives and especially siblings of celiac patients is quite high due to having the same HLA genotypes and environmental triggers such as gut microbiome[5-8]. It has been reported that the risk of developing CD is higher in siblings of celiac patients compared to other first-degree relatives[9-11]. CD may be asymptomatic for years or even be diagnosed 10 years after the first symptom appears[12]. It has been reported that approximately half of the first-degree relatives of celiac patients newly diagnosed with CD are completely asymptomatic[2,8,10]. Early diagnosis of CD is very important for the prevention of long-term complications of CD such as osteoporosis, growth retardation, infertility, and malignancy.

Although there are many studies on the frequency of CD in first-degree relatives of celiac patients, the number of studies investigating the frequency of CD and the distribution of HLA-DQ2/DQ8 in siblings of celiac patients is rare[8,10,13,14]. The aim of our study was to evaluate the frequency of CD and the distribution of HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

MATERIALS AND METHODS

This study was carried out between February 2017 and June 2020. Patients with biopsy-proven CD and their siblings were included in the study; those who did not have HLA genotyping were excluded from the study. All siblings were on a gluten-containing diet. The current study was approved by the Local Ethics Committee (Toros University, Mersin, Turkey, 17.06.2020/41). The patient who was first diagnosed with CD was defined as an index case.

CD was diagnosed according to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition 2012 guidelines[2]. In total, 57 celiac patients and their 112 siblings were included in the study. Three patients who did not have any siblings were not included in the study. The HLA genotyping, tissue transglutaminase antibody (tTG) IgA antibody test, and total IgA test were performed in all participants. tTG IgA antibody levels were measured by enzyme-linked immuno-

sorbent assay method (Diametra, Spello PG, Italy). The cutoff value for tTG IgA was 20 U/mL. Total IgA levels were measured by nephelometric method (Siemens Diagnostics, Marburg, Germany).

Gastroduodenoscopy and small intestinal biopsy were performed in all patients with tTG positivity. Four biopsies from the duodenum and at least one biopsy from the bulb were obtained. All intestinal biopsy specimens were evaluated according to the modified Marsh-Oberhuber classification[15] as follows: Marsh stage 0: normal mucosa; Marsh stage 1: increased intraepithelial lymphocytosis (> 40 lymphocytes per 100 epithelial cells); Marsh stage 2: increased intraepithelial lymphocytosis with crypt hyperplasia; Marsh stage 3a: increased intraepithelial lymphocytosis with crypt hyperplasia and partial villous atrophy; Marsh stage 3b: increased intraepithelial lymphocytosis with crypt hyperplasia and subtotal villous atrophy; and Marsh stage 3c: increased intraepithelial lymphocytosis with crypt hyperplasia and total villous atrophy. If the pathology result was compatible with Marsh stage 2 or stage 3, the patient was diagnosed with CD.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences software version 22.0 (SPSS Inc; Chicago, IL, United States). Frequency, percentage, and mean ± standard deviation were used as descriptive statistics. Independent sample *t*-test was used for nominal data. The Mann-Whitney *U* test was used to compare groups of numerical variables. χ^2 test was used for comparison of categorical variables.

RESULTS

A total of 57 celiac patients and their 112 siblings were included in the study. Of 112 siblings, 54 (48.20%) were female; 33 (57.89%) of the 57 celiac patients were female. The mean age of celiac patients and siblings were 10.30 ± 3.87 years and 9.90 ± 6.11 years, respectively (Table 1).

HLA-DQ2/DQ8 alleles were detected in 98.2% of patients with CD and 90.2% of siblings of celiac patients (Table 2). A total of 57 celiac patients (57.9%) had HLA-DQ2, 29.8% had HLA-DQ2/DQ8, and 10.5% had HLA-DQ8. Both alleles were found to be negative in 1.8% of them. HLA-DQ genotypes were present in all siblings diagnosed with CD (Table 3). tTG IgA test was found to be positive in 16 siblings. CD was diagnosed in 12 siblings by intestinal biopsy (Table 3). The pathology result of 10 siblings was compatible with Marsh stage 3. The prevalence of CD was found to be 10.7% in siblings of celiac patients in our study, and this rate was 22.7 times higher than the general population. Gastroduodenoscopy could not be performed in 4 of 16 siblings because of parental refusal. Out of 100 cases not diagnosed with CD, 59 had HLA-DQ2 positivity, 16 had HLA-DQ2/DQ8 positivity, 14 had HLA-DQ8 positivity, and 11 were negative for HLA-DQ2 and HLA-DQ8.

Seven of those twelve celiac patients had anemia, six of them had growth retardation, and four of them had no symptoms. HLA-DQ alleles were also positive in all 4 patients who refused to undergo gastroduodenoscopy. No IgA deficiency was detected in either group. Two siblings of three index cases were diagnosed with CD. The first sibling of the first index case was diagnosed 2 mo later, and the second sibling 1 year later (when looking at the second serology). The first sibling of the second index case was diagnosed with CD 4 years later (in the second serology examined with an interval of 2 years), and the second sibling was diagnosed with CD 4 mo after the first. The two siblings of the other index case were also diagnosed with CD within 3 mo.

DISCUSSION

The estimated prevalence of CD is 1% in the world, and this rate varies in different geographical regions [2,16]. The reason of that may be due to differences in genetic susceptibility and changes in dietary gluten intake.

With the identification of the major role of HLA-DQ2/DQ8 in genetically susceptible individuals, it has been reported that the negative detection of both HLA-DQ2 and HLA-DQ8 in first-degree relatives of celiac patients does not require further investigation for CD[17,18]. On the contrary, it has been reported that the risk of CD is higher in individuals with homozygous HLA-DQ2[19].

In the European Society for Paediatric Gastroenterology, Hepatology and Nutrition 2012 guidelines, HLA genotyping is recommended as the initial screening test for CD especially in risk groups such as first-degree relatives of celiac patients[2]. It has been shown that HLA-DQ analysis is helpful in predicting CD especially in first-degree relatives of celiac patients[20-22]. The absence of HLA-DQ2 and HLA-DQ8 most likely excludes CD, but celiac specific antibody tests are required to diagnose CD in the presence of those alleles[20]. While some authors have suggested that HLA analysis can be used in the diagnosis of CD, others have suggested that it is a good alternative for determining genetic predisposition[23,24].

Table 1 The demographic and laboratory characteristics of celiac patients and their siblings

	Celiac patients, *n* = 57	Siblings, *n* = 112	*P* value
Age (yr)	10.30 ± 3.87	9.90 ± 6.11	0.648
Sex (female/male)	33/24	54/58	0.234
Height (cm)	132.71 ± 20.29	130.27 ± 31.37	0.594
Weight (kg)	30.44 ± 12.82	33.22 ± 19.18	0.325
Hb (g/dL)	11.65 ± 3.87	12.71 ± 1.56	< 0.001
tTG IgA (U/mL)	108.65 ± 60.61	17.24 ± 41.14	< 0.001
Total IgA (mg/dL)	155.43 ± 78.44	124.33 ± 71.47	0.014

Hb: Hemoglobin; tTG: Tissue transglutaminase antibody.

Table 2 The distribution of human leucocyte antigen genotypes of celiac patients and their siblings

HLA genotypes	Celiac patients, *n* = 57 (100%)	Siblings, *n* = 112 (100%)
HLA-DQ2	33 (57.9)	68 (60.7)
HLA-DQ2/DQ8	17 (29.8)	18 (16.1)
HLA-DQ8	6 (10.5)	15 (13.4)
Both negative	1 (1.8)	11 (9.8)

HLA: Human leucocyte antigen.

Table 3 The laboratory and clinical data of siblings of celiac patients diagnosed with celiac disease

	Patient age at diagnosis (yr)	Symptoms	Hb (g/dL)	tTG (U/mL)	IgA (mg/dL)	HLA	Pathology
1	6	Failure to thrive, anemia	10.9	140	206	DQ2	Marsh 3a
2	8.5	-	13.4	94	87	DQ8	Marsh 3a
3	18	-	13.5	105	99	DQ2	Marsh 3a
4	4.3	Failure to thrive, anemia	10.4	46	33	DQ2	Marsh 3b
5	13.5	Failure to thrive, anemia	7.7	135	254	DQ2	Marsh 3b
6	5.5	Failure to thrive, anemia	11.7	35	66	DQ2	Marsh 3b
7	16.5	Anemia	11.7	41	86	DQ2	Marsh 3b
8	16	-	13.3	187	190	DQ2	Marsh 3b
9	14.5	-	14.3	37	179	DQ2/DQ8	Marsh 2
10	12	Anemia	11.9	46	122	DQ2/DQ8	Marsh 2
11	11.5	Failure to thrive	13.1	127	148	DQ2	Marsh 3a
12	10.5	Failure to thrive, anemia	10.9	34	70	DQ2	Marsh 3b

HLA: Human leucocyte antigen; Hb: Hemoglobin; tTG: Tissue transglutaminase antibody.

The prevalence of CD in siblings of celiac patients is 5.9%-18.3%[8,10,13,14,25]. As consistent with the literature, the prevalence of CD was found to be 10.7% in siblings of celiac patients in our study. Twelve siblings were diagnosed with CD by intestinal biopsy. Four siblings (25%) with positive tTG refused gastroduodenoscopy. In another study, the rate of those who did not accept biopsy (22.2%) was similar to our study[10]. The real prevalence of CD could not be estimated, as there were cases who refused the biopsy.

In a systematic review, it has been reported that the prevalence of CD in sisters of celiac patients is approximately two times higher than in brothers[25]. Contrary to this, the prevalence of CD was equal

in males and females in our study. The reason of that may be the study was cross-sectional, and 4 cases with positive serology did not accept endoscopy. For this reason, we may not have been able to fully determine the risk of CD. The other reason is that our study had a short follow-up period. Some seronegative individuals may be seropositive in the future and be diagnosed with CD.

In a multicenter study conducted in Europe, it was reported that 90% of celiac patients had the HLA-DQ2 genotype, and 5% to 10% of them had HLA-DQ8[26]. Those genotypes were found in 40%-65% of first-degree relatives of celiac patients and 18%-30% of the general population[10,11,27]. HLA-DQ8 positivity is higher in America, Asia, Chile, and Cuba compared to Europe[28-31]. In our study, 57.9% of celiac patients had HLA-DQ2, 29.8% had HLA-DQ2/DQ8, and 10.5% had HLA-DQ8. Both alleles were found to be negative in 1.8% of patients. HLA-DQ2/DQ8 ratios vary from region to region[26,28-31].

