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EDITORIAL

Cow's milk-induced gastrointestinal disorders: From infancy to adulthood

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Abstract

Milk is related to many gastrointestinal disorders from the cradle to the grave due to the many milk ingredients that can trigger gastrointestinal discomfort and disorders. Cow's milk protein allergy (CMPA) is the most common food allergy, especially in infancy and childhood, which may persist into adulthood. There are three main types of CMPA; immunoglobulin E (IgE)-mediated CMPA, non-IgE-mediated CMPA, and mixed type. CMPA appears before the first birthday in almost all cases. Symptoms may start even during the neonatal period and can be severe enough to simulate neonatal sepsis. CMPA (often non-IgE mediated) can present with symptoms of gastroesophageal reflux, eosinophilic esophagitis, hemorrhagic gastritis, food protein-induced protein-losing enteropathy, and food protein-induced enterocolitis syndrome. Most CMPAs are benign and outgrown during childhood. CMPA is not as common in adults as in children, but when

present, it is usually severe with a protracted course. Lactose intolerance is a prevalent condition characterized by the development of many symptoms related to the consumption of foods containing lactose. Lactose intolerance has four typical types: Developmental, congenital, primary, and secondary. Lactose intolerance and CMPA may be the underlying pathophysiologic mechanisms for many functional gastrointestinal disorders in children and adults. They are also common in inflammatory bowel diseases. Milk consumption may have preventive or promoter effects on cancer development. Milk may also become a source of microbial infection in humans, causing a wide array of diseases, and may help increase the prevalence of antimicrobial resistance. This editorial summarizes the common milk-related disorders and their symptoms from childhood to adulthood.

Key Words: Cow's milk; Adults; Children; Functional gastrointestinal disorders; Cow's milk protein allergy; Lactose intolerance, Inflammatory bowel disease; Zoonosis

Core Tip: Milk has been a basic human food for hundreds of centuries with a high nutritional value. However, milk can cause various gastrointestinal disorders from early childhood to late adulthood, as many milk ingredients, such as lactose and cow's milk proteins, can trigger gastrointestinal discomfort and disorders. Cow's milk protein allergy and lactose intolerance are the most common milk-related disorders. However, milk consumption is related to many functional gastrointestinal disorders, inflammatory bowel disease, milk-related cancer, and milk-born zoonotic infections. Awareness of these disorders is crucial for physicians and patients to avoid unnecessary nutritional mismanagement.

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INTRODUCTION

Milk is a comprehensive dietary liquid containing adequate amounts of highly bioavailable nutrients humans need. Humans have consumed animal milk for about 10000 years and as baby food for about 8000 years, as evidenced by the dental remains of Neolithic humans, ancient clay pottery vessels, and ancient baby bottles[1]. Many gastrointestinal disorders humans suffer are related to dietary components, and diet modification could be an essential step in disease management. As milk is a critical component in the human diet, milk is related to many gastrointestinal disorders from the cradle to the grave[2]. Many milk ingredients, such as lactose and cow's milk proteins, can trigger gastrointestinal discomfort and disorders. Milk decreases gut bacterial diversity. Dairy and dairy products, such as yogurt and kefir, can modulate and alter the gut microbiota[3]. In addition to its effects on gut microbiota, cow's milk may make humans prone to many food-borne infectious diseases. In this editorial, we discuss the various cow's milk-induced gastrointestinal disorders from infancy to adulthood that will be highlighted in the topics of this special issue. Table 1 summarizes the various gastrointestinal effects of cow's milk on humans.

METHODS AND RESULTS

In this editorial, we conducted a comprehensive literature review by searching electronic databases such as PubMed, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, Web of Science, Scopus, Library and Information Science Abstracts, and the National Library of Medicine catalog up to July 31, 2022, related to cow milk effects on the gastrointestinal tract in children and adults. Reference lists were inspected, and citation searches were performed on the included studies. We included open-access papers on English-language studies. Figure 1 shows the flow chart of the reviewed articles. We included 146 articles concerned with the various effects of cow's milk on humans, from birth to the elderly. We also cited high-quality articles in *Reference Citation Analysis* (https://www.referencecitationanalysis.com).

Table 1 The various gastrointestinal effects of cow's milk in humans

Items	Details
Cow's milk protein allergy	Pediatric onset: (1) IgE-mediated; (2) Non-IgE-mediated; and (3) Mixed type
	Adult onset: (1) Mostly IgE-mediated; and (2) Pregnancy-induced CMPA
	Pediatric onset with adulthood persistence
Lactose intolerance	Developmental
	Congenital (inherited)
	Primary (aging-induced)
	Secondary
Cow's milk-related functional gastrointestinal disorders	Functional dyspepsia
	Persistent regurgitation and gastroesophageal reflux
	Infant colic
	Functional constipation
	Irritable bowel syndrome
Cow's milk and inflammatory bowel diseases	Crohn's disease
Cow's milk-related gastrointestinal cancer	Anti-colorectal cancer
Milk-born gastrointestinal infections	*Mycobacterium avium*, *Mycobacterium bovis*, *Salmonella species*, brucellosis, streptococcal infections, "summer diarrhea", *Yersinia enterocolitica*, *diphtheria*, *Escherichia coli* (*E. coli*), *Campylobacter jejuni*, *Citrobacter species*, *Shiga toxin-producing E. coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Klebsiella species*

E. coli: *Escherichia coli*.

COW'S MILK PROTEIN ALLERGY

Cow's milk protein allergy (CMPA) is the most frequent food allergy, especially in infancy and childhood, but it can persist into adulthood. It is due to an abnormal immune response to CMP. It should be distinguished from the other adverse effects of cow's milk, such as lactose intolerance and infection-related disorders[4]. Both casein and whey (α-lactalbumin and β-lactoglobulin) proteins can cause allergic reactions. α-lactalbumin and casein are the most common cow's milk allergenic proteins, while β-lactoglobulin is associated with severe anaphylaxis[5]. In addition, β-lactoglobulin has a relative resistance to enzymatic degradation. Therefore, β-lactoglobulin could be implicated in non-immunoglobulin E (IgE)-immune-mediated CMPA with delayed gastrointestinal symptoms[6]. Besides cow's milk and dairy products, CMPs can be detected in some probiotics, oral polio vaccines, and lactulose. Some dry powder inhalers containing lactulose (such as Fluticasone/Salmeterol or Lanimavir) could be contaminated with CMPs. Some parenteral vaccines, such as the diphtheria-tetanus-pertussis vaccine, can be contaminated with CMP[7].

It should also be noted that cow's milk allergy is not only against cow's milk proteins but can also be triggered by other additives that could be added to modify cow's milk, such as artificial flavors or preservatives. Cross-reactivities with other mammals' milk (*e.g.*, goats and sheep) and raw beef are prevalent due to the composition of homologies of amino acids[8,9]. About 13%-20% of children with CMPA have a beef meat allergy. In addition, patients with beef meat allergies mostly have CMPA. Camel's milk proteins are unlikely to cross-react with cow's milk proteins due to phylogenetic differences, and consequently, camel's proteins cannot be recognized by circulating IgEs and monoclonal antibodies[10]. Even though soy milk is being used as a possible substitute for cow's milk in the case of CMPA, cross-reactivity between both occasionally exists due to cross-reactivity with bovine caseins and soybean protein p34[11].

There are three main types of CMPA: IgE-mediated CMPA, non-IgE-mediated CMPA, and mixed allergic reactions. The role of other kinds of immune-mediated reactions to CMP, especially those associated with IgG and IgA antibody isotypes, is presently controversial[12]. The rate of IgE-mediated CMPA decreases while other non-IgE-mediated CMPA increases with increasing age. High cow's milk-specific IgE levels are rare in adults[13]. CMPA may manifest as an isolated gut reaction or be associated with other systemic manifestations such as skin, respiratory, or cardiovascular manifestations. CMPA can affect any part of the gastrointestinal tract, from the mouth to the anus, and at any age, from newborn to the elderly[14].

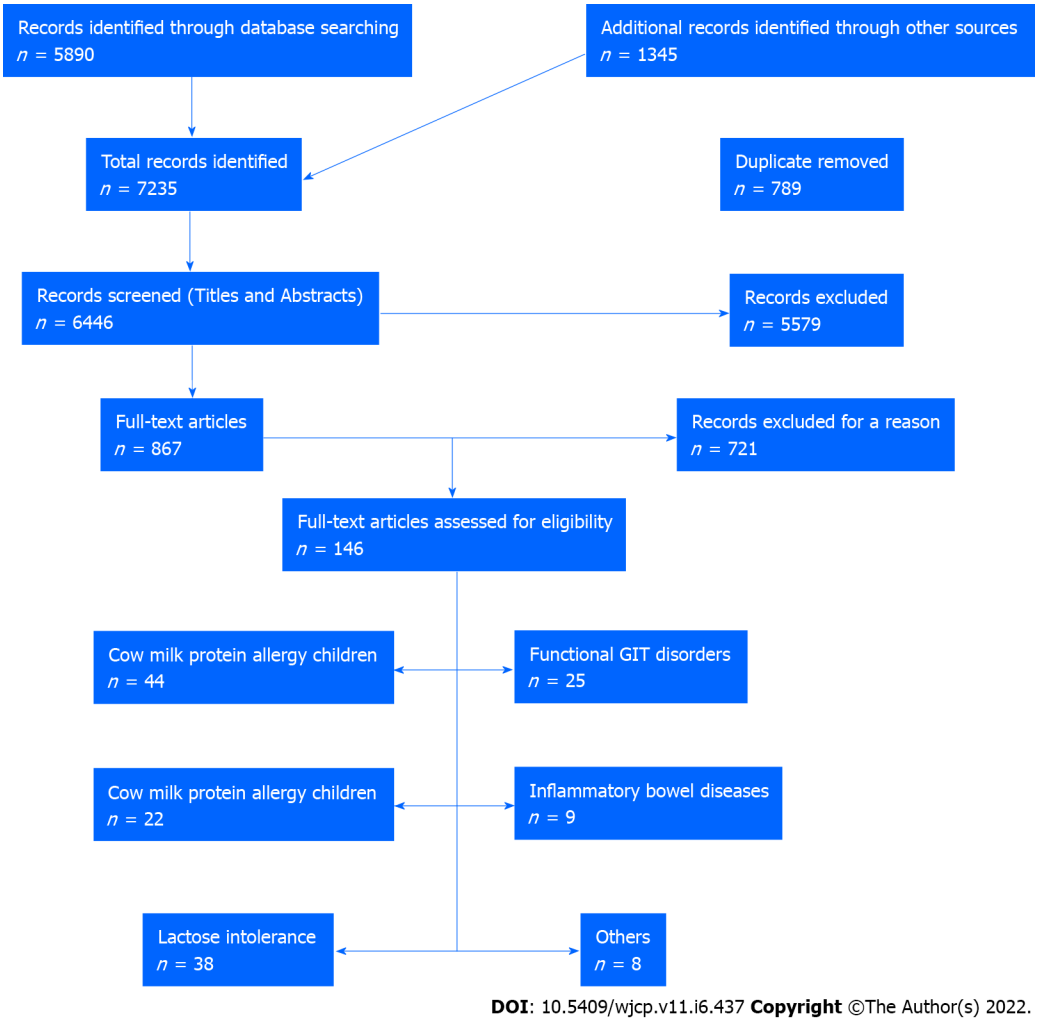

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Figure 1 The flow chart of the included studies. GIT: Gastrointestinal tract.