HLA analysis was performed on all siblings of celiac patients in the current study. HLA antigens were positive in 90.2% of siblings of celiac patients. As consistent with our study, HLA antigens were found to be positive in all siblings of celiac patients (100%) in another study conducted in our country [14].

In our study, out of 100 cases not diagnosed with CD, 59 had HLA-DQ2 positivity, 16 had HLA-DQ2/DQ8 positivity, 14 had HLA-DQ8 positivity, and 11 were negative for both HLA-DQ2 and HLA-Dq8. In a study with the same number of cases, 49 of 100 cases whose siblings of celiac patients were not diagnosed with CD had HLA-DQ2 positivity, 6 had HLA-DQ8 positivity, 2 had HLA-DQ2/DQ8 positivity, and 43 were negative for both HLA-DQ2 and HLA-DQ8[10]. The reason may be due to the HLA-DQ2/DQ8 ratios varying from region to region[26,28-31].

In the study by Bonamico *et al*[10], it was shown that the use of HLA genotyping as a first step can be used to exclude one-third of first-degree relatives, but it has been reported that patients negative for HLA-DQ2 and HLA-DQ8 can be overlooked. Also, it has been suggested that it may be more useful to evaluate the first-degree relatives of celiac patients together with tTG antibody test and HLA typing.

HLA antigens were detected in 94.7%-100% of siblings of celiac patients diagnosed with CD[10,14]. In parallel with the literature, HLA antigens were detected in all 12 siblings of celiac patients diagnosed with CD in our study.

It has been known that HLA-DQ alleles have a high prevalence among celiac patients[2,14,20,32,33]. Those alleles may determine susceptibility to CD in risk groups such as first-degree relatives of celiac patients[19]. It has been reported that the frequency of HLA-DQ2/DQ8 is high in risk groups such as first-degree relatives of celiac patients[2,34]. We found a high rate of positive HLA-DQ alleles in celiac patients and their siblings as compatible with the literature.

It has been reported that 30.0%-78.9% of siblings of celiac patients diagnosed with CD are asymptomatic[8,13,14,34]. As consistent with the literature, one-third of our patients were found to be asymptomatic. Since patients diagnosed with silent CD have a high prevalence, asymptomatic siblings of celiac patients should be screened for CD.

It has been suggested that HLA genotyping can be used to exclude 25%-33% of first-degree relatives from serological follow-up[10,23,35-37]. The absence of HLA-DQ alleles has a high negative predictive value for CD; positive results indicate only a genetic predisposition[38].

CD can occur at any age. A negative serological test once does not mean that there will be no CD in the future. Many studies have been conducted on serologically negative celiac patients[39-42]. In the study by Pittschieler *et al*[39], serological positivity was detected in 3 cases with HLA-DQ2 positivity after more than 10 years of follow-up, and then CD was diagnosed. In parallel with that study, CD was diagnosed in 1 of 2 cases with HLA-DQ2 positive 1 year later and the other 4 years later in our study. CD may be seen in any period of life. Since the follow-up period was short in our study, we think that other cases with positive HLA antigens may be diagnosed with CD in the future. Therefore, we recommend that cases in a high-risk group should be followed clinically and serologically.

In a Western cohort, only 0.5% of celiac patients were found to have HLA-DQ negativity[18]. In a recent study, it has been reported that HLA-DQ typing is insufficient to identify individuals susceptible to CD and could not be used to diagnose CD[43]. In another study conducted in Iran, HLA-DQ negativity was found to be 3.9%[44]. HLA-DQ2 and HLA-DQ8 were found to be negative in 5% of cases in another study[10]. In parallel with those studies, HLA-DQ antigens were found to be negative in 1.8% of celiac patients in our study. In those studies, it has been reported that the risk of developing CD is very low in cases with negative HLA-DQ. It has been suggested that cases negative for HLA-DQ2/DQ8 negative should be followed clinically and serologically every 2 years or 3 years[10]. For this reason, it has been suggested that HLA analysis would be more appropriate in cases where it is difficult to diagnose.

In a study conducted in healthy school children in our country, the prevalence of CD was found to be 0.47%[45]. In the current study, the prevalence of CD in siblings of celiac patients was found to be 10.7%. That is, we found that the prevalence was 22.7 times higher than in the general population.

One of the limitations of the study was that 15 celiac patients and their 28 siblings refused to participate in the study. If they did, the results would have been different, and the power of study would have been better. Another limitation was the short follow-up period. CD may develop over time in our serologically negative cases. For these reasons, we think that we were unable to estimate the real prevalence of CD.

CONCLUSION

In conclusion, the prevalence of CD was found to be 10.7% in siblings of celiac patients in our study, and this rate was 22.7 times higher than the general population. One-third of the siblings diagnosed with CD were asymptomatic. We detected HLA-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. Thus, CD has been shown to be associated with HLA-DQ2 and HLA-DQ8 genotypes. In addition, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later. Therefore, we suggest that siblings of celiac patients should be followed up with clinical findings as well as HLA analysis and serological examination. Since the risk of developing CD is much higher in asymptomatic siblings, we recommend that siblings should be screened for CD even if they are asymptomatic.

ARTICLE HIGHLIGHTS

Research background

Celiac disease (CD) is a systemic autoimmune disease triggered by gluten intake in genetically susceptible individuals. It is a multifactorial disease, but genetic factors play a major role in its etiology. It has been known that human leucocyte antigen (HLA)-DQ2/DQ8 genotypes are one of the most important predisposing genetic factors. The risk of developing CD in siblings of celiac patients is quite high because of having the same HLA genotypes and environmental triggers such as gut microbiome.

Research motivation

Although there are many studies on the frequency of CD in first-degree relatives of celiac patients, the number of studies investigating the frequency of CD and the distribution of HLA-DQ2/DQ8 in siblings of celiac patients is rare. Because of that, we aimed to evaluate the frequency of CD and the distribution of HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

Research objectives

To investigate the frequency of CD and the distribution of HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

Research methods

The current study was carried out between February 2017 and June 2020. Biopsy-proven celiac patients and their siblings were included in the study. CD was diagnosed according to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition 2012 guidelines. In total, 57 celiac patients and their 112 siblings were included in the study. All siblings were on a gluten-containing diet. The HLA genotyping, tissue transglutaminase antibody IgA antibody test, and total IgA test were performed in all participants. Gastroduodenoscopy was performed in all patients with tissue transglutaminase antibody positivity. Four biopsies from the duodenum and at least one biopsy from the bulb were obtained. All intestinal biopsy specimens were evaluated according to the modified Marsh-Oberhuber classification.

Research results

HLA-DQ2/DQ8 alleles were detected in 98.2% of patients with CD and 90.2% of siblings of celiac patients. Tissue transglutaminase antibody IgA test was found to be positive in 16 siblings. CD was diagnosed in 12 siblings by intestinal biopsy. Seven of those twelve celiac patients had anemia, six of them had growth retardation, and four of them had no symptoms.

Research conclusions

The prevalence of CD was found to be 10.7% in siblings of celiac patients in our study, and this rate was 22.7 times higher than the general population. One-third of the siblings diagnosed with CD was asymptomatic. We detected HLA-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. Thus, CD has been shown to be associated with HLA-DQ2 and HLA-DQ8 genotypes. In addition, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later.

Research perspectives

According to the current study, we suggest that the siblings of celiac patients should be followed up with clinical findings as well as HLA analysis and serological examination. Since the risk of developing CD is much higher in asymptomatic siblings, we recommend that siblings should be screened for CD even if they are asymptomatic.

ACKNOWLEDGEMENTS

We would like to thank the pathologists, pediatricians and Derya Aydin Sahin for their help in the study.

FOOTNOTES

Author contributions: Sahin Y designed the study, analyzed the data, interpreted the data and wrote the manuscript; Mermer S designed the study and collected and analyzed the data; All authors had read and approved the final manuscript.

Institutional review board statement: The current study was approved by the Local Ethics Committee (Toros University, Mersin, Turkey, 17.06.2020/41).

Informed consent statement: Written informed consent was not obtained as the study is retrospective. However, the Local Ethics Committee approved the current study.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: No additional data are available.

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S-Editor: Liu JH
L-Editor: Filipodia
P-Editor: Liu JH

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World J Clin Pediatr 2022 July 9; 11(4): 360-368

DOI: 10.5409/wjcp.v11.i4.360

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Observational Study

Adipocytokine profile in children with Kawasaki disease at a mean follow-up period of 5.5 years: A study from North India

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Corso G, Italy; Maglio C, Sweden

Received: March 31, 2021
Peer-review started: March 31, 2021
First decision: July 30, 2021
Revised: August 21, 2021
Accepted: May 12, 2022
Article in press: May 12, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Kawasaki disease (KD) is an acute self-limited vasculitis with a predilection for coronary arteries. Children with KD may have altered lipid metabolism and abnormal lipid profiles that may last for prolonged periods. However, there is a paucity of literature on the role of adipocytokines in KD.

AIM

To estimate the levels of adipocytokines (adiponectin, leptin and resistin) during the convalescent phase of KD.

METHODS

Twenty children, who had KD at least three years earlier, were enrolled in this study. In addition, 20 healthy controls were also enrolled. Clinical and laboratory profiles of patients were obtained from hospital records. Serum adiponectin, leptin and resistin levels were estimated by enzyme-linked immunosorbent assay.

RESULTS

Mean age of the patients in the study group was 10.15 ± 3 years and the male: female ratio was 1.5:1. Median serum resistin levels in patients with KD (27.77 ng/mL; [IQR: 18.66, 48.90]) were decreased compared to controls (21.20 ng/mL; [IQR: 14.80, 27.00]) (P = 0.04). Median serum leptin levels in cases and controls were 1.83 ng/mL; (IQR: 1.13, 3.80), and 1.10 ng/mL; (IQR: 0.41, 2.88), respectively (P = 0.09). Median serum adiponectin levels were similar in both cases (12.20 µg/mL; [IQR: 9.76, 17.97]) and controls (13.95 µg/mL; [IQR: 11.17, 22.58]); (P = 0.18). There was no significant difference in all 3 adipocytokines between children with (4/20) and without coronary artery abnormalities (16/20).