CMPA in infancy and childhood

CMPA commonly occurs early in life, and almost all cases appear before the first birthday. The average age for CMPA to appear during childhood is 3.5 mo (ten days-to-ten months). The symptoms usually appear in the first week after the introduction of CMP (95% of cases). About 60% of patients developed symptoms with the first formula feeding[15].

Risk factors for CMPA include immature gastric acid production, defective intestinal and pancreatic enzymes, low vitamin D levels, and a deficit of regulatory T cells[16,17]. Other risk factors include male sex, parental atopy, maternal allergy, maternal smoking during pregnancy, amnionitis, maternal vaginitis, febrile infection during pregnancy, gestational diabetes, hypertension, stress, decreasing maternal age, and difficult delivery (early or threatened labor, malpresentation of the fetus, cesarean section, breech and instrumental delivery, low APGAR score). Post-natal risk factors include neonatal jaundice, Erythema toxicum neonatorum, antibiotic use in the first week of life, and indoor air contaminants such as mold and smoking[18,19]. Another important risk factor for CMPA during infancy is gut microbial dysbiosis. Gut microbiotas play a vital role in modifying intestinal regulatory T (Treg) cell responses to develop an oral tolerance that could protect against IgE-mediated CMPA and other types of food allergies[20]. On the other hand, non-IgE-mediated CMPA can induce gut microbial dysbiosis, affecting intestinal immune homeostasis and tolerance[21]. Tan *et al*[22] showed that *Lactobacillus rhamnosus* (*L. rhamnosus*) could help promote oral tolerance in children suffering from CMPA and assist with intestinal symptom recovery.

Sensitization can occur before and after birth, resulting in non-IgE mediated CMPA as indicated by the presence of CMP-specific tumor necrosis factor-α in the cord blood and the appearance of the symptoms shortly after birth[23]. The onset of symptoms in infancy and childhood usually develops within a week of cow's milk exposure, although symptoms may take many weeks (up to 24 and 36 wk). Most cases appear after cow's milk exposure (raw or formula milk), but some may appear after cow's milk-based foods. However, some exclusively breastfed infants may develop CMPA after exposure to CMP excreted in breast milk[24,25]. Most CMPAs are benign and outgrown during childhood. Non-IgE-mediated CMPA usually resolves more quickly than IgE-mediated allergy. Signs of persistence of

CMPA include the presence of acute manifestations, multiple food allergies, especially to eggs, concomitant bronchial asthma, allergic rhinitis, and reactivity to CMP in baked milk on exposure or first challenge[26,27].

Gastrointestinal symptoms of CMPA in infancy and children

Acute manifestations of IgE-mediated CMPA include nausea, vomiting, diarrhea, bloody stools, gastroesophageal reflux (GER), and colicky abdominal pain. The symptoms usually appear rapidly within minutes of exposure. Anaphylaxis may also manifest in young infants with angioedema of the lips, tongue, and palate, oral pruritus, pallor, and floppiness[28]. Symptoms may occur even during the neonatal period and can be so severe as to be misdiagnosed as neonatal sepsis[29]. Non-IgE-mediated CMPA is common (50% of pediatric CMPA) and is presented with faltering growth, frequent "spitting up", feeding problems, food refusal or aversion, pallor and tiredness, abdominal colic, upper digestive bleeding, gastroesophageal reflux with or without disease (GERD), abnormal stool habitus such as chronic diarrhea or constipation, blood and/or mucus in the stools, perianal redness, and skin manifestations such as atopic eczema[30,31].

CMPA (often non-IgE mediated) can present with symptoms of GERD, such as poor appetite, crying, fussiness, regurgitation, vomiting, and sleep disturbances. Oral milk elimination and rechallenge tests, esophageal pH impedance, and gastrointestinal endoscopy are advised for a correct clinical diagnosis, but they are not always achievable in all patients[32]. Eosinophilic esophagitis is an immune-mediated disease by Th2 interleukins affecting the esophagus with age-dependent symptoms such as GER, abdominal pain, and food impaction. Various allergens, including CMP can trigger it. Endoscopy shows characteristic features of mucosal eosinophilic infiltration of more than 15 eosinophils/high power field [33]. It can be treated with proton-pump inhibitors, but dietary treatment is the cornerstone of therapy after confirming the diagnosis with endoscopy and a 4- to 12-wk elimination test. The dietary approaches involve amino acid-based formula, allergy testing-based directed diet, or empirical six-food elimination diet (milk, soy, wheat, eggs, fish/seafood, and peanut/nuts)[34,35].

Hemorrhagic gastritis: Hemorrhagic gastritis is not common in infants with CMPA but is recorded in some cases. A possible cause is *in utero* CMP sensitization. It may be present with persistent vomiting and with subacute or chronic hematemesis. Occasionally, it may be present with subclinical hemorrhage. Endoscopy is usually needed to confirm the diagnosis. Nevertheless, etiological diagnosis is made according to clinical guidelines to diagnose CMPA with an elimination diet and rechallenge test. The outcome is usually favorable, with complete spontaneous resolution within one week after a period of bowel rest using either parenteral nutrition or amino acid formula[36,37]. Acute pancreatitis was recorded in one case with eosinophilic gastroenteritis due to CMPA[38].

Food protein-induced protein-losing enteropathy: Food protein-induced protein-losing enteropathy in infancy is a mixed IgE and non-IgE immune-mediated food allergy characterized by villous atrophy that leads to enteral loss of proteins, causing hypoproteinemia/hypoalbuminemia, diarrhea, edema, malabsorption, and poor weight gain. Laboratory work-up showed anemia, eosinophilia, hypoalbuminemia, raised fecal α1-antitrypsin (α1AT), raised specific-IgE, and positive allergy skin prick test (SPT) for milk proteins[39]. Hypoalbuminemia results from protein loss in the stool. α1AT is a part of the plasma protein not digested in the intestines and is not present in animal or plant food. The increased fecal α1AT is a good marker of protein loss through the digestive system[40]. A diagnosis relies mainly on the response to an elimination diet, with clinical improvement usually occurring within 3-4 d, but it may take weeks to resolve fully[41].

Food protein-induced enterocolitis syndrome: Food protein-induced enterocolitis syndrome (FPIES) is mainly a non-IgE-mediated disease caused mainly by CMP. It is caused by IgE-mediated mechanisms in 25% of cases, especially in patients with more protracted and persistent courses. Those with multiple allergies present with copious, repetitive vomiting, abdominal pain, and frequent diarrhea, causing acute dehydration with lethargy. Weight loss and failure to thrive occur in chronic conditions. FPIES is frequently misdiagnosed as acute viral gastroenteritis, sepsis, or surgical conditions, which delays the diagnosis for many months. FPIES occasionally results in symptoms similar to protein-induced protein-losing enteropathy and protein-induced proctocolitis[42,43]. The diagnosis is mainly clinical. However, open food challenges, milk-specific IgE, and SPTs can help diagnose FPIES. Milk-specific IgE is positive in about 25% of cases. Ondansetron may help in acute conditions. FPIES usually resolves by 3-5 years [44]. However, we still need future investigations and treatment guidelines to improve patient care for those with FPIES.

Food protein-induced allergic proctocolitis: Food protein-induced allergic proctocolitis (FPIAP) is a benign non-IgE-mediated delayed immune response to allergenic foods such as a cow or soymilk protein. It usually presents with a bloody mucoid stool in a well-appearing healthy infant aged one to four weeks. It occurs mainly in exclusively breastfed infants (60%) and resolves when the mother eliminates CMP and soy proteins from their diet[45]. As skin allergy tests and IgE are negative in infants with FPIAP, the diagnosis is usually made by exclusion and confirmed with an elimination/rechallenge test with CMP or soymilk protein[46]. The symptoms usually disappear within 1-3 d of the elimination

of the offending CMP or soy protein from the diet of breastfeeding mothers. However, it may take a longer time to resolve the symptoms. With a dairy-eliminated diet, the mother should be supported with a daily calcium intake of at least 800 mg and multivitamins as needed. Bottle-feeding babies may benefit from extensively hydrolyzed formulas or sometimes amino acid-based formulas. FPIAP is benign, and most cases resolve by the first birthday[47].

CMPA in adults

CMPA is not as common in adults as in children, but when present, it usually has a severe and protracted course. The symptoms can be elicited by traces of milk as small as 0.3 mg of CMPs[40]. Adults with CMPA have allergies to the same major allergenic milk proteins (casein and whey). However, they usually display robust immune responses, as illustrated by powerful SPTs and high IgE reactivity[48]. Even dermal or respiratory exposure to CMP can induce a severe form of CMPA, including anaphylaxis. Repeated exposure to CMP by food handling or inhalation of dairy products could induce cutaneous sensitization in adult patients with a personal history of atopy[49,50]. Hansen *et al*[51] showed that only 1%-3% of children with CMPA would continue to have CMPA as an adult, usually severe and life-threatening. Stöger and Wüthrich[52] showed that CMPA was more common in females (92%); 39% of them developed CMPA during or shortly after pregnancy. Casein was the predominant sensitizing allergen in 71%, while whey protein sensitization (alpha-lactalbumin and beta-lactoglobulin) was rare. He *et al*[53] demonstrated that A1 β-casein is the responsible component of casein that can induce CMPA, whereas A2 β-casein alleviates the acute gastrointestinal symptoms in Chinese adult patients with CMPA. The presence of other autoimmune diseases could increase the risk of CMPA. Kristjánsson *et al*[54] showed that 50% of adult patients with coeliac disease developed a mucosal inflammatory response similar to that of gluten with rectal CMP. Casein was the main allergic protein. About one-quarter of patients with irritable bowel syndrome (IBS) have food hypersensitivity, including CMPA[55].

Different factors can affect the prevalence of CMPA in adults, such as ethnic origin and geographical area. A study by Domínguez-García *et al*[56] on young adult students (18- to 25-year-olds) in a Mexican university showed that the prevalence of CMPA among them was 1/400 compared to 1/10 for lactose intolerance. A risk factor for developing CMPA in adulthood is the excessive intake of dairy products [57]. Sousa *et al*[58] reported a 24-year-old man who developed CMPA after excessive intake of hydrolyzed casein and whey CMPs for bodybuilding for two years. CMPA was confirmed by positive IgE against cow's milk α-lactalbumin, β-lactoglobulin, and casein extracts, suggesting that excessive CM intake may induce CMPA. On the other hand, adult patients with CMPA have lower IgG levels than controls[58]. The respiratory tract and skin are the main organs affected in adulthood CMPA in adults, while gastrointestinal and cardiovascular manifestations are less frequent than in childhood CMPA[59]. Due to the higher rate of lactose intolerance compared to CMPA in adults, some cases of CMPA are wrongly diagnosed as lactose intolerance due to the common symptoms. Lactose intolerance can be excluded by the negative hydrogen breath test for lactose, the positive cow's milk challenge and SPTs, and high IgE levels against CMP[60]. Therefore, cases with refractory lactose intolerance should be investigated for CMPA, as IgE-mediated sensitivity to CMP is a common comorbidity in patients with refractory lactose intolerance not responding to a lactose-free diet[61]. Although most CMPAs reported in adults are IgE-mediated, non-IgE-mediated CMPAs may also occur. For example, FPIES, which are non-IgE-mediated CMPAs, can also be observed in older children and adults[62,63]. IgG-mediated CMPAs were also reported by Anthoni *et al*[12]. They reported a significant association of high IgG levels with self-reported milk-provoked gastrointestinal symptoms, especially constipation, in the adult population. However, the serum IgG levels decrease with the increasing age of the affected patients[10].

Despite adulthood CMPA prevalence being about one-quarter of childhood CMPA, the adulthood type is more severe and more liable to complications and even death. CMPA is rarely implicated in the worsening of coexisting atopic dermatitis during adolescence and adulthood[64]. Recurrent acute pancreatitis was reported as a rare complication of IgE-mediated CMPA. de Diego Lorenzo *et al*[65] reported recurrent episodes of acute pancreatitis in a 23-year-old patient with characteristic abdominal pain and high serum pancreatic enzyme levels, confirmed by the presence of swelling and edema of the pancreas on the sonogram. The episodes were induced by milk consumption and associated with diarrhea and signs of generalized urticaria, such as conjunctival injection, facial erythema, and generalized pruritus. The blood showed eosinophilia and high serum levels of CMP-specific IgE and anti-beta-lactoglobulin IgE[66].

In addition, young adults with CMPA in infancy are at an increased risk of failing to reach their growth potential and height. Therefore, they are candidates for proper growth and nutritional monitoring and need appropriate dietary intervention[65]. They are more prone to reduced bone mass density and developing early osteoporosis. This effect could be reversed by milk desensitization, adequate calcium supplements, and optimal nutritional rules for these patients. Eliminating dairy products in treating adult patients with CMPA may increase the risk of gout and hyperuricemia, as milk consumption protects against gout[67].

LACTOSE INTOLERANCE

Lactose is a disaccharide composed of galactose linked to glucose that can be hydrolyzed in the small intestine brush border membrane by β-galactosidase (lactase enzyme). After infancy, lactase activity progressively decreases due to a gradual decrease in lactase synthesis ability. Therefore, adults do not tolerate large amounts of lactose[68]. Lactose intolerance is a common condition of food intolerance characterized by the development of many symptoms following the consumption of foods containing lactose, the primary milk sugar, due to absolute or relative deficiency of the lactase enzyme in the mucosal brush border of the small intestine. As a result of inadequate lactose digestion, the lactose reaches the colon undigested, where the gut microbiota ferments it, causing nonspecific symptoms such as abdominal pain, bloating, flatulence, and mushy to watery diarrhea. The symptoms usually develop within 30 min to a few hours after lactose ingestion. The severity of the symptoms correlates with the deficiency of the lactase enzyme. Therefore, nausea and vomiting may occur after consuming large amounts of lactose-containing foods such as dairy products[69-71].

There are four main types of lactose intolerance; developmental lactose intolerance, which occurs in premature babies as lactase enzyme production starts after 34 wk of gestation; congenital lactose intolerance, which is inherited from lactase deficiency due to a defect in the gene responsible for lactase synthesis; primary lactose intolerance, which results from the normal aging process and is the most common cause of lactose intolerance; and secondary lactose intolerance which results from damage of the brush border of the intestinal mucosa due to infection, inflammation, or trauma and improves with treatment of the cause[72]. Lactose intolerance can be isolated or part of a broader intolerance to variable saccharides, including monosaccharides, disaccharides, oligosaccharides, and polyols. It is crucial to determine whether lactose intolerance is isolated or compounded during the treatment to ensure successful therapy of a lactose-free diet[73].

The manifestations of lactose intolerance depend on many factors, in addition to the degree of lactase deficiency. These factors include the dose of ingested lactose; the osmolality of the food; the dietary fat content; gut motility and gastric emptying time; gut microbiota and its ability to ferment lactose; small intestinal bacterial overgrowth; water absorptive capacity of the colon; and the pain threshold due to sensitivity of the intestine to the generated gases and other fermented substrates due to lactose fermentation[73]. For example, a patient with lactose intolerance may tolerate up to 12 g of lactose (equivalent to a glass of milk); an amount between 12 and 18 g can be tolerated when mixed with other types of food; while an amount between 18 and 50 g starts to produce symptoms of lactose intolerance and the symptoms increase with increased the amount. Lactose over 50 g causes significant symptoms in most patients. However, the relation between the amount of ingested lactose and the severity of the symptoms needs more valid evidence[70]. These symptoms include abdominal distension, bloating, colic, abdominal pain, increased borborygmi, flatus, and osmotic diarrhea induced by lactose in dairy products. Nonspecific symptoms of lactose intolerance may include headaches, muscle pain, chronic fatigue, depression, and concentration problems[74].

Diagnosis of lactose intolerance

Diagnosis of lactose intolerance depends on self-reported symptoms, dietary challenges, and investigative testing, including physiological, genetic, and endoscopic testing. Physiologic testing depends on the evaluation of lactase activity by different methods. It is also essential to rule out secondary causes. When lactose intolerance is assumed, a trial of a lactose-free diet should be conducted for 2-4 wk with the elimination of all lactose sources, including hidden lactose sources. Then, lactose is reintroduced to the diet. If symptoms recover during the 2-4 wk period and reappear with lactose reintroduction, a lactose intolerance diagnosis can be made[75]. Indirect evidence of lactose malabsorption due to lactase deficiency includes measuring stool pH and reducing substances. Fecal pH of less than 6.0 may suggest lactose intolerance. However, this test is not recommended in infants less than two years of age due to the high rate of false negative results[76]. Fecal-reducing substances are another indirect tool to diagnose lactose (or other carbohydrates) maldigestion and malabsorption. Positive results may suggest an absence of the related enzyme[77]. However, false negative results could occur if the patient has not recently ingested lactose.

The lactose hydrogen breath test: The lactose hydrogen breath test is commonly done in suspected lactose-intolerant patients. The test depends on the principle that lactase deficiency causes lactose indigestion, which undergoes gut microbiota fermentation and subsequent hydrogen gas production. The patient ingests 25 to 50 g of lactose, and then the hydrogen gas is checked every 15 min for 3-6 h. The increasing hydrogen concentration in the breath by more than 20 ppm (parts per million) over baseline after lactose ingestion indicates hypolactasia. However, the test needs a long duration (3-6 h) with a risk of a false negative in 10% of cases[78]. A false negative test may be related to the presence of non-hydrogen-producing fermenting bacteria. In this situation, methane-producing bacteria may cause methane gas production in about one-third of the adult population and may have additional health consequences worse than excess hydrogen levels. Therefore, combined measuring of hydrogen and methane significantly improves the diagnosis of malabsorption syndromes, including lactose intolerance and small intestinal bacterial overgrowth, compared with a single hydrogen breath test[79].

The lactose tolerance test: The lactose tolerance test examines the ability to digest lactose to its components by checking the glucose level after administering 50 g of lactose orally. The blood glucose levels are checked before and after 30, 60, and 120 min of lactose intake. The absence of increased blood glucose levels after oral lactose intake indicates the inability of the body to digest lactose and hence possible lactase deficiency. However, this test is affected by other factors, such as gastric emptying time and mechanisms of glucose metabolism, and has lower sensitivity and specificity, with false positive and negative results in 20% of patients. Therefore, it is rarely performed. However, it can detect patients with lactose intolerance and a negative hydrogen breath test due to a lack of hydrogen gas-producing bacteria. Patients with diabetes mellitus are not candidates for this test as their blood sugar will increase even in the presence of lactose intolerance[80,81].

The gaxilose test: The gaxilose test is considered the new gold standard for lactose intolerance diagnosis. It uses gaxilose, a synthetic disaccharide formed of -O-β-D-galactopyranosyl-D-xylose that can be metabolized with lactase enzyme into galactose and xylose due to its structural similarity to lactose. Xylose is absorbed by the enterocyte, reaches the blood, and is then excreted in the urine. Therefore, the blood and urine levels of xylose will reflect the activity of the lactase enzyme available to metabolize gaxilose. However, this recent test needs more studies to confirm its efficacy, safety, sensitivity, and specificity[82-84].

Genetic tests: Genetic tests apply real-time polymerase chain reaction or sequencing of DNA extracted from buccal mucosa or venous blood to detect the genetic type of lactose intolerance. Determining the lactase enzyme activity on intestinal biopsies is done for other reasons to detect a primary or secondary cause of lactose intolerance. The patchy activity of lactase should be considered during the biopsy. Therefore, more than a single biopsy may be needed to achieve optimal test accuracy. The genetic test is a good predictor of lactase persistence or non-persistence in specific populations[85-87].

Lactose intolerance comorbidities

Lactose intolerance should not be considered an isolated disorder as it may trigger many other diseases. There are significant correlations between lactose intolerance and the prevalence of osteoporosis, mental status changes, and the existence of other food intolerances[74]. Infant colic is a common problem. Subclinical lactose intolerance could be an underlying pathophysiologic mechanism[88]. About one-third of patients with IBS have lactose intolerance as a part of their malabsorption syndrome. Therefore, a trial of a lactose-free diet is a common practice in managing IBS. Consequently, a hydrogen breath test is recommended in newly diagnosed patients with IBS to identify those who would benefit from a lactose-free diet[89]. At the same time, patients with inflammatory bowel disease (IBD) have a 2.7-fold increased risk of lactose intolerance, indicating the need to screen patients with IBD for lactose intolerance to avoid overlapping or confusing symptoms[90].

CMPA could be a comorbidity of lactose intolerance or the underlying cause as the CMP-immune mediated inflammation destroys the brush border of the intestinal mucosa that contains lactase enzyme, resulting in lactase deficiency and lactose intolerance. In addition, CMPA is commonly mistaken for lactose intolerance as both have common symptoms. Therefore, CMPA should be considered in lactose-free diet-refractory lactose intolerance. However, there are critical differences between cow's milk allergy and lactose intolerance which could limit misunderstandings in diagnosing these two conditions [60,91]. Grundmann *et al*[92] showed that 21.4% of patients with chronic pruritus had lactase deficiency, and 38.3% had an excellent anti-pruritic effect after four weeks of a lactose-free diet. Therefore, lactase deficiency could be an independent underlying cause of chronic pruritus. Hence, lactase deficiency screening is a reasonable diagnostic step in investigating chronic pruritus. A lactose-free diet should be tried if lactose intolerance is confirmed in patients with chronic pruritus[92]. Patients with systemic sclerosis have a 44% higher prevalence of lactose intolerance than those in control. Lactose intolerance occurs as a part of the malabsorption syndrome that results from gut inflammation as a feature of systemic inflammation associated with systemic sclerosis[93]. Other saccharides malabsorption, such as fructose malabsorption, is also common in patients with systemic sclerosis[94]. On the other hand, a cross-sectional study over ten years showed that patients with lactose intolerance might have a reduced risk of gastric and colon cancer[95].

Management of lactose intolerance

Management of lactose intolerance is sometimes tricky. First, we should confirm the diagnosis, detect secondary causes, and determine the amount of lactose the patient can tolerate. This step is crucial in the management, as complete lactose restriction is not advised. Usually, 12-15 g of daily lactose can be tolerated by most adult patients and up to 5 g by most children, especially when mixed with foods. We start with a lactose-restricted diet, then gradually reintroduce milk and milk products according to the person's tolerance to improve the symptoms and induce tolerance[96]. Mixing lactose with other foods causes slow lactose release in the small intestine and better tolerance. Some lactose-containing foods can be more easily tolerated than others. Yogurt is better tolerated as it contains partially hydrolyzed lactose. On the same track, high-fat-containing dairy products cause delayed gastric emptying and slow

lactose release, while skimmed milk can produce severe symptoms due to low fat and high lactose content[71,97].