CONCLUSION

Serum resistin levels were significantly elevated in patients with KD during the convalescent phase compared to controls. Serum leptin levels appeared to be higher in patients with KD, although the difference was not statistically significant. Adiponectin levels were similar in both cases and controls. Raised resistin and leptin levels may partially explain lipid perturbations observed during the convalescent phase of KD.

Key Words: Adipocytokines; Adiponectin; Resistin; Leptin; Lipid metabolism; Kawasaki disease; Convalescent phase

Core Tip: The present study suggests that serum adipocytokine levels may impact lipid abnormalities observed during the convalescent phase of Kawasaki disease (KD). Serum resistin levels were significantly elevated in patients with KD during the convalescent phase compared to controls. Serum leptin levels appeared to be higher in patients with KD, although the difference was not statistically significant. Adiponectin levels were similar in both cases and controls.

Citation: Praharaj DL, Rawat A, Gupta A, Arora K, Pilania RK, Bhattad S, Singh S. Adipocytokine profile in children with Kawasaki disease at a mean follow-up period of 5.5 years: A study from North India. *World J Clin Pediatr* 2022; 11(4): 360-368
URL: https://www.wjgnet.com/2219-2808/full/v11/i4/360.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.360

INTRODUCTION

Kawasaki disease (KD) is a medium vessel vasculitis and the most common cause of acquired heart disease in children in most developed countries[1]. There are data to support that the incidence of KD is also rising in the developing world, including India[1]. Coronary artery abnormalities (CAAs) have been noted in 15%-25% of untreated children and treatment with intravenous immunoglobulin (IVIg) reduces this risk to 3%-5%[2]. Children with KD are known to have lipid abnormalities in the acute phase that may persist long after the initial episode of the disease[3-8]. It is known that serum lipid profiles may remain deranged for prolonged periods after the acute stage of the illness and this may contribute to the premature and accelerated atherosclerosis seen in patients with KD[9,10].

Adipocytokines play a significant role in lipid metabolism, inflammation and diseases associated with accelerated atherosclerosis[11-13]. Moreover, their levels may impact lipid abnormalities[11-14]. As some of the lipid abnormalities associated with KD persist during the convalescent phase, we hypothesized that the adipocytokine perturbations seen during the acute phase of KD, may also persist during follow-up. There is a paucity of literature on this subject[15-19], and the results are difficult to interpret. We, and others, have previously shown that children with KD in India have a different clinical phenotype compared to those reported in the developed world[20]. We have also shown that lipid abnormalities are seen in up to 25.9% of children with KD at a mean follow-up of 5 years[6,7]. We, therefore, conducted this study to determine whether adipocytokines are responsible for some of these lipid abnormalities.

MATERIALS AND METHODS

Patients and methods

The present study was a cross-sectional descriptive study conducted in the Paediatric Rheumatology Clinic, Advanced Paediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh. Our institute is a federally funded not-for-profit tertiary care centre catering to the population of North-West India. We follow the largest cohort of KD in India. Twenty consecutive cases of KD with at least 3 years of follow-up, and 20 healthy controls were enrolled in the present study. Children with acute KD and convalescent cases with less than 3 years of follow-up were excluded. The diagnosis of KD was based on the American Heart Association guidelines[21]. During the acute phase, children had received standard treatment *i.e.* IVIg 2 g/kg along with aspirin (initially in higher doses [30-50 mg/kg/d], followed by antiplatelet doses [3-5 mg/kg/d]). Written informed consent was obtained from the parents/guardians at study enrolment. Clinical records were reviewed. The study protocol was approved by the Institute Thesis Committee and Institute Ethics Committee. This

manuscript has been approved by the Departmental Review Board.

Evaluation of different adipocytokines

Collection of blood sample: Two milliliters of peripheral venous blood was collected from cases and controls in plain vials under aseptic conditions. Serum was extracted and collected in cryovials and immediately stored at-80°C. Hemolyzed and turbid samples were discarded.

Estimation of serum resistin: Serum resistin level was estimated using the AssayMax Human Resistin enzyme-linked immunosorbent assay (ELISA) kit designed for determining human resistin in plasma, serum, urine, saliva and cell culture samples as per the manufacturer's recommendations. Sensitivity of the assay was 0.2 ng/mL; intra-assay coefficient of variability (CV) was 4.5% and inter-assay CV was 7.0%. Absorbance was measured at 450 nm on a microplate ELISA reader (Infinite PRO 2000 TECAN Austria).

Estimation of serum adiponectin: Serum adiponectin level was estimated using the AssayMax Human Adiponectin ELISA kit designed for measuring human adiponectin in plasma, serum, urine, saliva and cell culture samples. Sensitivity of the assay was 0.7 ng/mL, intra-assay CV was 4.3% and inter-assay CV was 7.2%.

Estimation of serum leptin: Serum leptin level was similarly estimated using the DRG Human Leptin ELISA kit designed for determining human leptin in plasma and serum samples. Sensitivity of the assay was 1.0 ng/mL, intra-assay CV was 6%-7% and inter-assay CV was 8.5%-11.5%.

All 3 adipocytokines were measured in convalescent cases of KD and in healthy controls. Serum lipids were also estimated in 18 children in the study group during follow-up. Reference values for lipids in healthy Indian children were obtained from the study by Marwaha *et al*[22].

Statistical analysis

Data were collected on a pre-designed proforma and transferred to a Microsoft Office Excel sheet. Preliminary analysis was conducted by descriptive statistics, expressed as means (SD), medians (range) and proportions (centiles). A comparison of the study and control group with regard to levels of individual adipocytokines (*i.e.* leptin, resistin, and adiponectin) was performed using the Mann-Whitney test wherever data had skewed distribution and the Student's t test was used for normal distribution. Analysis was carried out using the Statistical Package for Social Sciences Version 20.0 for Windows.

RESULTS

Observation and results

The mean age of patients with KD and controls was 10.1 and 9.1 years, respectively. The male:female ratio in patients with KD was 1.5:1. Mean duration of follow-up in the cases was 5.5 years. No case of IVIg resistance was documented in this cohort. Four children (20%) had CAAs at first admission that resolved on follow-up of 6-8 wk. Eighteen of 20 cases had lipid estimations during follow-up. Lipid abnormalities noted in these children are shown in Table 1. No association was observed between the occurrence of CAAs and the presence of lipid abnormalities.

Median serum resistin levels in patients with KD (27.77 ng/mL; [IQR: 18.66, 48.90]) were increased compared to controls (21.20 ng/mL; [IQR: 14.80, 27.00]) (P = 0.04). Median serum leptin levels in cases and controls were 1.83 ng/mL; (IQR: 1.13, 3.80), and 1.10 ng/mL; (IQR: 0.41, 2.88), respectively (P = 0.09). Median serum adiponectin levels were similar in both cases (12.20 μg/mL; [IQR: 9.76, 17.97]) and controls (13.95 μg/mL; [IQR: 11.17, 22.58]); (P = 0.18) (Table 2). There was no significant difference in all 3 adipocytokines between children with CAAs (4/20) and without CAAs (16/20). We performed a correlation analysis of different lipid profiles with adipocytokines (Table 3). No significant correlation was observed between adipocytokines and lipid values. Body mass index (BMI) has also been shown to have a significant positive correlation with leptin levels. No significant correlation between BMI and resistin or adiponectin was observed.

DISCUSSION

KD is the most common cause of acquired heart disease in children in the developed world[1]. KD is being increasingly reported in several developing countries, including India[23]. Hospital-based studies at our centre have shown that the incidence of KD has risen significantly over the last 2 decades[23]. Whether, this increase represents a true increase in incidence, or an increased ascertainment of the disease as a result of heightened awareness, remains unknown. We, and others, have previously shown that KD in India has a different phenotype inasmuch as a higher proportion of older children are seen in

Table 1 Clinical and laboratory features of the study population

	Study group (*n* = 20)	Controls (*n* = 20)
Male:female ratio	1.5:1	1.5:1
Age at diagnosis < 5 yr	9	-
Age at diagnosis >5 yr	11	-
Mean age at enrolment (yr)	10.1	9.1
Mean duration of follow-up (yr)	5.5	-
Treatment received during the acute phase		-
IVIg (mg/dL)	20	
Aspirin (mg/dL)	20	
CAAs (mg/dL)	4/20	-
Lipid profile	mean ± SD	-
LDL (mg/dL)	74.73 ± 27.82	
TG (mg/dL)	118.72 ± 104.32	
VLDL (mg/dL)	16.96 ± 6.72	
HDL (mg/dL)	44.93 ± 11.40	
TC (mg/dL)	139.76 ± 27.16	
Body mass index (kg/m^2)	16.68 ± 3.25	-
Lipid profile (18/20)		-
High TC (mg/dL)	2	
High LDL (mg/dL)	2	
Low HDL (mg/dL)	6	
Borderline HDL (mg/dL)	11	
High TG (mg/dL)	4	
High VLDL (mg/dL)	0	

IVIg: Intravenous immunoglobulin; KD: Kawasaki disease; TC: Total cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein; VLDL: Very low density lipoprotein; TG: Triglycerides, CAAs: Coronary artery abnormalities; SD: Standard deviation.

Table 2 Adipocytokine profile in patients with Kawasaki disease and healthy controls

	Study group (*n* = 20), Median (IQR)	Controls (*n* = 20), Median (IQR)	*P* value
Adiponectin (μg/mL)	12.20 (9.76, 17.97)	13.95 (11.17, 22.58)	0.18
Leptin (ng/mL)	1.83 (1.13, 3.80)	1.10 (0.41, 2.88)	0.09
Resistin (ng/mL)	27.77 (18.66, 48.90)	21.20 (14.80, 27.00)	0.04[a]

[a]*P* value < 0.05 was taken as significant. IQR: Interquartile range.

Indian cohorts[20,23,24]. Furthermore, periungual desquamation and thrombocytosis seem to appear earlier in children with KD in India[25].