Consistent and continuous gradual administration of lactose often improves the number and effectiveness of colonic bacteria metabolizing lactose, generating fewer symptoms[98]. Probiotics containing lactose-fermenting bacteria such as *Streptococcus thermophilus, L. reuteri*, *L. rhamnosus*, *L. acidophilus*, *L. bulgaricus*, and *Bifidobacterium longum* promote lactose digestion and help to improve gastrointestinal symptoms of lactose intolerance[99].

Therefore, lactose-free milk is usually unnecessary except when a large daily amount of milk is needed, such as during infancy or in severe cases when small doses produce marked symptoms of lactose intolerance. Milk alternatives such as coconut, almond, rice, or oat milk should not be used as the primary nutritional milk source for children below the age of five years. These types of milk should also be fortified with vitamin D. Soy milk, or any plant-based milk, is not recommended for infants below the age of one year. However, soy milk might be considered in infants older than six months if they cannot tolerate satisfactory amounts of cows' milk formula[100,101]. Children with lactose intolerance using lactose-free milk or plant-based formula are more likely to develop osteoporosis and decreased bone density due to a deficiency of calcium, vitamin D, riboflavin, and protein. They should be supplemented with adequate calcium and vitamin D intake to ensure optimal peak bone mass in childhood and adolescence. Adequate vitamin D and calcium intake can be achieved by increasing consumption of calcium-rich non-dairy foods such as fish, dark green leafy vegetables, tofu, seeds, and nuts, as well as getting enough sunlight exposure through daily walks and other outdoor activities[102,103].

If symptoms of lactose intolerance are still present despite adequate nutritional management, lactase enzyme supplements can be tried as an adjunct and not a replacement for dietary management. Enzyme replacement therapy may not completely alleviate symptoms, and it is hard to calculate the effective dose[96]. However, a recent study showed that oral lactase enzyme supplementation significantly lessened the clinical symptoms and diminished hydrogen breath excretion in subjects with lactose intolerance[104]. Breastfeeding mothers of infants with lactose intolerance do not need to have a low or free-lactose diet, as the lactose content of the breast milk has no relation to the lactose intake by the mother. On the other side, formula-fed infants benefit from a lactose-free formula with a trial of lactose-containing reintroduction food over 2-4 wk[105].

COW'S MILK-RELATED FUNCTIONAL GASTROINTESTINAL DISORDERS

Functional gastrointestinal disorders (FGIDs) are frequent disorders in infants, children, and adults, characterized by persistent and recurring gastrointestinal symptoms (*e.g.*, dysphagia, abdominal pain, dyspepsia, bloating, constipation, or diarrhea) in the absence of clear underlying pathological conditions. However, diet is an essential factor in the pathogenesis and management of FGIDs[106]. Functional dyspepsia is characterized by recurrent symptoms and signs of indigestion without apparent cause. The link between cow's milk and functional dyspepsia is not well established. Unfortunately, intolerance of dairy products is usually not one of the differential diagnoses of functional dyspepsia. In their study, Wortmann *et al*[107] showed that adult-type lactose intolerance was present in 44.7% of patients with functional dyspepsia. Mishkin *et al*[108] showed that the prevalence of lactose intolerance in patients with functional dyspepsia is affected by ethnic group and age, with a decreased prevalence between 25-55 years and an increase after 55 years.

Persistent regurgitation is a common nonspecific symptom of CMPA in infants. It usually presents with excessive crying, irritability, pain, respiratory symptoms, and feeding or sleep disturbance. CMPA was documented in up to 50% of infants with persistent GER, which could be just an association or CMPA-induced GER. The likelihood of CMPA increases in the presence of atopy and multiorgan symptoms such as failure to thrive, diarrhea, rectal bleeding, or atopic dermatitis[32,109,110]. A negative SPT does not rule out CMPA as it is IgE-and non-IgE-mediated. At the same time, clinical improvement with a cow's milk-free diet is not solid proof of immune system involvement. Therefore, esophageal pH impedance, oral food challenge, and endoscopy are recommended to reach a correct clinical diagnosis and classification, but they are not always possible in all infants[111]. We should consider using 2-4 wk of a protein hydrolysate or amino acid-based formula in a formula-fed infant or eliminating cow's milk in the maternal diet in breastfed infants[112]. However, there is not enough evidence to avoid drinking milk for GER. Patients with GER who tolerate cow's milk may continue to consume it. Avoidance of milk consumption should be avoided only if symptoms of GER increase with milk consumption[113]. Due to its acid-neutralizing properties, milk has long been used to treat the symptoms of peptic ulcers and GERD. However, the high calcium and protein content significantly increased acid production by 30% for every 250 mL of milk. In addition, patients with peptic ulcers are more vulnerable to the effects of milk on the gastric parietal cells[114]. As confirmed by an endoscopic study[115], patients with peptic ulcers who avoided a milk-based diet had better ulcer cicatrization results than those who consumed milk. However, patients with a peptic ulcer can consume a moderate amount of dairy products according to their tolerance to benefit from their high nutritional content[116].

Infant colic is a functional disorder characterized by full-force crying for a minimum of three hours per day for a minimum of three days per week in infants younger than five months. It is a worldwide disorder affecting many infants and families. The precise mechanisms are not well known. While it does not indicate the presence of disease, it occasionally represents an underlying severe disorder in a small percentage of infants who may require a medical assessment[117]. Cow's milk may precipitate infant colic through CMPA and lactose intolerance. Both conditions can induce colic through gut inflammation (as indicated by fecal calprotectin) and gut dysmotility and dysbiosis, with fewer Bifidobacilli inducing abnormal peristalsis and colicky pain[118]. Colic may arise as a delayed reaction within a few hours to days of CMP consumption. Infant colic may be one of the many symptoms of CMPA. A cohort of 100 infants with colic showed a positive challenge-proven CMPA in 44% of the infants during a cow's-milk challenge[119]. Moravej *et al*[120] showed that the SPT for CMP was positive in 2.6% of infants with colic who responded well to cow's milk elimination from the mothers' diet. Many infants with colic have transient lactose intolerance, causing excessive gas production. Lactase enzyme activity may be low in many infants during the first weeks of life and may take a few weeks to improve. Pretreatment of feeds with lactase can improve colic[121]. For breastfeeding colicky infants, a trial of dairy product exclusion by the mother for 2-4 wk could produce symptomatic improvement. For bottle-fed infants, a partially hydrolyzed formula with Galacto-Oligosaccharides/Fructo-Oligosaccharides and added β-palmitate might be beneficial in cases where CMPA is not suspected. The mother can also use a formula containing prebiotics and/or ferments or a lactose-reduced formula[122].

Functional constipation is a common disorder in children, negatively impacting their quality of life. Simeone *et al*[123] showed that 17.3% of children with functional constipation had evidence of CMPA and improved with a CMP elimination diet. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition-North American Society for Paediatric Gastroenterology, Hepatology and Nutrition advised that a CMP-free diet be tried only in cases of laxative-resistant constipation and only after consulting an expert. However, a literature review by Sopo *et al*[124] showed that 28% to 78% of children with functional constipation benefited from a CMP-free diet. The review results give solid scientific evidence for a causal relationship between functional constipation and CMPA. Therefore, they recommended a two-to-four-week restricted diet as a first-line diagnostic and therapeutic strategy in children with functional constipation[124]. The same result was also found in the literature review by Gelsomino *et al*[125]. They propose that a CMP-free diet should be considered a first-line treatment for functional constipation, at least in preschool children and children with a previous diagnosis of CMPA or a personal or family history of atopy.

IBS is one of the most common FGIDs with poorly understood mechanisms that affect a significant proportion of the population with a strong negative impact on the quality of life[126]. The lack of well-understood underlying pathophysiologic mechanisms makes choosing effective treatment strategies difficult. Clinicians commonly recommend a lactose-free diet to manage this syndrome[118]. Approximately one-third of patients with IBS have some degree of lactose intolerance, which could be present with diarrhea, gas, and bloating. Milk lactose irritates the already vulnerable intestines of people with IBS. However, a systematic review by Vaiopoulou *et al*[127] did not find convincing evidence to indicate an objective relationship between IBS and any recognized malabsorption syndrome involving lactose intolerance.

On the other hand, a significant portion of people with IBS and self-reported lactose intolerance and negative hydrogen breath testing were proved to be due to underlying immune-mediated reactions to CMP. Carroccio *et al*[55] in a study with retrospective and prospective phases, showed that a percentage of self-reported milk intolerance in patients with IBS was not related to lactose intolerance; instead, they clinically reacted when subjected to whole cow's milk, indicating CMPA. Patients with IBS and lactose intolerance had more severe symptoms and a higher degree of fatigue, anxiety, and depression[128, 129]. Therefore, we should consider that a significant minority of patients with IBS could benefit from a dairy elimination diet, especially in the presence of evidence of CMPA. More studies are necessary to identify the complex pathogenic mechanisms of FGIDs and to improve their management[130].

COW'S MILK AND IBDS

The relationship between cow's milk and IBD is cause and effect. There is much evidence of an increased prevalence of ulcerative colitis in children with a previous history of CMPA. Knoflach *et al* [131] found high IgG and IgM against CMP in patients with IBD than in controls, with a good correlation between disease activity and the levels of IgG and IgA against certain CMPs. In addition, Virta *et al*[132] found in two separate studies that a past history of CMPA increases the prevalence of pediatric IBD. In contrast, asthma increases the likelihood of Crohn's disease[132,133].

On the other hand, lactose malabsorption prevalence is significantly more common in patients with Crohn's disease affecting the small intestine than in patients with Crohn's disease affecting the colon or patients with ulcerative colitis. In IBD affecting the colon, lactose malabsorption prevalence is affected by other factors, such as ethnic risk determined by genetic factors. The degree of lactose malabsorption in Crohn's disease of the small intestine is also affected by bacterial overgrowth and small intestine

transit time, in addition to lactase enzyme activity[132].

Avoiding dairy products is common dogmatic advice given by many physicians to patients with IBD. However, Strisciuglio *et al*[134] showed that dietary CMP elimination has no substantial role in managing ulcerative colitis in non-sensitized children. Due to dairy product restrictions in patients with IBD (either due to unnecessary fear of the presence of CMPA or due to the occurrence of secondary lactose intolerance), there is an increased risk of inadequate intake of calcium, an essential element to prevent the decrease in bone mineral density, which consequently increases the risk of osteoporosis. Therefore, proper dietary management is crucial to prevent osteoporosis through education and adequate dietary management with low/free-lactose milk, fermented milk, plant-based milk supplemented with calcium and vitamin D, calcium-rich foods, and calcium supplements[135]. The exclusion of certain types of foods should be based on solid science. Indiscriminate exclusion of certain foods increases the risk of nutritional deficiencies. Lim *et al*[136] showed that the mean daily calcium, vitamin A, and zinc intake were significantly decreased in the food exclusion group. Milk was the most common restricted food, followed by dairy products, raw fish, deep-spicy foods, and ramen. Therefore, the magnitude of osteoporosis will be further increased by dairy product restriction, in addition to the effects of IBD itself[137].

Fermented milk using specific lactic acid bacteria could help avoid dairy product restrictions. Fermented milk with lactic acid-producing bacteria contains exopolysaccharides, peptides, and short-chain fatty acids that help to modulate intestinal lumen pH, help recovery of intestine mucosa, modulate the gut microbiota, and alleviate the inflammatory response by modifying the innate and adaptive immune system. As a result, bioactive compounds derived from fermented milk can alleviate the negative symptoms of IBD[138]. Consequently, the disease activity can be significantly reduced by the oral administration of specific probiotics containing *B. subtilis* JNFE0126. Zhang *et al*[139] showed that *B. subtilis*-containing fermented milk could decrease the intestinal mucosa inflammatory response, induce intestinal stem cell proliferation, and promote mucosal barrier reconstruction. *B. subtilis*-containing fermented milk helps to rebalance the gut mucosa through the enrichment of *Lactobacillus, Bacillus*, and *Alistipes* and decrease *Escherichia* and *Bacteroides* abundance.

COW'S MILK-RELATED GASTROINTESTINAL CANCER

Despite data from the geographic distribution of colon cancer showing increased milk consumption [140], a meta-analysis found that milk and whole milk products are associated with a lower risk of colorectal cancer[141]. The protective effects of milk and whole dairy products are related to the high calcium content of milk. Calcium is the primary anti-carcinogen, especially in doses equal to or higher than 1200 mg/d. Therefore, calcium supplementation is indicated in patients with a contraindication to milk intake[142]. Vitamin D is another milk ingredient that protects against colon cancer. However, Baron *et al*[143] showed that daily vitamin D3 (1000 IU), calcium (1200 mg), or supplementation with both after surgical removal of colorectal adenomas did not show significant risk reduction of recurrent colorectal adenomas over a follow-up period of three to five years.

MILK AND GASTROINTESTINAL INFECTIONS

As milk is a part of everyday human food from birth onwards, it may be a source of microbial infection in humans, causing many diseases. Milk is rich in sugars, lipids, and proteins, which are ideal media for the growth of a broad spectrum of organisms. Diseases produced by milk-borne organisms include *Mycobacterium avium, Mycobacterium bovis, Salmonella species,* brucellosis, streptococcal infections, "summer diarrhea", *Yersinia enterocolitica*, *diphtheria*, *Escherichia coli* (*E. coli*), *Campylobacter jejuni*, *Citrobacter species*, *Shiga toxin-producing E. coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Klebsiella species*[144]. Campylobacter species and Salmonella species are the most common identified etiological agents, while other zoonotic infections, particularly yersiniosis and listeriosis, are increasingly reported. Most infections were due to improperly treated cows' milk or dairy products and increasingly polluted "heat-treated" milk products. Milk pasteurization decreased infectious diseases and their high infant mortality rates by only 50%, even with concurrent medical and dairy hygiene advances, particularly in the less developed world[145]. Most of these infections presented with manifestations of gastroenteritis, food poisoning, and hepatosplenomegaly, in addition to systemic manifestations such as fever, muscle aches, severe headache, meningitis, sepsis, pneumonia, and renal failure. Raw milk consumption, a common practice by milk producers on their farms, is a significant risk factor for milk-transmitted infection, despite the other health benefits of drinking fresh milk over pasteurized milk. In addition, raw milk consumption increases the risk of horizontal gene transfer of antimicrobial resistance genes where the bovine strains may meet the human microbiota and change them into resistant pathogenic strains, a fundamental reason for increasing the prevalence of antimicrobial resistance[146].

CONCLUSION

Cow's milk induces various gastrointestinal and systemic manifestations from birth to the elderly with various underlying mechanisms. Cow's milk allergy is a common disorder, especially at pediatric age, with different presentations according to the site of major implication. However, when it is present in adulthood, it is usually severe. Eliminating the offending CMP from breastfeeding mothers' diets and using extensively hydrolyzed or amino acid-based formulas are the main lines of treatment in infancy and childhood. Avoiding dairy and dairy products is also conducted for adults with CMPA. Different types of lactose intolerance can occur with different presentations and prevalence according to age and ethnicity. It can be isolated or be a part of a broader intolerance to various saccharides. CMPA and lactose intolerance, in addition to milk-induced gut microbiota dysbiosis, are commonly associated with various FGIDs such as gastroesophageal reflux, peptic ulcers, infant colic, IBS, and constipation. Cow's milk consumption may be implicated in the pathogenesis of some cancers and the prevention of others. In addition, cow's milk is a significant source of many zoonotic infections that could affect human health. It may also play a role in the development of antimicrobial resistance. This special issue will cover these various topics in more detail. Physicians and patients should be well oriented with milk-related disorders to avoid unnecessary nutritional mismanagement.

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REFERENCES

1 **Zeder MA**. Domestication and early agriculture in the Mediterranean Basin: Origins, diffusion, and impact. *Proc Natl Acad Sci U S A* 2008; **105**: 11597-11604 [PMID: 18697943 DOI: 10.1073/pnas.0801317105]
2 **Corsello A**, Pugliese D, Gasbarrini A, Armuzzi A. Diet and Nutrients in Gastrointestinal Chronic Diseases. *Nutrients* 2020; **12** [PMID: 32899273 DOI: 10.3390/nu12092693]
3 **Aslam H**, Marx W, Rocks T, Loughman A, Chandrasekaran V, Ruusunen A, Dawson SL, West M, Mullarkey E, Pasco JA, Jacka FN. The effects of dairy and dairy derivatives on the gut microbiota: a systematic literature review. *Gut Microbes* 2020; **12**: 1799533 [PMID: 32835617 DOI: 10.1080/19490976.2020.1799533]
4 **Giannetti A**, Toschi Vespasiani G, Ricci G, Miniaci A, di Palmo E, Pession A. Cow's Milk Protein Allergy as a Model of Food Allergies. *Nutrients* 2021; **13** [PMID: 33946553 DOI: 10.3390/nu13051525]
5 **Shokouhi Shoormasti R**, Fazlollahi MR, Barzegar S, Teymourpour P, Yazdanyar Z, Lebaschi Z, Nourizadeh M, Tazesh B, Movahedi M, Kashani H, Pourpak Z, Moin M. The Most Common Cow's Milk Allergenic Proteins with Respect to Allergic Symptoms in Iranian Patients. *Iran J Allergy Asthma Immunol* 2016; **15**: 161-165 [PMID: 27090370]
6 **Sletten GB**, Halvorsen R, Egaas E, Halstensen TS. Changes in humoral responses to beta-lactoglobulin in tolerant patients suggest a particular role for IgG4 in delayed, non-IgE-mediated cow's milk allergy. *Pediatr Allergy Immunol* 2006; **17**: 435-443 [PMID: 16925689 DOI: 10.1111/j.1399-3038.2006.00408.x]
7 **Mastrorilli C**, Santoro A, Caffarelli C. Primary Prevention of Allergic Diseases: The Role of Early Exposure to Cow's

Milk Formula. *Front Pediatr* 2020; **8**: 420 [PMID: 32850536 DOI: 10.3389/fped.2020.00420]
8 **Landi N**, Ragucci S, Di Maro A. Amino Acid Composition of Milk from Cow, Sheep and Goat Raised in Ailano and Valle Agricola, Two Localities of 'Alto Casertano' (Campania Region). *Foods* 2021; **10** [PMID: 34681478 DOI: 10.3390/foods10102431]
9 **Martelli A**, De Chiara A, Corvo M, Restani P, Fiocchi A. Beef allergy in children with cow's milk allergy; cow's milk allergy in children with beef allergy. *Ann Allergy Asthma Immunol* 2002; **89**: 38-43 [PMID: 12487203 DOI: 10.1016/s1081-1206(10)62121-7]
10 **Restani P**, Gaiaschi A, Plebani A, Beretta B, Cavagni G, Fiocchi A, Poiesi C, Velonà T, Ugazio AG, Galli CL. Cross-reactivity between milk proteins from different animal species. *Clin Exp Allergy* 1999; **29**: 997-1004 [PMID: 10383602 DOI: 10.1046/j.1365-2222.1999.00563.x]
11 **Candreva AM**, Smaldini PL, Curciarello R, Cauerhff A, Fossati CA, Docena GH, Petruccelli S. Cross-reactivity between the soybean protein p34 and bovine caseins. *Allergy Asthma Immunol Res* 2015; **7**: 60-68 [PMID: 25553264 DOI: 10.4168/aair.2015.7.1.60]
12 **Anthoni S**, Savilahti E, Rautelin H, Kolho KL. Milk protein IgG and IgA: the association with milk-induced gastrointestinal symptoms in adults. *World J Gastroenterol* 2009; **15**: 4915-4918 [PMID: 19842221 DOI: 10.3748/wjg.15.4915]
13 **Anthoni S**, Elg P, Haahtela T, Kolho KL. Should milk-specific IgE antibodies be measured in adults in primary care? *Scand J Prim Health Care* 2008; **26**: 197-202 [PMID: 18609255 DOI: 10.1080/02813430802117442]
14 **Bischoff S**, Crowe SE. Gastrointestinal food allergy: new insights into pathophysiology and clinical perspectives. *Gastroenterology* 2005; **128**: 1089-1113 [PMID: 15825090 DOI: 10.1053/j.gastro.2004.08.015]
15 **Martorell A**, Plaza AM, Boné J, Nevot S, García Ara MC, Echeverria L, Alonso E, Garde J, Vila B, Alvaro M, Tauler E, Hernando V, Fernández M. Cow's milk protein allergy. A multi-centre study: clinical and epidemiological aspects. *Allergol Immunopathol (Madr)* 2006; **34**: 46-53 [PMID: 16606545 DOI: 10.1157/13086746]
16 **Sakai K**, Yoshino K, Satter MA, Ota F, Nii Y, Fukuta K, Ueda N, Shimizu Y, Yamamoto S. Effects of pH variation and NaCl on in vitro digestibility of cow's milk proteins in commercially available infant formulas. *J Nutr Sci Vitaminol (Tokyo)* 2000; **46**: 325-328 [PMID: 11227806 DOI: 10.3177/jnsv.46.325]
17 **Perezabad L**, López-Abente J, Alonso-Lebrero E, Seoane E, Pion M, Correa-Rocha R. The establishment of cow's milk protein allergy in infants is related with a deficit of regulatory T cells (Treg) and vitamin D. *Pediatr Res* 2017; **81**: 722-730 [PMID: 28099424 DOI: 10.1038/pr.2017.12]
18 **Vandenplas Y**, Al-Hussaini B, Al-Mannaei K, Al-Sunaid A, Helmi Ayesh W, El-Degeir M, El-Kabbany N, Haddad J, Hashmi A, Kreishan F, Tawfik E. Prevention of Allergic Sensitization and Treatment of Cow's Milk Protein Allergy in Early Life: The Middle-East Step-Down Consensus. *Nutrients* 2019; **11** [PMID: 31248015 DOI: 10.3390/nu11071444]
19 **Gil F**, Amezqueta A, Martinez D, Aznal E, Etayo V, Durá T, Sánchez-Valverde F. Association between Caesarean Delivery and Isolated Doses of Formula Feeding in Cow Milk Allergy. *Int Arch Allergy Immunol* 2017; **173**: 147-152 [PMID: 28787733 DOI: 10.1159/000477725]
20 **Molloy J**, Allen K, Collier F, Tang ML, Ward AC, Vuillermin P. The potential link between gut microbiota and IgE-mediated food allergy in early life. *Int J Environ Res Public Health* 2013; **10**: 7235-7256 [PMID: 24351744 DOI: 10.3390/ijerph10127235]
21 **Wang J**, Zheng S, Yang X, Huazeng B, Cheng Q. Influences of non-IgE-mediated cow's milk protein allergy-associated gut microbial dysbiosis on regulatory T cell-mediated intestinal immune tolerance and homeostasis. *Microb Pathog* 2021; **158**: 105020 [PMID: 34089791 DOI: 10.1016/j.micpath.2021.105020]
22 **Tan W**, Zhou Z, Li W, Lu H, Qiu Z. *Lactobacillus rhamnosus* GG for Cow's Milk Allergy in Children: A Systematic Review and Meta-Analysis. *Front Pediatr* 2021; **9**: 727127 [PMID: 34746056 DOI: 10.3389/fped.2021.727127]
23 **Ward CM**, Geng L, Jyonouchi H. Fetal sensitization to cow's milk protein and wheat: cow's milk protein and wheat-specific TNF-alpha production by umbilical cord blood cells and subsequent decline of TNF-alpha production by peripheral blood mononuclear cells following dietary intervention. *Pediatr Allergy Immunol* 2007; **18**: 276-280 [PMID: 17584308 DOI: 10.1111/j.1399-3038.2007.00536.x]
24 **Høst A**. Frequency of cow's milk allergy in childhood. *Ann Allergy Asthma Immunol* 2002; **89**: 33-37 [PMID: 12487202 DOI: 10.1016/s1081-1206(10)62120-5]
25 **Venter C**, Pereira B, Grundy J, Clayton CB, Roberts G, Higgins B, Dean T. Incidence of parentally reported and clinically diagnosed food hypersensitivity in the first year of life. *J Allergy Clin Immunol* 2006; **117**: 1118-1124 [PMID: 16675341 DOI: 10.1016/j.jaci.2005.12.1352]
26 **Saarinen KM**, Pelkonen AS, Mäkelä MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol* 2005; **116**: 869-875 [PMID: 16210063 DOI: 10.1016/j.jaci.2005.06.018]
27 **Vanto T**, Helppilä S, Juntunen-Backman K, Kalimo K, Klemola T, Korpela R, Koskinen P. Prediction of the development of tolerance to milk in children with cow's milk hypersensitivity. *J Pediatr* 2004; **144**: 218-222 [PMID: 14760265 DOI: 10.1016/j.jpeds.2003.10.063]
28 **Kvenshagen B**, Halvorsen R, Jacobsen M. Adverse reactions to milk in infants. *Acta Paediatr* 2008; **97**: 196-200 [PMID: 18254909 DOI: 10.1111/j.1651-2227.2007.00599.x]
29 **Jacob S**, Bonito Vitor A. [Cow's milk protein intolerance imitating septic shock in a young infant]. *An Pediatr (Engl Ed)* 2019; **90**: 52-53 [PMID: 29650430 DOI: 10.1016/j.anpedi.2018.01.020]
30 **Walsh J**, Meyer R, Shah N, Quekett J, Fox AT. Differentiating milk allergy (IgE and non-IgE mediated) from lactose intolerance: understanding the underlying mechanisms and presentations. *Br J Gen Pract* 2016; **66**: e609-e611 [PMID: 27481986 DOI: 10.3399/bjgp16X686521]
31 **Yimyaem P**, Chongsrisawat V, Vivatvakin B, Wisedopas N. Gastrointestinal manifestations of cow's milk protein allergy during the first year of life. *J Med Assoc Thai* 2003; **86**: 116-123 [PMID: 12678148]
32 **Salvatore S**, Agosti M, Baldassarre ME, D'Auria E, Pensabene L, Nosetti L, Vandenplas Y. Cow's Milk Allergy or Gastroesophageal Reflux Disease-Can We Solve the Dilemma in Infants? *Nutrients* 2021; **13** [PMID: 33494153 DOI:

10.3390/nu13020297]
33 **Teoh T**, Mill C, Chan E, Zimmer P, Avinashi V. Liberalized Versus Strict Cow's Milk Elimination for the Treatment of Children with Eosinophilic Esophagitis. *J Can Assoc Gastroenterol* 2019; **2**: 81-85 [PMID: 31294369 DOI: 10.1093/jcag/gwy030]
34 **Vinit C**, Dieme A, Courbage S, Dehaine C, Dufeu CM, Jacquemot S, Lajus M, Montigny L, Payen E, Yang DD, Dupont C. Eosinophilic esophagitis: Pathophysiology, diagnosis, and management. *Arch Pediatr* 2019; **26**: 182-190 [PMID: 30827775 DOI: 10.1016/j.arcped.2019.02.005]
35 **Machado RS**, Kawakami E, Goshima S, Patrício FR, Fagundes Neto U. [Hemorrhagic gastritis due to cow's milk allergy: report of two cases]. *J Pediatr (Rio J)* 2003; **79**: 363-368 [PMID: 14513137 DOI: 10.1590/s0021-75572003000400016]
36 **Alabsi HS**, Reschak GL, Fustino NJ, Beltroy EP, Sramek JE, Alabsi SY. Neonatal eosinophilic gastroenteritis: possible in utero sensitization to cow's milk protein. *Neonatal Netw* 2013; **32**: 316-322 [PMID: 23985469 DOI: 10.1891/0730-0832.32.5.316]
37 **Suzuki S**, Homma T, Kurokawa M, Matsukura S, Adachi M, Wakabayashi K, Nozu F, Tazaki T, Kimura T, Matsuura T, Fukuda M, Shiozawa E, Takimoto M. Eosinophilic gastroenteritis due to cow's milk allergy presenting with acute pancreatitis. *Int Arch Allergy Immunol* 2012; **158** Suppl 1: 75-82 [PMID: 22627371 DOI: 10.1159/000337782]
38 **Lyngbaek S**, Adamsen S, Aru A, Bergenfeldt M. Recurrent acute pancreatitis due to eosinophilic gastroenteritis. Case report and literature review. *JOP* 2006; **7**: 211-217 [PMID: 16525206 DOI: 10.1097/01.smj.0000139403.55785.1c]
39 **Feketea G**, Popp A, Ionescu DM, Berghea EC. Case Report: Food Protein-Induced Protein Losing Enteropathy (FPIPLE) in Infancy. *Front Nutr* 2022; **9**: 810409 [PMID: 35174199 DOI: 10.3389/fnut.2022.810409]
40 **Umar SB**, DiBaise JK. Protein-losing enteropathy: case illustrations and clinical review. *Am J Gastroenterol* 2010; **105**: 43-9; quiz 50 [PMID: 19789526 DOI: 10.1038/ajg.2009.561]
41 **Feuille E**, Nowak-Węgrzyn A. Food Protein-Induced Enterocolitis Syndrome, Allergic Proctocolitis, and Enteropathy. *Curr Allergy Asthma Rep* 2015; **15**: 50 [PMID: 26174434 DOI: 10.1007/s11882-015-0546-9]
42 **Nowak-Węgrzyn A**. Food protein-induced enterocolitis syndrome and allergic proctocolitis. *Allergy Asthma Proc* 2015; **36**: 172-184 [PMID: 25976434 DOI: 10.2500/aap.2015.36.3811]
43 **Järvinen KM**, Nowak-Węgrzyn A. Food protein-induced enterocolitis syndrome (FPIES): current management strategies and review of the literature. *J Allergy Clin Immunol Pract* 2013; **1**: 317-322 [PMID: 24565536 DOI: 10.1016/j.jaip.2013.04.004]
44 **Bulsa K**, Standowicz M, Baryła-Pankiewicz E, Czaja-Bulsa G. Chronic Milk-Dependent Food Protein-Induced Enterocolitis Syndrome in Children from West Pomerania Region. *Nutrients* 2021; **13** [PMID: 34836392 DOI: 10.3390/nu13114137]
45 **Vassilopoulou E**, Feketea G, Konstantinou GN, Zekakos Xypolias D, Valianatou M, Petrodimopoulou M, Vourga V, Tasios I, Papadopoulos NG. Food Protein-Induced Allergic Proctocolitis: The Effect of Maternal Diet During Pregnancy and Breastfeeding in a Mediterranean Population. *Front Nutr* 2022; **9**: 843437 [PMID: 35433785 DOI: 10.3389/fnut.2022.843437]
46 **Martin VM**, Virkud YV, Seay H, Hickey A, Ndahayo R, Rosow R, Southwick C, Elkort M, Gupta B, Kramer E, Pronchick T, Reuter S, Keet C, Su KW, Shreffler WG, Yuan Q. Prospective Assessment of Pediatrician-Diagnosed Food Protein-Induced Allergic Proctocolitis by Gross or Occult Blood. *J Allergy Clin Immunol Pract* 2020; **8**: 1692-1699.e1 [PMID: 31917366 DOI: 10.1016/j.jaip.2019.12.029]
47 **Vandenplas Y**, Koletzko S, Isolauri E, Hill D, Oranje AP, Brueton M, Staiano A, Dupont C. Guidelines for the diagnosis and management of cow's milk protein allergy in infants. *Arch Dis Child* 2007; **92**: 902-908 [PMID: 17895338 DOI: 10.1136/adc.2006.110999]
48 **Lam HY**, van Hoffen E, Michelsen A, Guikers K, van der Tas CH, Bruijnzeel-Koomen CA, Knulst AC. Cow's milk allergy in adults is rare but severe: both casein and whey proteins are involved. *Clin Exp Allergy* 2008; **38**: 995-1002 [PMID: 18384430 DOI: 10.1111/j.1365-2222.2008.02968.x]
49 **Morfín-Maciel BM**, Castillo-Morfín BM. [Anaphylaxis caused by dermal exposure with cow's milk in an adult with food allergy. A case report]. *Rev Alerg Mex* 2020; **67**: 73-78 [PMID: 32447869 DOI: 10.29262/ram.v67i1.669]
50 **Quirantes Sierra B**, Lara Jiménez A, Skodova M. Sensitization to cow's milk protein in a dairy worker. *Occup Med (Lond)* 2017; **67**: 579-580 [PMID: 29016916 DOI: 10.1093/occmed/kqx101]
51 **Hansen MM**, Nissen SP, Halken S, Høst A. The natural course of cow's milk allergy and the development of atopic diseases into adulthood. *Pediatr Allergy Immunol* 2021; **32**: 727-733 [PMID: 33350002 DOI: 10.1111/pai.13440]
52 **Stöger P**, Wüthrich B. Type I allergy to cow milk proteins in adults. A retrospective study of 34 adult milk- and cheese-allergic patients. *Int Arch Allergy Immunol* 1993; **102**: 399-407 [PMID: 8241802 DOI: 10.1159/000236589]
53 **He M**, Sun J, Jiang ZQ, Yang YX. Effects of cow's milk beta-casein variants on symptoms of milk intolerance in Chinese adults: a multicentre, randomised controlled study. *Nutr J* 2017; **16**: 72 [PMID: 29070042 DOI: 10.1186/s12937-017-0275-0]
54 **Kristjánsson G**, Venge P, Hällgren R. Mucosal reactivity to cow's milk protein in coeliac disease. *Clin Exp Immunol* 2007; **147**: 449-455 [PMID: 17302893 DOI: 10.1111/j.1365-2249.2007.03298.x]
55 **Carroccio A**, Brusca I, Mansueto P, Soresi M, D'Alcamo A, Ambrosiano G, Pepe I, Iacono G, Lospalluti ML, La Chiusa SM, Di Fede G. Fecal assays detect hypersensitivity to cow's milk protein and gluten in adults with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2011; **9**: 965-971.e3 [PMID: 21839707 DOI: 10.1016/j.cgh.2011.07.030]
56 **Domínguez-García V**, Flores-Merino MV, Morales-Romero J, Bedolla-Pulido A, Mariscal-Castro J, Bedolla-Barajas M. [Allergy to cow's milk protein, or lactose intolerance: a cross-sectional study in university students]. *Rev Alerg Mex* 2019; **66**: 394-402 [PMID: 32105423 DOI: 10.29262/ram.v66i4.640]
57 **Carroccio A**, Soresi M, Mantia B, Fayer F, La Blasca F, Seidita A, D'Alcamo A, Florena AM, Tinè C, Garlisi C, Mansueto P. Whole Cow's Milk but Not Lactose Can Induce Symptoms inPatients with Self-Reported Milk Intolerance: Evidence of Cow's Milk Sensitivity in Adults. *Nutrients* 2021; **13** [PMID: 34836089 DOI: 10.3390/nu13113833]
58 **Sousa MJCS**, Reis Ferreira AL, Moreira da Silva JP. Bodybuilding protein supplements and cow's milk allergy in adult. *Eur Ann Allergy Clin Immunol* 2018; **50**: 42-44 [PMID: 29350021 DOI: 10.23822/EurAnnACI.1764-1489.28]