Newburger and colleagues previously reported that KD was associated with significant abnormalities of lipid metabolism and derangement of serum lipid profiles[3]. In the first few d of the illness, mean plasma concentration of total cholesterol and HDL- cholesterol was profoundly depressed, whereas mean triglyceride level was very high. Total cholesterol values rapidly returned to normal and remained stable more than three months after the onset of illness. HDL-cholesterol concentration recovered more slowly after illness onset. Mean HDL-cholesterol level was significantly reduced, even after three years of illness onset. Lipid abnormalities in KD are in part attributable to concurrent reductions in lipoprotein lipase and hepatic lipase activities[4]. Several other authors have also reported

Table 3 Correlation of adipocytokines with different lipoproteins, body mass index and age of the patients with Kawasaki disease

Characteristics	Leptin		Adiponectin		Resistin	
	Correlation coefficient	*P* value	Correlation coefficient	*P* value	Correlation coefficient	*P* value
LDL (mg/dL)	0.030	0.90	-0.223	0.34	-0.003	0.99
TG (mg/dL)	0.076	0.75	-0.018	0.94	0.169	0.47
VLDL (mg/dL)	-0.076	0.75	0.330	0.15	0.105	0.65
HDL (mg/dL)	-0.037	0.87	0.505	0.47	0.470	0.03[a]
Total cholesterol (mg/dL)	0.033	0.89	-0.379	0.09	-0.217	0.35
BMI (kg/m^2)	0.574	0.02[a]	-0.334	0.20	-0.280	0.29
Age (yr)	0.379	0.09	-0.057	0.81	-0.128	0.59

[a]*P* value < 0.05 was taken as significant. LDL: Low density lipoprotein; TG: Triglycerides; VLDL: Very low density lipoprotein; HDL: High-density lipoprotein.

similar abnormalities in the lipid profile of children with KD[4,6,26]. We have shown that HDL-cholesterol was low in 6/18 and borderline in 11/18 patients with convalescent KD. Thus, 17/18 patients had abnormal HDL-cholesterol at follow-up. The persistence of low HDL-cholesterol for many years in our cohort suggests a long-lasting effect of KD on endothelial function, perhaps attributable to the diminished activity of lipoprotein lipase. Normal lipid levels in the general population have been studied in Indian children by Marwaha *et al* and these were used as historical reference standards in the present study[22].

Adipose tissue has long been considered an inert organ and a depot for energy storage. However, new advances have revealed that it is also an important endocrine organ that produces numerous adipocytokines[11]. Perturbations in adipocytokines are well known in obesity. These play a fundamental role in obesity-linked disorders such as diabetes mellitus and metabolic syndrome[12]. It is now well recognized that adipocytokines play a pivotal role in immune response and inflammation[13]. Studies have shown that adipokines may be important biomarkers for inflammation in chronic diseases [27,28]. While some adipocytokines can induce pro-inflammatory effects (*e.g.* leptin, resistin, IL-6, TNF-α), others have predominantly anti-inflammatory effects (*e.g.* adiponectin and IL-10)[14]. Therefore, analysis of specific adiponectin isoforms may be necessary to prove these diverse effects. An imbalance between pro-inflammatory and anti-inflammatory adipocytokines leads to persistent inflammation and may contribute to accelerated atherosclerosis. Low adiponectin, high resistin and high leptin levels have been reported to produce this phenomenon.

As children with KD have lipid abnormalities[6,26], it is plausible that a disturbed adipocytokine milieu may contribute to early development of atherosclerosis. This may, in turn, predispose children with KD to acute coronary events at a young age. Adiponectin, resistin and leptin are the most examined adipocytokines in disorders of lipid metabolism and we, therefore, conducted this study in the convalescent phase of KD. To the best of our knowledge, there are no published data on adipocytokine levels in children with KD from the Indian subcontinent.

Studies on adipocytokines profile in the follow-up of KD are sparse and have yielded conflicting results[5,9,19] (Tables 3 and 4). Fukunaga *et al*[19] reported low, medium molecular weight (MMW) and LMW adiponectin levels in convalescent cases of KD compared to controls. In the present study, serum resistin levels were significantly elevated in patients with KD during the convalescent phase compared to controls. Serum leptin levels appeared to be higher in patients with KD, although the difference was not statistically significant. Adiponectin levels were similar in both cases and controls. Cai *et al*[29] performed a meta-analysis to assess the association of adiponectin and resistin in patients with KD. These authors showed that while serum resistin levels in patients with KD were significantly higher compared with those in controls, adiponectin levels were similar in patients with KD and controls. Our results are also in accordance with these findings.

CONCLUSION

Our results suggest that serum adipocytokine levels may impact lipid abnormalities observed during the convalescent phase of KD. The strength of our study is that it is a single centre study wherein all children were diagnosed and treated by the senior author of this study (SS), thereby ensuring uniformity in sample recruitment. Furthermore, the diagnosis of KD was based on standard criteria (AHA 2004). One of the obvious weaknesses is the small sample size, but this was unavoidable as the study had to be completed in a given time frame for the dissertation of the first author (DP). It is

Table 4 Comparison of published literature on circulating adipocytokines in children with Kawasaki disease

Ref.	Number of cases/controls	Stage of disease	CAA	Resistin	Leptin	Adiponectin
Takeshita *et al*[30], 2006	Cases-20; Febrile controls-15; Healthy controls-15	Acute phase (day 4-6); Convalescent phase (day 25-39)	NA	-	-	Adiponectin levels were significantly reduced in the acute phase compared to the convalescent phase. No difference between the convalescent phase and controls.
Nozue *et al* [15], 2010	Cases-44; Controls-17	Acute	0	Increased during the acute phase and returned to normal after IVIg administration	Not assessed	Not assessed
Fukunaga *et al*[19], 2010	Acute phase KD-9; Convalescent phase KD-20; Controls-21	Both acute and convalescent (> 2 yr from KD onset); 6.72 ± 3.2 yr following KD (for convalescent cases)	NA	Not assessed	Not assessed	Total and HMW adiponectin levels were lower in acute KD compared to controls; MMW and LMW adiponectin levels decreased in convalescent cases compared to controls
Qi *et al*[31], 2012	Cases-40; Controls-15	Acute; Afebrile; Subacute phase	6	Significantly high in the acute stage of KD and decreased with the course of the disease; No difference between patients with KD in the afebrile and subacute phase compared with the controls		
Liu *et al* [16], 2012	KD-80; Controls-85	Acute	39	Increased compared to controls. No difference between KD with and without CAAs	No difference	Increased compared to controls. No difference between KD with and without CAAs
Kemmotsu *et al*[17], 2012	Cases-56; Healthy controls-30; Febrile controls-31	Acute	4	Markedly elevated in acute stage and returned to normal after IVIg administration. Non-responders to IVIg had very high resistin levels	No difference	No difference
Kim *et al* [18], 2014	Cases-40; Febrile controls-32; Healthy controls-15	Acute	12	Markedly elevated in the acute stage but did not predict development of CAAs	Not assessed	Not assessed
Zhang *et al* [32], 2018	Cases-80; Febrile controls-20; Healthy controls-20	Acute phase	24			Decreased compared to febrile controls. However, no difference compared with healthy controls
Zhang *et al* [33], 2021	Cases-42; Controls-20	Acute phase (1-10 d); Subacute phase (11-20 d); Convalescent phase (21-30 d)	18			Serum adiponectin was significantly lower compared to controls
Present study, 2021	KD convalescent phase-20; Controls-20	Convalescent; > 3 yr of follow-up; (mean 5.5 yr)	4	Elevated in patients with KD compared to controls	Trend towards higher levels of leptin in patients with KD compared to controls	No difference

CAAs: Coronary artery abnormalities; HMW: High molecular weight; IVIg: Intravenous immunoglobulin; KD: Kawasaki disease; LMW: Low molecular weight MMW: Medium molecular weight; NA: Not available.

suggested that the leads provided by our work should be applied in a larger and preferably multicentric study.

ARTICLE HIGHLIGHTS

Research background

Patients with Kawasaki disease (KD) may have abnormal lipid profiles that may last for prolonged periods. The reasons underlying the persistence of lipid abnormalities are unclear in patients with KD.

Research motivation

There is a paucity of literature on the role of adipocytokines and their effect on abnormal lipid metabolism in patients with KD.

Research objectives

To estimate the levels of adipocytokines (adiponectin, leptin and resistin) during the convalescent phase of KD.

Research methods

Serum adiponectin, leptin and resistin levels were estimated by enzyme-linked immunosorbent assay in patients with KD and controls.

Research results

The mean age of patients in the study group was 10.15 ± 3 years. Median serum resistin levels in patients with KD (27.77 ng/mL; [IQR: 18.66, 48.90]) were increased compared to controls (21.20 ng/mL; [IQR: 14.80, 27.00]) (P = 0.04). Median serum leptin levels and adiponectin levels in cases and controls were similar. There was no significant correlation between adipocytokines and the lipid profile in patients with KD. There was no significant difference in all 3 adipocytokines between children with CAAs and without CAAs.

Research conclusions

Our results suggest that serum adipocytokine levels may impact lipid abnormalities observed during the convalescent phase of KD.

Research perspectives

The leads provided by our work should be applied in a larger and preferably multicentric study to confirm these results.

FOOTNOTES

Author contributions: Praharaj DL, Rawat A, Gupta A and Singh S conceived and designed the research; Praharaj DL, Rawat A, Arora K, and Pilania RK collected data and performed the research; Praharaj DL, Arora K, Pilania RK, and Bhattad S were involved in writing the first draft; Praharaj DL, Rawat A and Arora K performed laboratory tests; Praharaj DL, Rawat A, Arora K, and Pilania RK analyzed the data; Gupta A, Pilania RK, Bhattad S and Singh S were involved in patient management; Praharaj DL, Rawat A, Gupta A, Arora K, Pilania RK, Bhattad S, Singh S reviewed the literature; Rawat A, Pilania RK, and Singh S edited the manuscript, performed critical revision at all stages and final approval of the manuscript; all the authors read and approved the final manuscript.

Institutional review board statement: The study protocol was approved by the Institute Thesis Committee and Institute Ethics Committee. The manuscript has been approved by the Departmental Review Board.

Informed consent statement: Written informed consent was obtained from the parents/guardians at study enrolment.

Conflict-of-interest statement: The authors declare no "conflicts of interest".

Data sharing statement: The data on the findings of this paper are all included in the tables.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Wang LL
L-Editor: Webster JR

P-Editor: Wang LL

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 July 9; 11(4): 369-374

DOI: 10.5409/wjcp.v11.i4.369

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Observational Study

Children with lysinuric protein intolerance: Experience from a lower middle income country

Syed Bilal Hashmi, Sibtain Ahmed

Specialty type: Pathology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Dai DL, China; Yang X, China
A-Editor: Liu X, China

Received: December 29, 2021
Peer-review started: December 29, 2021
First decision: March 16, 2022
Revised: March 21, 2022
Accepted: June 3, 2022
Article in press: June 3, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Lysinuric protein intolerance (LPI) is an inborn error of metabolism consequential to recessive mutations in the *SLC7A7* gene. The metabolic imbalance in absorption and excretion of dibasic amino acids is considered the basis of LPI. The disease results from protein intolerance with signs and symptoms oscillating from cerebral impairment, respiratory involvement, renal failure and autoimmune complications.

AIM

To determine biochemical and clinical presentation of cases with biochemical picture suggestive of LPI in Pakistani children.

METHODS

The study was conducted at the Biochemical Genetic Lab, Department of Pathology and Laboratory Medicine, AKU Plasma, and urine amino acid quantification data from January 2013 to October 2018 was included in this study. The amino acids were analyzed by high performance liquid chromatography. Prestructured requisition forms were used to obtain the clinicopathological data. Statistical analysis was done by Microsoft Excel 2017.

RESULTS

A total of 6 patients were recognized. All the patients were male (100%). The mean age was 24 mo ± 10 d. All the patients had low plasma concentration of lysine, ornithine and arginine, whereas increased levels of lysine, ornithine and arginine in urine were observed in 2 patients. History of consanguineous marriage was present in all patients (100%). The most observed clinical symptom was feeding difficulty followed by failure to thrive (83.3%) and developmental delay (66.6%). Hepatomegaly was present in all patients (100%). No mutation analysis was done.

CONCLUSION
This study portrays the biochemical and clinical spectrum of LPI in Pakistan. Although clinical manifestations appeared in the first 2 years of life, most of them suffered a delay in undergoing diagnostic workup.

Key Words: Lysinuric protein intolerance; Consanguinity; Pakistan; Retrospective study

Core Tip: Lysinuric protein intolerance is an inherited biochemical disorder with just over 140 individuals worldwide. In this disorder, there is defective absorption and excretion of dibasic amino acids, such as lysine, arginine and ornithine. This is the first study from Pakistan, which has a high prevalence of inherited metabolic disorders. Only 4 previously reported cases were identified from South Asia. This study shows the biochemical pattern and clinical characteristics in patients with a suggestive diagnosis of lysinuric protein intolerance on biochemical workup.

Citation: Hashmi SB, Ahmed S. Children with lysinuric protein intolerance: Experience from a lower middle income country. *World J Clin Pediatr* 2022; 11(4): 369-374
URL: https://www.wjgnet.com/2219-2808/full/v11/i4/369.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.369

INTRODUCTION

Lysinuric protein intolerance (LPI) is a multi-organ congenital metabolic disorder. The recessive mutations of the *SLC7A7* gene located at chromosome 14q11.2 causes faulty transport of cationic amino acids of the epithelial cells, mainly at the basolateral membrane of the kidney and intestine[1]. This leads to an imbalance in absorption and excretion of cationic amino acids like lysine, ornithine and arginine. Hence their plasma levels are decreased, but urine levels are raised. The presence of the transport defect in the hepatocytes distinguishes LPI from other hyper-dibasic aminoacidurias[2]. There is co-occurrence of increased neutral amino acids (alanine, citrulline, glycine, proline and glutamine) on plasma amino acid testing[3,4].

The conventional presentation of LPI is after weaning from breast milk. It can present with upper and lower gastrointestinal symptoms, such as nausea, vomiting and diarrhea. Due to protein intolerance, most patients ultimately develop micronutrient and macronutrient deficiencies. Neurological manifestations such as hypotonia, lethargy, abnormal behavior, seizures and coma can result from episodic postprandial hyperammonemia[5,6]. This hyperammonemia is due to decreased levels of arginine and ornithine. The epitome of most of the symptoms is a secondary urea cycle defect. This combination of vague symptoms often causes a diagnostic delay[7], progressive disease and apprehension among caregivers. Clinical history and quantitative measurement of plasma and urine amino acids is required to reach the diagnosis. However, if a patient is on total parenteral nutrition, plasma amino acid profile may be falsely normal. The actual incidence of LPI in Pakistani population is unidentified. Therefore, this study was initiated to determine the clinicopathological spectrum of patients with a biochemical picture suggestive of LPI.

MATERIALS AND METHODS

The study was conducted at the Biochemical Genetic Lab, Department of Pathology and Laboratory Medicine, Aga Khan University Hospital, Karachi. Plasma amino acid (PAA) and urine amino acid (UAA) quantification data from January 2013 to October 2018 was included in the study.

The study was conducted in two phases. In the initial phase, a chemical pathologist reviewed PAA and UAA reports, and reports suggestive of LPI were outlined. In the subsequent phase, clinical details were retrieved from the history forms received with test requisition.

Biochemical analysis

First, 3-4 mL blood was taken in a lithium heparin tube for PAA quantification. Samples were centrifuged then delivered in dry ice to the Biochemical Genetic Lab. The samples were kept at -20 °C until analysis.

The amino acid level was measured by cation-exchange high performance liquid chromatography. To deproteinize the standard, the control and the samples, 10% sulfosalicylic acid was used. Norleucine was used as an internal standard. EZ chrome 3.31 was used to determine the results. Quality control and proficiency testing validation for amino acids were completed per the Clinical and Laboratory Standards Institution guidelines[8]. High and low levels of quality control samples were analyzed with each batch of 10 samples. The study commenced after receiving approval from the ethical review committee.

Data analysis

Statistical analysis was performed by Microsoft Excel 2017. Frequencies and percentages were generated for gender, consanguinity, clinical presentations and biochemical features of LPI.

RESULTS

Demographics

Over a span of 6 years, PAA estimation of 3057 patients was performed. Six patients were recruited in the study having PAA concentrations suggestive of LPI. All of them were males (100%). The mean age was 24 mo ± 10 d. Parental consanguinity was observed in all 6 (100%) patients (Figure 1).

Clinical and biochemical features

The most common clinical features recorded were feeding difficulty (6; 100%), failure to thrive (5; 83.3%) and developmental delay (4; 66.6%) as shown in Figure 2. Also, hepatosplenomegaly was observed in all patients (100%) and respiratory distress in 2 patients (33.3%). All the patients had decreased blood concentrations of lysine, ornithine and arginine (100%). The urinary concentrations of lysine, ornithine and arginine were increased in 2 patients (33.3%), while UAA was not undertaken for the remaining cases.

Follow-up and outcomes

Out of 6 patients, only 2 patients were followed up. They were put on a protein restricted natural diet along with L-citrulline and L-carnitine supplementation. The remaining patients refused any further diagnostic testing and treatment due to economic reasons.

DISCUSSION

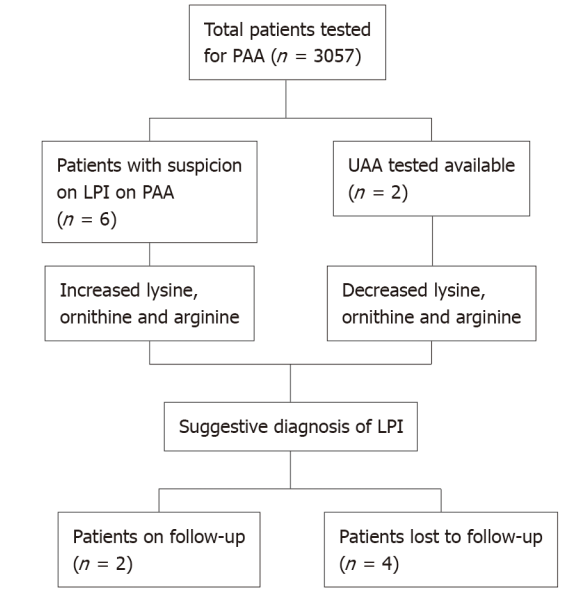
LPI is a rare disorder, and just over 140 individuals with LPI have been reported in the world, of which one-third are of Finnish origin[9]. There are no reported cases in Pakistan. An LPI patient usually presents with hepatosplenomegaly, impaired growth, protein intolerance and poor feeding. Long-term protein restriction and citrulline and nitrogen scavenging drugs are the drugs of choice. The prevention and treatment of the complications such as lung, renal and musculoskeletal system are also an important part of managing LPI. Being an autosomal recessive disorder, genetic counseling can form an important part of the management.

The cases reported in the current study presented after weaning with gastrointestinal disturbance, poor feeding, growth retardation and enlargement of the liver and spleen. Increased levels of lysine and arginine in the urine are diagnostic of LPI as was seen in our patients. Another method of making a definitive diagnosis of LPI is confirming the presence of the mutated *SLC7A7* gene by methods such as targeted mutation analysis and sequence analysis[1], which could not be done in this study.

A suspicion of LPI is aroused when a child shows an inability to digest proteins, whereas clinical findings include growth retardation, developmental delay and pulmonary and cerebral impairment. However, LPI may often be confused with other disorders such as hyperammonemia, lysosomal storage diseases, malabsorptive diseases and autoimmune disorders, such as systemic lupus erythematosus[10], which show similar clinical findings. Therefore, a confirmed diagnosis of LPI requires the combination of the above-mentioned signs along with positive laboratory findings.

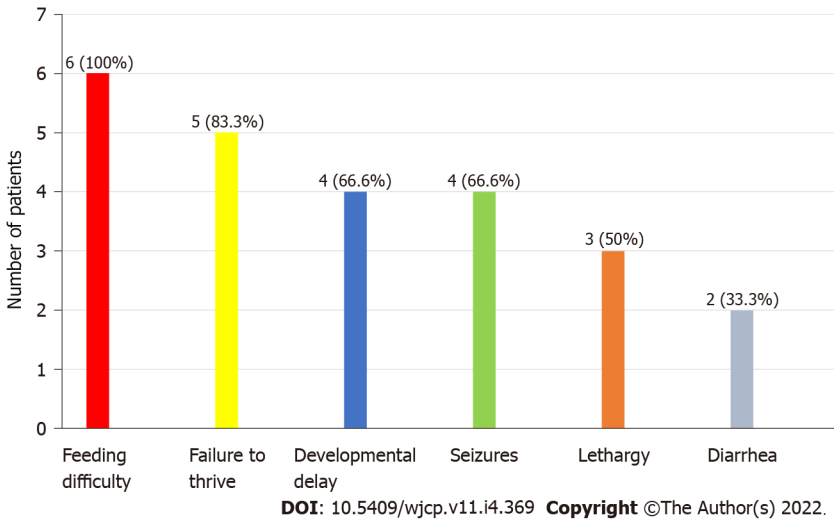
In addition to the small sample size from a single center, there are a few notable limitations of this study including the lack of gene sequencing for the confirmation of diagnosis and study population based on symptomatic cases following a high-risk screening. Gene sequencing for the disorder is not available in Pakistan, and additional cost of outsourcing the samples to laboratories abroad further leads to constraints for the confirmatory diagnosis.