59 **Tedner SG**, Asarnoj A, Thulin H, Westman M, Konradsen JR, Nilsson C. Food allergy and hypersensitivity reactions in children and adults-A review. *J Intern Med* 2022; **291**: 283-302 [PMID: 34875122 DOI: 10.1111/joim.13422]

60 **Olivier CE**, Lorena SL, Pavan CR, dos Santos RA, dos Santos Lima RP, Pinto DG, da Silva MD, de Lima Zollner R. Is it just lactose intolerance? *Allergy Asthma Proc* 2012; **33**: 432-436 [PMID: 23026186 DOI: 10.2500/aap.2012.33.3584]

61 **Leonard SA**, Nowak-Węgrzyn A. Food Protein-Induced Enterocolitis Syndrome. *Pediatr Clin North Am* 2015; **62**: 1463-1477 [PMID: 26456444 DOI: 10.1016/j.pcl.2015.07.011]

62 **Du YJ**, Nowak-Węgrzyn A, Vadas P. FPIES in adults. *Ann Allergy Asthma Immunol* 2018; **121**: 736-738 [PMID: 30121366 DOI: 10.1016/j.anai.2018.08.003]

63 **Celakovská J**, Ettlerová K, Ettler K, Vanecková J, Bukac J. Evaluation of cow's milk allergy in a large group of adolescent and adult patients with atopic dermatitis. *Acta Medica (Hradec Kralove)* 2012; **55**: 125-129 [PMID: 23297520 DOI: 10.14712/18059694.2015.49]

64 **Sinai T**, Goldberg MR, Nachshon L, Amitzur-Levy R, Yichie T, Katz Y, Monsonego-Ornan E, Elizur A. Reduced Final Height and Inadequate Nutritional Intake in Cow's Milk-Allergic Young Adults. *J Allergy Clin Immunol Pract* 2019; **7**: 509-515 [PMID: 30529059 DOI: 10.1016/j.jaip.2018.11.038]

65 **de Diego Lorenzo A**, Robles Fornieles J, Herrero López T, Cos Arregui E. Acute pancreatitis associated with milk allergy. *Int J Pancreatol* 1992; **12**: 319-321 [PMID: 1289425 DOI: 10.1007/BF02924372]

66 **Nachshon L**, Goldberg MR, Schwartz N, Sinai T, Amitzur-Levy R, Elizur A, Eisenberg E, Katz Y. Decreased bone mineral density in young adult IgE-mediated cow's milk-allergic patients. *J Allergy Clin Immunol* 2014; **134**: 1108-1113.e3 [PMID: 25091435 DOI: 10.1016/j.jaci.2014.06.026]

67 **Min KB**, Min JY. Increased risk for hyperuricemia in adults sensitized to cow milk allergen. *Clin Rheumatol* 2017; **36**: 1407-1412 [PMID: 27838787 DOI: 10.1007/s10067-016-3457-9]

68 **Kaskous S**. Cow's milk consumption and risk of disease. *Emir J Food Agric* 2021; **33**: 1-11 [DOI: 10.9755/ejfa.2021.v33.i1.2558]

69 **Vesa TH**, Marteau P, Korpela R. Lactose intolerance. *J Am Coll Nutr* 2000; **19**: 165S-175S [PMID: 10759141 DOI: 10.1080/07315724.2000.10718086]

70 **Mattar R**, de Campos Mazo DF, Carrilho FJ. Lactose intolerance: diagnosis, genetic, and clinical factors. *Clin Exp Gastroenterol* 2012; **5**: 113-121 [PMID: 22826639 DOI: 10.2147/CEG.S32368]

71 **Szilagyi A**, Ishayek N. Lactose Intolerance, Dairy Avoidance, and Treatment Options. *Nutrients* 2018; **10** [PMID: 30558337 DOI: 10.3390/nu10121994]

72 **Amiri M**, Diekmann L, von Köckritz-Blickwede M, Naim HY. The Diverse Forms of Lactose Intolerance and the Putative Linkage to Several Cancers. *Nutrients* 2015; **7**: 7209-7230 [PMID: 26343715 DOI: 10.3390/nu7095332]

73 **Deng Y**, Misselwitz B, Dai N, Fox M. Lactose Intolerance in Adults: Biological Mechanism and Dietary Management. *Nutrients* 2015; **7**: 8020-8035 [PMID: 26393648 DOI: 10.3390/nu7095380]

74 **Schiffner R**, Kostev K, Gothe H. Do patients with lactose intolerance exhibit more frequent comorbidities than patients without lactose intolerance? *Ann Gastroenterol* 2016; **29**: 174-179 [PMID: 27065730 DOI: 10.20524/aog.2016.0009]

75 **Rocco A**, Compare D, Sgamato C, Martino A, De Simone L, Coccoli P, Melone ML, Nardone G. Blinded Oral Challenges with Lactose and Placebo Accurately Diagnose Lactose Intolerance: A Real-Life Study. *Nutrients* 2021; **13** [PMID: 34068318 DOI: 10.3390/nu13051653]

76 **Su HM**, Jiang Y, Hu YL, Yang H, Dong TJ. [Lactose intolerance in neonates with non-infectious diarrhea]. *Zhongguo Dang Dai Er Ke Za Zhi* 2016; **18**: 306-310 [PMID: 27097573 DOI: 10.7499/j.issn.1008-8830.2016.04.005]

77 **Caballero B**, Solomons NW, Torún B. Fecal reducing substances and breath hydrogen excretion as indicators of carbohydrate malabsorption. *J Pediatr Gastroenterol Nutr* 1983; **2**: 487-490 [PMID: 6620056 DOI: 10.1097/00005176-198302030-00016]

78 **Yang JF**, Fox M, Chu H, Zheng X, Long YQ, Pohl D, Fried M, Dai N. Four-sample lactose hydrogen breath test for diagnosis of lactose malabsorption in irritable bowel syndrome patients with diarrhea. *World J Gastroenterol* 2015; **21**: 7563-7570 [PMID: 26140004 DOI: 10.3748/wjg.v21.i24.7563]

79 **de Lacy Costello BP**, Ledochowski M, Ratcliffe NM. The importance of methane breath testing: a review. *J Breath Res* 2013; **7**: 024001 [PMID: 23470880 DOI: 10.1088/1752-7155/7/2/024001]

80 **Domínguez-Jiménez JL**, Fernández-Suárez A, Ruiz-Tajuelos S, Puente-Gutiérrez JJ, Cerezo-Ruiz A. Lactose tolerance test shortened to 30 minutes: An exploratory study of its feasibility and impact. *Rev Esp Enferm Dig* 2014; **106**: 381-385 [PMID: 25361448]

81 **Ghoshal UC**, Kumar S, Chourasia D, Misra A. Lactose hydrogen breath test versus lactose tolerance test in the tropics: does positive lactose tolerance test reflect more severe lactose malabsorption? *Trop Gastroenterol* 2009; **30**: 86-90 [PMID: 19760990 DOI: 10.1515/almed-2020-0102]

82 **Hermida C**, Corrales G, Martínez-Costa OH, Fernández-Mayoralas A, Aragón JJ. Noninvasive evaluation of intestinal lactase with 4-galactosylxylose: comparison with 3- and 2-galactosylxylose and optimization of the method in rats. *Clin Chem* 2006; **52**: 270-277 [PMID: 16384892 DOI: 10.1373/clinchem.2005.058446]

83 **Monsalve-Hernando C**, Crespo L, Ferreiro B, Martín V, Aldeguer X, Opio V, Fernández-Gil PL, Gaspar MJ, Romero E, Lara C, Santander C, Torrealba L, Savescu T, Hermida C. Phase IV noninferiority controlled randomized trial to evaluate the impact on diagnostic thinking and patient management and the test-retest reproducibility of the Gaxilose test for hypolactasia diagnosis. *Medicine (Baltimore)* 2018; **97**: e13136 [PMID: 30431582 DOI: 10.1097/MD.0000000000013136]

84 **Aragón JJ**, Hermida C, Martínez-Costa OH, Sánchez V, Martín I, Sánchez JJ, Codoceo R, Cano JM, Cano A, Crespo L, Torres Y, García FJ, Fernández-Mayoralas A, Solera J, Martínez P. Noninvasive diagnosis of hypolactasia with 4-Galactosylxylose (Gaxilose): a multicentre, open-label, phase IIB-III nonrandomized trial. *J Clin Gastroenterol* 2014; **48**: 29-36 [PMID: 23722657 DOI: 10.1097/MCG.0b013e318297fb10]

85 **Catanzaro R**, Sciuto M, Marotta F. Lactose Intolerance-Old and New Knowledge on Pathophysiological Mechanisms, Diagnosis, and Treatment. *SN Compr Clin Med* 2021; **3**: 499-509 [DOI: 10.1007/s42399-021-00792-9]

86 **Santonocito C**, Scapaticci M, Guarino D, Annicchiarico EB, Lisci R, Penitente R, Gasbarrini A, Zuppi C, Capoluongo E. Lactose intolerance genetic testing: is it useful as routine screening? *Clin Chim Acta* 2015; **439**: 14-17 [PMID: 25281930 DOI: 10.1016/j.cca.2014.09.026]

87 **Buzás GM**. [Lactose intolerance: past and present. Part 1]. *Orv Hetil* 2015; **156**: 1532-1539 [PMID: 26550699 DOI: 10.1556/650.2015.30261]

88 **Gordon M**, Biagioli E, Sorrenti M, Lingua C, Moja L, Banks SS, Ceratto S, Savino F. Dietary modifications for infantile colic. *Cochrane Database Syst Rev* 2018; **10**: CD011029 [PMID: 30306546 DOI: 10.1002/14651858.CD011029.pub2]

89 **Cancarevic I**, Rehman M, Iskander B, Lalani S, Malik BH. Is There a Correlation Between Irritable Bowel Syndrome and Lactose Intolerance? *Cureus* 2020; **12**: e6710 [PMID: 32104635 DOI: 10.7759/cureus.6710]

90 **Asfari MM**, Sarmini MT, Kendrick K, Hudgi A, Uy P, Sridhar S, Sifuentes H. Association between Inflammatory Bowel Disease and Lactose Intolerance: Fact or Fiction. *Korean J Gastroenterol* 2020; **76**: 185-190 [PMID: 33100313 DOI: 10.4166/kjg.2020.76.4.185]

91 **Di Costanzo M**, Berni Canani R. Lactose Intolerance: Common Misunderstandings. *Ann Nutr Metab* 2018; **73** Suppl 4: 30-37 [PMID: 30783042 DOI: 10.1159/000493669]

92 **Grundmann SA**, Stratmann E, Brehler R, Luger TA, Ständer S. Lactase deficiency: a potential novel aetiological factor in chronic pruritus of unknown origin. *Acta Derm Venereol* 2011; **91**: 698-703 [PMID: 21879247 DOI: 10.2340/00015555-1150]