Treatment of LPI includes protein restriction; compensation for the loss of lysine and arginine involves carnitine supplementation, as it has been found to be effective by having a lysine-sparing effect. Citrulline has also been found effective as a treatment option in LPI as it is converted to arginine in the body. In cases of an acute hyperammonemic crisis, pharmacologic treatment with arginine chloride, which blocks the production of ammonia, and a blend of medicines like sodium benzoate and



DOI: 10.5409/wjcp.v11.i4.369

Figure 1 Flow chart showing patients with lysinuric protein intolerance. PAA: Plasma amino acids; LPI: Lysinuric protein intolerance; UAA: Urine amino acid.



DOI: 10.5409/wjcp.v11.i4.369

Figure 2 Clinical features in patients with lysinuric protein intolerance (*n* = 6).

sodium phenylacetate has been suggested[10]. LPI is often associated with pulmonary and renal complications, and treatment of such complications with corticosteroids is found to be effective in some patients[1]. Therapy with bisphosphonates is currently under investigation as osteopenia leading to osteoporosis is a major feature[11].

Short stature, growth retardation and failure to thrive is usually observed in LPI patients due to protein malnutrition. Many studies have concluded that various amino acids and hormones influence the growth of these children. Awrich *et al*[12] reported that amino acids in combination such as citrulline with lysine and arginine with lysine had potent effects on growth and development of these children. A study also showed that an ample supply of arginine also helped in improving growth retardation in LPI [13]. The quality of life of these patients is dependent on lifelong monitoring and management of complications. The prognosis of a child with LPI varies on the involvement of lung and the successful resolution of its complications, with pulmonary involvement representing an increased fatal outcome [11]. Being an autosomal recessive disorder, an antenatal diagnosis of LPI can be made by the DNA analysis of fetal cells extracted by amniocentesis usually performed at 15-18 wk of gestation[10]. Table 1 shows the summary of studies from South Asia.

Table 1 Summary of studies on lysinuric protein intolerance in South Asia

Country	No. of cases	Ref.	Presenting symptoms	PAA findings	UAA findings	↑NH3
India	4	Bijarnia-Mahay *et al* [14], 2016	Neurodevelopmental symptoms	↓Lysine; ↓Ornithine; ↓ Arginine	↑Lysine; ↑Ornithine; ↑ Arginine	Yes
		Moosa *et al*[15], 2005	Neurodegenerative symptoms	↓Lysine; ↓Ornithine; ↓ Arginine	↑Lysine; ↑Ornithine; ↑ Arginine	Yes
		Deogaonkar *et al* [16], 2016	Skin pustules, decreased feeding, sepsis	Normal	↑Lysine; ↑Arginine	Yes
		Nalini *et al*[17], 2015	Failure to thrive, recurrent chest infections	↓Lysine; ↓Ornithine; ↓ Arginine	↑Lysine; ↑Ornithine; ↑ Arginine	Yes
Pakistan	6	This study, 2022	Feeding problems, failure to thrive, developmental delay	↓Lysine; ↓Ornithine; ↓ Arginine (in all patients)	↑Lysine; ↑Ornithine; ↑ Arginine (in 2 patients)	Yes

↑: Above the reference range; ↓: Blow the reference range; PAA: Plasma amino acids; UAA: Urine amino acids.

CONCLUSION

This study portrays the biochemical and clinical spectrum of LPI in Pakistani children. LPI is an inherited metabolic disorder. The treatment of which involves a protein-restricted diet and supplement of lysine, ornithine and citrulline. The clinical diagnosis of LPI can be delayed due to a combination of non-specific symptoms. In patients with hyperammonemia, LPI should be kept for differential diagnosis. There is need for wide spread local availability of PAA and UAA measurement to aid clinicians.

ARTICLE HIGHLIGHTS

Research background

Lysinuric protein intolerance (LPI) is an inherited metabolic disorder caused by alterations in the *SLC7A7* gene.

Research motivation

To create awareness among the clinical community and describe the spectrum of this rare disorder in Pakistan.

Research objectives

To present the biochemical and clinical presentation of cases with suggestive LPI in Pakistan.

Research methods

Descriptive cross sectional study.

Research results

Six cases with a suggestive diagnosis of LPI based on amino acid profiling were reported.

Research conclusions

Although clinical manifestations appeared in the first 2 years of life, a delay in diagnosis was evident.

Research perspectives

A high rate of inherited metabolic disorders in Pakistan is known.

FOOTNOTES

Author contributions: Ahmed S designed and conceived the idea, assisted in the write-up of the first draft and critically reviewed the manuscript; Hashmi SB performed the data collection, literature review and the majority of the write-up in the first draft.

Institutional review board statement: Study commenced after approval was obtained from the institutional ethics

committee (No. 2018-0553-894).

Conflict-of-interest statement: No conflict-of-interest to declare.

Data sharing statement: Dataset available from the corresponding author at ude.uka@demha.niatbis. Consent was not obtained as the presented data are anonymized and risk of identification is low.

Country/Territory of origin: Pakistan

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S-Editor: Zhang H
L-Editor: Filipodia CL
P-Editor: Zhang H

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2022 July 9; 11(4): 375-384

DOI: 10.5409/wjcp.v11.i4.375

ISSN 2219-2808 (online)

SYSTEMATIC REVIEWS

Impact of sports participation on cardiovascular health markers of children and adolescents: Systematic review and meta-analysis

Wesley Torres, Santiago Maillane-Vanegas, Jacqueline Bexiga Urban, Romulo Araujo Fernandes

Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Abdelbasset WK, Saudi Arabia
A-Editor: Yao QG, China

Received: July 29, 2021
Peer-review started: July 29, 2021
First decision: November 11, 2021
Revised: December 17, 2021
Accepted: May 26, 2022
Article in press: May 26, 2022
Published online: July 9, 2022

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Abstract

BACKGROUND

Cardiovascular diseases have a high prevalence in adults and their development begins in the first decades of life. On the other hand, sports participation in childhood and adolescence provides benefits which can delay the onset of these diseases.

AIM

To synthesize the available literature on the impact of sports participation on cardiovascular outcomes in children and adolescents.

METHODS

This systematic review was conducted on studies of children and adolescents (aged 8-18 years) who regularly practiced a sport and had reported cardiovascular outcomes (blood pressure and intima-media thickness) recorded. The Medline/PubMed, SciELO, Reference Citation Analysis (https://www.referencecitationanalysis.com/) and Bireme databases were searched.

RESULTS

In total, 3314 publications for blood pressure and 122 publications for intima-media thickness were identified in the databases. After exclusions (*e.g.*, duplicate articles, animal studies and those that did not meet the inclusion criteria), four publications for blood pressure (449 adolescents) and two publications for intima-media thickness were included (402 adolescents). For blood pressure, all publications were longitudinal in design (follow-up ranging from 12 wk to 12 mo) and involved adolescents aged from 8 years to 18 years of age. For intima-media thickness, both publications were longitudinal in design and involved adolescents aged from 11 years to 18 years of age.

CONCLUSION

Sports participation seems to promote benefits to cardiovascular structure and

function in adolescents. However, studies with adolescents are scarce and further research is needed to understand this phenomenon.

Key Words: Pediatrics; Adolescents; Sports; Blood pressure; Intima-media thickness

Core Tip: Obesity, poor diet and a sedentary lifestyle increases the risk for cardiovascular disease in adulthood. On the other hand, sports participation reduces blood pressure and children and adolescents engaged in sports tend to present better arterial thickness values. In this way, those who practice sports regularly may present better cardiovascular health. In this review we seek to characterize the results of sports practice in adolescence on aspects related to cardiovascular health.

Citation: Torres W, Maillane-Vanegas S, Urban JB, Fernandes RA. Impact of sports participation on cardiovascular health markers of children and adolescents: Systematic review and meta-analysis. *World J Clin Pediatr* 2022; 11(4): 375-384
URL: https://www.wjgnet.com/2219-2808/full/v11/i4/375.htm
DOI: https://dx.doi.org/10.5409/wjcp.v11.i4.375

INTRODUCTION

Cardiovascular diseases are the main cause of death among adults[1,2] with arterial hypertension being the most prevalent[3]. Although arterial hypertension is frequently observed in adults, high blood pressure is its manifestation in children and adolescents. In fact, the prevalence of high blood pressure in early life has increased in recent years[4,5] which is concerning for health professionals as it predicts mortality related to cardiovascular diseases in adulthood[6,7].

Blood pressure monitoring is a simple and useful way to screen cardiovascular problems in clinical practice. In addition, measures of intima-media thickness (IMT) also constitute a relevant marker of cardiovascular health, being a non-invasive method used to screen atherosclerosis[8,9].

Although the occurrence of cardiovascular diseases in children and adolescents is low, habits assumed in early life are able to affect health outcomes later in life[8,10]. Increased time spent in sedentary behavior[11] and insufficient physical activity[12] are behaviors that contribute to the development of cardiovascular diseases including arterial thickening[13].

Physical activity is a relevant behavior with huge potential to affect pediatric health. In terms of cardiovascular health, regular engagement in physical exercise helps to prevent a large variety of cardiovascular diseases in adulthood[14-18], but the effects in children and adolescents are still under investigation. Similarly, the pathways by which routines of physical exercise are able to promote cardiovascular health have been widely investigated in pediatric and adult groups[19], however, relevant questions still remain, mainly in pediatric groups.

For example, there are limited data about the impact of sports participation on cardiovascular health during adolescence. This question is relevant because in the real world (different from exercise protocols performed in the laboratory), sports participation is the main manifestation of physical exercise in adolescence helping adolescents to reach moderate-to-vigorous physical activity recommendations[20-23].

However, in the literature it is unclear whether engagement in sports is beneficial to the cardiovascular system in apparently healthy adolescents. Most publications involving physical exercise and cardiovascular aspects in adolescents are focused on obese groups and the exercise protocols rarely consider sports participation[24]. Thus, the objective of this review is to synthesize the available literature on the impact of sports participation on cardiovascular outcomes (blood pressure and IMT) in children and adolescents.

MATERIALS AND METHODS

Search strategy

The present systematic review was conducted according to the Preferred reporting Items for Systematic Review and Meta-Analyses recommendations. The Problem was "sports participation and cardiovascular outcomes in adolescents", the Intervention was "engagement in sports", the Comparator was "cardiovascular outcomes in adolescents non-engaged in sports", and the Outcome was "blood pressure

and intima-media thickness".

The main outcome of this review was to identify changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mmHg) and femoral and carotid IMT (mm) attributed to sports participation in children and adolescents. Due to the limited number of publications, there was no stratification according to sports.

Literature search and selection

Two authors independently performed the literature search from March to July 2021 and studies published until June 2021 were accessed. The search was restricted to publications in the following electronic databases: Medline/PubMed (National Library of Medicine), SciELO, Reference Citation Analysis (https://www.referencecitationanalysis.com/) and BIREME (Latin American and Caribbean Center on Health Sciences information). The search strategy considered the combination of nine keywords (DeCS): *Children*, *adolescents*, *youth*, *teenagers*, *pediatrics*, *sports*, *sports participation*, *organized sports*, *blood pressure*, *intima-media thickness* and *vessel thickness*, as follows.

Blood pressure: ((((((Children) OR (Adolescents)) OR (Youth)) OR (Teenagers)) OR (Pediatrics)) AND (((Sports) OR (Sports participation)) OR (Organized sport))) AND (Blood pressure).

Intima-media thickness: ((((((Children) OR (Adolescents)) OR (Youth)) OR (Teenagers)) OR (Pediatrics)) AND (((Sports) OR (Sports participation)) OR (Organized sport))) AND ((Intima-Media Thickness) OR (Vessel Thickness)).

Inclusion criteria

In terms of language, only publications in English were considered. Data from reviews, expert opinions, case reports, editorials, rodent studies and computational studies were excluded. Cross-sectional studies were also excluded because the aim was to consider longitudinal studies that identified changes in blood pressure and IMT in adolescents engaged in sports. Finally, longitudinal studies that investigated adolescents (girls and boys) aged between 8 years and 18 years who were regularly engaged in any sport were considered eligible.

Data extraction

A standardized Cochrane Consumers and Communication Review Groups data extraction method was used, whereby the age of the participants, sample size, sex, sports participation definition and cardiovascular health marker outcomes (systolic blood pressure, diastolic blood pressure, carotid intima media thickness and femoral intima media thickness) were collated from each study.

Initially, two independent researchers (SMV and JBU) identified potential studies eligible for this review by screening titles and abstracts. Subsequently, the same reviewers observed the inclusion and exclusion criteria, assessed the full texts and extracted data from the included studies using a standardized extraction form. In case of discrepancy, another reviewer (WT) was available throughout the screening process to verify and resolve any issue.

Quality assessment

The Newcastle-Ottawa quality assessment scale was used, which adopts a star system to assess the quality of eight items in three different domains (selection, comparability and exposure). Each item can receive one star, except for the comparability domain (two stars). The total score of the instrument ranges from 0 to 9[25].

Statistical analysis

In cases where standard error of the mean (SEM) and mean values for the intervention or control group were available, the SD was calculated using the following formula: $SD = SEM \times \sqrt{n}$.

In cases where 95% confidence intervals (95%CI) were provided for the intervention or control group, the SD was calculated as follows: SD = $\sqrt{n}$ × (upper limit - lower limit)/t statistic).

The meta-analysis was performed using Review Manager software (Version 5, Cochrane Collaboration). Differences in means and 95%CI were calculated using a continuous random-effect model to incorporate heterogeneity among studies. If the number of available studies was small ($n \leq 3$), a fixed effect model was applied to estimate the between study heterogeneity.

Heterogeneity between studies was assessed using the chi square test expressed by means of inconsistency indices (I^2) (0%–25%: None, 26%–50%: Low, 51%–75%: Moderate, and 76%–100%: High). Statistical significance was set at $P < 0.05$.

Table 1 Blood pressure

Ref.	Title of paper	Aim/purpose	Total sample, *n* = 326	Sample age	Follow-up time	Sports	Main results	Quality assessment[1]
Cayres-Santos *et al*[29], 2020	Sports participation improves metabolic profile in adolescents: ABCD growth study	To analyze the impact of participation in sports with different CRF demands on changes in metabolic and cardiovascular markers in adolescents	184 adolescents (*n* = 122 engaged in sports and *n* = 62 not engaged in sports)	Between 11-18	12 mo	High CRF: Basketball, swimming, tennis, and track and field. Low CRF: Baseball, gymnastics, judo, karate, and kung fu	SBP increased in both sports with high [2.299 mmHg (95%CI: 0.142-4.456)) and low CRF [2.806 mmHg (95%CI: 0.261-5.351)]. DBP increased in sports with high [1.896 mmHg (95%CI: 0.499-3.293)], but not in sports with low CRF [0.948 mmHg (95%CI: -0.271 to 4.562)]	7
Cayres *et al* [30], 2018	Sport-based physical activity recommendations and modifications in C-reactive protein and arterial thickness	We analyzed the effects of 1 yr of engagement in ≥ 300 min/wk of organized sports on inflammatory levels and vascular structure in adolescents	89 adolescents (*n* = 15 sport practice and *n* = 74 non-sport practice)	Between 11-14	12 mo	Soccer, swimming, and others not shown	SBP did not change in the sports participation group [-0.309 mmHg (95%CI: -4.149 to 3.532)], but DBP did [-6.269 mmHg (95%CI: -9.313 to -3.224)]	7
Seabra *et al* [31], 2020	School-based soccer practice is an effective strategy to improve cardiovascular and metabolic risk factors in overweight children	We examined the effects of a 6-mo school-based soccer program on CV and metabolic risk factors in overweight children	40 overweight boys aged 8 to 12 yr (*n* = 20 soccer group and *n* = 20 control group)	Between 8–12	6 mo	Soccer	SBP did not change in the soccer group (2.7 mmHg), but DBP did (-4.0 mmHg)	9
Vasconcellos *et al*[26], 2021	Does Recreational Soccer Change Metabolic Syndrome Status in Obese Adolescents? A Pilot Study	To evaluate whether a soccer program (RSP) might lower risk factors related to MetS in obese adolescents	13 adolescents aged 13-17 yr (*n* = 6 soccer program and *n* = 7 control)	Between 12-17	12 wk	Soccer	SBP (-7.0 mmHg) and DBP (-3.0 mmHg) did not change significantly in the soccer group	8

[1]Quality Assessment according to Newcastle-Ottawa Scale (range 0 to 9) for cohort studies. ABCD Growth Study: Analysis of Behaviors of Children During Growth; CRF: Cardiorespiratory fitness; CV: Cardiovascular; MetS: Metabolic syndrome; RSP: Randomly assigned to experimental.

RESULTS

Study selection

The research team searched for publications considering two outcomes, the impact of sports participation on blood pressure and IMT.

A total of 3436 relevant studies were identified in the databases. The majority of the studies assessed blood pressure [*n* = 3314 (96.4%)], while 122 (3.6%) assessed intima media thickness. After removal of duplicates and screening of study titles and abstracts, 2307 studies remained. Following the final full-text screening process, 4 studies for systolic and diastolic blood pressure (*n* = 326) and 2 studies for intima media thickness (*n* = 273) were included in the meta-analysis. The study selection process is presented in Figure 1.

Study outcomes

The characteristics of participants included in each study are presented in Table 1 for blood pressure and Table 2 for intima media thickness issues. Comparisons between the two groups (sports participation and control groups) are shown in Figure 2.

Table 2 Arterial thickness

Ref.	Title of paper	Aim/purpose	Total sample, *n* = 273	Sample age	Follow-up time	Sports participation definition	Main results	Quality assessment[1]
Cayres-Santos *et al*[29], 2020	Sports participation improves metabolic profile in adolescents: ABCD growth study	To analyze the impact of participation in sports with different CRF demands on changes in metabolic and cardiovascular markers in adolescents	184 adolescents (*n* = 122 engaged in sports and *n* = 62 not engaged in sports)	Between 11-18	12 mo	High CRF: Basketball, swimming, tennis, and track and field. Low CRF: Baseball, gymnastics, judo, karate, and kung fu	Carotid IMT did not change in both sports with high [0.002 mm (95%CI: -0.018 to 0.023)] and low CRF [-0.001 mm (95%CI: -0.024 to 0.023)]. Femoral IMT did not change in both sports with high [0.013 mm (95%CI: -0.010 to 0.037)] and low CRF [-0.004 mm (95%CI: -0.024 to 0.033)]	8
Cayres *et al*[30], 2018	Sport-based physical activity recommendations and modific-ations in C-reactive protein and arterial thickness	We analyzed the effects of 1 yr of engagement in ≥ 300 min/wk of organized sports on inflammatory levels and vascular structure in adolescents	89 adolescents (*n* = 15 Sport practice and *n* = 74 non-sport practice)	Between 11-14	12 mo	Soccer, swimming, and others not shown	Carotid IMT did not change in the sports participation group [0.006 mm (95%CI: -0.013 to 0.024)], but Femoral IMT did [-0.043 mm (95%CI: -0.081 to -0.006)]	8

[1]Quality Assessment according to Newcastle-Ottawa Scale (range 0 to 9) for cohort studies. CRF: Cardiorespiratory fitness; IMT: Intima-media thickness.

Study characteristics and meta-analysis

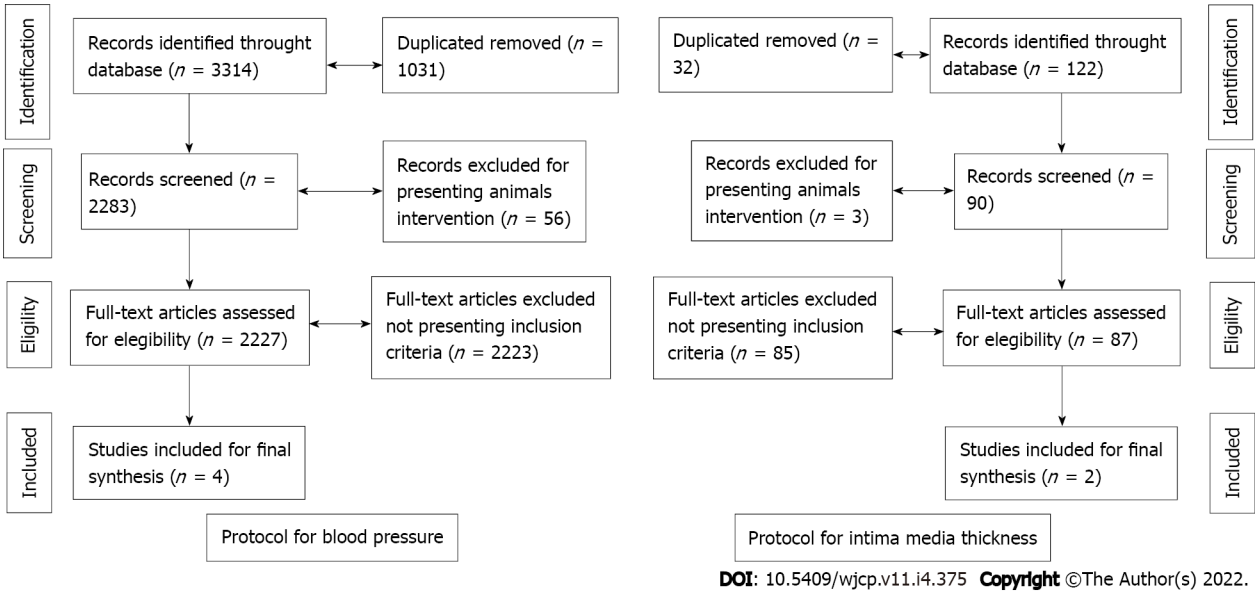
Blood pressure: The four publications included 326 adolescents aged from eight to 18 years (163 engaged in sports and 163 defined as control). All the studies had a longitudinal design and the findings are detailed in Table 1. The four publications varied according to the time of follow-up (ranging from 3 mo to 12 mo) and the sports considered included soccer, swimming, judo, karate, kung fu, gymnastics, basketball, track and field and baseball. All studies were published from 2018 to 2021.

In an individual way, studies did not show relevant changes through the follow-up for SBP and DBP. However, the meta-analysis model with the sum of all studies identified a decrease in DBP in favor of the sports participation group [-1.67 mmHg (95%CI: -2.90 to -0.43)].

IMT: The two papers included 402 adolescents aged from 11 years to 17 years. Both studies had a longitudinal design and the findings are detailed in Table 2. The studies were conducted between 2018 and 2020 and both recorded a 12-mo follow-up. No relevant changes were observed between sports participation and control groups in either the analysis of the individual results or in the meta-analysis model (Figure 2A and D).

Quality assessment

All 6 studies that met the inclusion criteria and from which data were extracted, presented a quality rating between good (Cayres-Santos 2020 and 2018) and high quality (Seabra 2020 and Vasconcellos). All studies clearly defined the objectives, the participants included, inclusion/exclusion criteria adopted, independent variables, outcome measures and exposure status (sport), along with training history. No studies reported investigators being blinded to participant sport/training exposures.



DOI: 10.5409/wjcp.v11.i4.375

Figure 1 Flowchart.

DISCUSSION

The aims of this review were to synthesize and analyze the available literature about the impact of sports participation on cardiovascular outcomes in children and adolescents, particularly blood pressure and intima media thickness.

For blood pressure, only four studies met the inclusion criteria. The limited number of longitudinal studies considering the impact of sports participation on cardiovascular health of pediatric groups highlights the absence of data assessing the impact of physical exercise in the real world mainly because sports participation is the most common manifestation of physical exercise in the pediatric groups[22]. Most of the literature available on this issue relies on exercise protocols carried out in research laboratories and limits application in non-laboratorial settings.

In terms of findings, sports participation seems to be related to lower DBP. In fact, the beneficial impact of physical exercise on blood pressure of obese children and adolescents seems relevant but is still unclear in non-obese groups[26]. In fact, the pathways linking physical exercise and reductions in blood pressure strongly rely on the presence of obesity mainly due to its pro-inflammatory role in the organism[26]. The four included manuscripts considered children and adolescents with and without obesity which demonstrates the potential of sports participation to affect blood pressure in non-obese children and adolescents. However, the reduced number of manuscripts limits further interpretations of the findings.

For intima media thickness, sports participation was not significantly related to any modifications. Among adults, the literature recognizes that physical exercise improves the morphometry of arteries (arterial diameter increases improving dilation capacity which leads to reduced wall thickness)[27]. Thus, regular engagement in physical exercise is pointed out as effective in primary and secondary prevention strategies to reduce arterial wall thickness and arterial stiffness, especially in at-risk populations[27,28]. However, in our study with pediatric groups, both studies were carried out by the same research team and only cohort studies were found (no randomized clinical trials) which also limits further interpretations.

Limitations

In terms of limitations, some aspects should be considered. First, our search was restricted only to the English language, not considering manuscripts published in different languages. Second, some relevant data in our meta-analysis (*e.g.*, standard deviation of the difference) were estimated by the authors and not provided by the authors of the publication considered in the meta-analysis. Third, the reduced number of publications limits further inferences about the findings.

CONCLUSION

In summary, although sports participation seems to be related to improvements in blood pressure (diastolic), the literature assessing the impact of sports participation on cardiovascular health in children

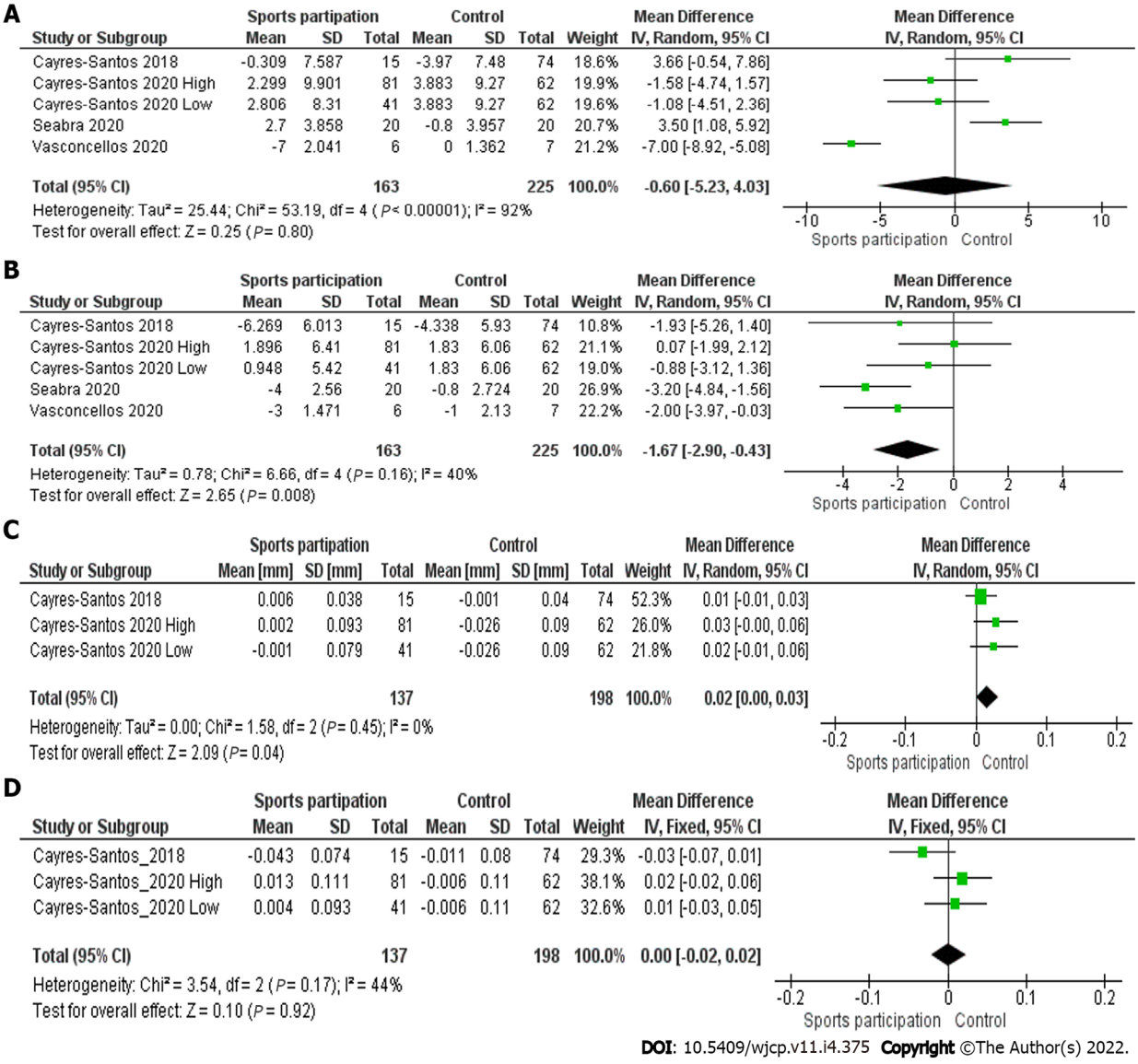


Figure 2 Sports participation *vs* control. A: Sports participation *vs* control for systolic blood pressure; B: Sports participation *vs* control for diastolic blood pressure; C: Sports participation *vs* control for carotid intima media thickness; D: Sports participation *vs* control for femoral intima media thickness.

and adolescents is extremely scarce.

ARTICLE HIGHLIGHTS

Research background

Adolescents are commonly engaged in sports but its impact on pediatric health is poorly explored in the literature.

Research motivation

There are many adolescents engaged in sports around the world and many organizations recommend sports participation as promoters of health among adolescents. However, little is known about its impacts on pediatric health.

Research objectives

To identify in the literature the potential benefits of sports participation on the cardiovascular health of children and adolescents.

Research methods
We ran a systematic review with meta-analysis.

Research results
Sports participation is related to blood pressure but not related to intima-media thickness. However, the amount of literature about the issue is extremely scarce.

Research conclusions
The literature assessing the impact of sports participation on cardiovascular health in children and adolescents is extremely scarce and it is unclear its impact on pediatric health.

Research perspectives
We hope these findings will be useful to motivate researchers to expand the amount of data about the impact of sports participation on the cardiovascular health of pediatric groups.

FOOTNOTES

Author contributions: Torres W, Maillane-Vanegas S, Urban JB and Fernandes RA were involved in the conception, data collection, performing the analysis and interpretation of data.

Supported by FAPESP, No. 2015/19710-3 and No. 2018/22593-7; FAPESP to Wésley Torres, No. 2018/09131-4; and CNPq, No. 2893293992696924.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Brazil

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S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

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