93 **Marie I**, Leroi AM, Gourcerol G, Levesque H, Menard JF, Ducrotte P. Lactose malabsorption in systemic sclerosis. *Aliment Pharmacol Ther* 2016; **44**: 1123-1133 [PMID: 27677253 DOI: 10.1111/apt.13810]

94 **Marie I**, Leroi AM, Gourcerol G, Levesque H, Ménard JF, Ducrotte P. Fructose Malabsorption in Systemic Sclerosis. *Medicine (Baltimore)* 2015; **94**: e1601 [PMID: 26426642 DOI: 10.1097/MD.0000000000001601]

95 **Asfari MM**, Hamid O, Sarmini MT, Kendrick K, Pappoppula LP, Sifuentes H, Sridhar S. The Association of Lactose Intolerance With Colon and Gastric Cancers: Friend or Foe? *Cureus* 2022; **14**: e24713 [PMID: 35676992 DOI: 10.7759/cureus.24713]

96 **Rozenberg S**, Body JJ, Bruyère O, Bergmann P, Brandi ML, Cooper C, Devogelaer JP, Gielen E, Goemaere S, Kaufman JM, Rizzoli R, Reginster JY. Effects of Dairy Products Consumption on Health: Benefits and Beliefs--A Commentary from the Belgian Bone Club and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases. *Calcif Tissue Int* 2016; **98**: 1-17 [PMID: 26445771 DOI: 10.1007/s00223-015-0062-x]

97 **Misselwitz B**, Pohl D, Frühauf H, Fried M, Vavricka SR, Fox M. Lactose malabsorption and intolerance: pathogenesis, diagnosis and treatment. *United European Gastroenterol J* 2013; **1**: 151-159 [PMID: 24917953 DOI: 10.1177/2050640613484463]

98 **Bayless TM**, Brown E, Paige DM. Lactase Non-persistence and Lactose Intolerance. *Curr Gastroenterol Rep* 2017; **19**: 23 [PMID: 28421381 DOI: 10.1007/s11894-017-0558-9]

99 **Leis R**, de Castro MJ, de Lamas C, Picáns R, Couce ML. Effects of Prebiotic and Probiotic Supplementation on Lactase Deficiency and Lactose Intolerance: A Systematic Review of Controlled Trials. *Nutrients* 2020; **12** [PMID: 32443748 DOI: 10.3390/nu12051487]

100 **Mäkinen OE**, Wanhalinna V, Zannini E, Arendt EK. Foods for Special Dietary Needs: Non-dairy Plant-based Milk Substitutes and Fermented Dairy-type Products. *Crit Rev Food Sci Nutr* 2016; **56**: 339-349 [PMID: 25575046 DOI: 10.1080/10408398.2012.761950]

101 Concerns for the use of soy-based formulas in infant nutrition. *Paediatr Child Health* 2009; **14**: 109-118 [PMID: 19436562]

102 **Katoch GK**, Nain N, Kaur S, Rasane P. Lactose Intolerance and Its Dietary Management: An Update. *J Am Nutr Assoc* 2022; **41**: 424-434 [PMID: 33831336 DOI: 10.1080/07315724.2021.1891587]

103 **Gordon CM**, Zemel BS, Wren TA, Leonard MB, Bachrach LK, Rauch F, Gilsanz V, Rosen CJ, Winer KK. The Determinants of Peak Bone Mass. *J Pediatr* 2017; **180**: 261-269 [PMID: 27816219 DOI: 10.1016/j.jpeds.2016.09.056]

104 **Baijal R**, Tandon RK. Effect of lactase on symptoms and hydrogen breath levels in lactose intolerance: A crossover placebo-controlled study. *JGH Open* 2021; **5**: 143-148 [PMID: 33490624 DOI: 10.1002/jgh3.12463]

105 **Heine RG**, AlRefaee F, Bachina P, De Leon JC, Geng L, Gong S, Madrazo JA, Ngamphaiboon J, Ong C, Rogacion JM. Lactose intolerance and gastrointestinal cow's milk allergy in infants and children - common misconceptions revisited. *World Allergy Organ J* 2017; **10**: 41 [PMID: 29270244 DOI: 10.1186/s40413-017-0173-0]

106 **Fikree A**, Byrne P. Management of functional gastrointestinal disorders. *Clin Med (Lond)* 2021; **21**: 44-52 [PMID: 33479067 DOI: 10.7861/clinmed.2020-0980]

107 **Wortmann AC**, Simon D, Mazzoleni LE, Sander GB, Francesconi CFM, Nabinger DD, Grott CS, Rech TF, Mazzoleni F, Lunge VR, Bona LR, Milbradt TC, Silveira TRD. The association between adult-type hypolactasia and symptoms of functional dyspepsia. *Genet Mol Biol* 2018; **41**: 92-97 [PMID: 29384557 DOI: 10.1590/1678-4685-GMB-2017-0015]

108 **Mishkin D**, Sablauskas L, Yalovsky M, Mishkin S. Fructose and sorbitol malabsorption in ambulatory patients with functional dyspepsia: comparison with lactose maldigestion/malabsorption. *Dig Dis Sci* 1997; **42**: 2591-2598 [PMID: 9440643 DOI: 10.1023/a:1018841402133]

109 **Salvatore S**, Vandenplas Y. Gastroesophageal reflux and cow milk allergy: is there a link? *Pediatrics* 2002; **110**: 972-984 [PMID: 12415039 DOI: 10.1542/peds.110.5.972]

110 **Iacono G**, Carroccio A, Cavataio F, Montalto G, Kazmierska I, Lorello D, Soresi M, Notarbartolo A. Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. *J Allergy Clin Immunol* 1996; **97**: 822-827 [PMID: 8613639 DOI: 10.1016/s0091-6749(96)80160-6]

111 **Rosen R**, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, Gupta S, Langendam M, Staiano A, Thapar N, Tipnis N, Tabbers M. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; **66**: 516-554 [PMID: 29470322 DOI: 10.1097/MPG.0000000000001889]

112 **Martin CR**, Ling PR, Blackburn GL. Review of Infant Feeding: Key Features of Breast Milk and Infant Formula.

Nutrients 2016; **8** [PMID: 27187450 DOI: 10.3390/nu8050279]

113 **Uscanga-Domínguez LF**, Orozco-García IJ, Vázquez-Frias R, Aceves-Tavares GR, Albrecht-Junnghans RE, Amieva-Balmori M, Bazaldua-Merino LA, Bernal-Reyes R, Camacho-de León ME, Campos-Gutiérrez JA, Carmona-Sánchez RI, Castro-Marín LV, Coss-Adame E, Cuevas-Estrada AJ, Escobedo-Martínez JA, González-Franco LR, Huerta-Iga FM, Lozano-Lozano R, Martínez-Vázquez SE, Milke García MP, Nogueira-de Rojas JR, Padilla-González M, Pérez Y López N, Silva-Campechano F, Treviño-Mejía MC, Velázquez-Alva MC. Technical position on milk and its derivatives in adult health and disease from the Asociación Mexicana de Gastroenterología and the Asociación Mexicana de Gerontología y Geriatría. *Rev Gastroenterol Mex (Engl Ed)* 2019; **84**: 357-371 [PMID: 31167744 DOI: 10.1016/j.rgmx.2019.03.002]

114 **Colemont L**. Gastro-duodenal ulcers. Who? *Acta Gastroenterol Belg* 1998; **61**: 303-304 [PMID: 9795459 DOI: 10.1016/s0016-5085(56)80051-6]

115 **Kumar N**, Kumar A, Broor SL, Vij JO, Anand BS. Effect of milk on patients with duodenal ulcers. *Br Med J (Clin Res Ed)* 1986; **293**: 666 [PMID: 3092974 DOI: 10.1136/bmj.293.6548.666]

116 **Kulshreshtha M**, Srivastava G, Singh MP. Pathophysiological status and nutritional therapy of peptic ulcer: An Update. *Environ Dis* 2017; **2**: 76-86 [DOI: 10.4103/ed.ed_11_17]

117 **Ong TG**, Gordon M, Banks SS, Thomas MR, Akobeng AK. Probiotics to prevent infantile colic. *Cochrane Database Syst Rev* 2019; **3**: CD012473 [PMID: 30865287 DOI: 10.1002/14651858.CD012473.pub2]

118 **Rhoads JM**, Collins J, Fatheree NY, Hashmi SS, Taylor CM, Luo M, Hoang TK, Gleason WA, Van Arsdall MR, Navarro F, Liu Y. Infant Colic Represents Gut Inflammation and Dysbiosis. *J Pediatr* 2018; **203**: 55-61.e3 [PMID: 30177353 DOI: 10.1016/j.jpeds.2018.07.042]

119 **Bishop JM**, Hill DJ, Hosking CS. Natural history of cow milk allergy: clinical outcome. *J Pediatr* 1990; **116**: 862-867 [PMID: 2348289 DOI: 10.1016/s0022-3476(05)80641-9]

120 **Moravej H**, Imanieh MH, Kashef S, Handjani F, Eghterdari F. Predictive value of the cow's milk skin prick test in infantile colic. *Ann Saudi Med* 2010; **30**: 468-470 [PMID: 21060160 DOI: 10.4103/0256-4947.72269]

121 **Vandenplas Y**. Lactose intolerance. *Asia Pac J Clin Nutr* 2015; **24** Suppl 1: S9-13 [PMID: 26715083 DOI: 10.6133/apjcn.2015.24.s1.02]

122 **Vandenplas Y**, Alturaiki MA, Al-Qabandi W, AlRefaee F, Bassil Z, Eid B, El Beleidy A, Almehaidib AI, Mouawad P, Sokhn M. Middle East Consensus Statement on the Diagnosis and Management of Functional Gastrointestinal Disorders in <12 Months Old Infants. *Pediatr Gastroenterol Hepatol Nutr* 2016; **19**: 153-161 [PMID: 27738596 DOI: 10.5223/pghn.2016.19.3.153]

123 **Simeone D**, Miele E, Boccia G, Marino A, Troncone R, Staiano A. Prevalence of atopy in children with chronic constipation. *Arch Dis Child* 2008; **93**: 1044-1047 [PMID: 18562455 DOI: 10.1136/adc.2007.133512]

124 **Sopo SM**, Arena R, Scala G. Functional constipation and cow's-milk allergy. *J Pediatr Gastroenterol Nutr* 2014; **59**: e34 [PMID: 24918979 DOI: 10.1097/MPG.0000000000000460]

125 **Gelsomino M**, Vescovo ED, Bersani G, Sopo SM. Functional constipation related to cow's milk allergy in children: A management proposal. *Allergol Immunopathol (Madr)* 2021; **49**: 17-20 [PMID: 33938184 DOI: 10.15586/aei.v49i3.72]

126 **Saha L**. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine. *World J Gastroenterol* 2014; **20**: 6759-6773 [PMID: 24944467 DOI: 10.3748/wjg.v20.i22.6759]

127 **Vaiopoulou A**, Karamanolis G, Psaltopoulou T, Karatzias G, Gazouli M. Molecular basis of the irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 376-383 [PMID: 24574707 DOI: 10.3748/wjg.v20.i2.376]

128 **Rana SV**, Malik A. Breath tests and irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 7587-7601 [PMID: 24976698 DOI: 10.3748/wjg.v20.i24.7587]

129 **Dainese R**, Casellas F, Mariné-Barjoan E, Vivinus-Nébot M, Schneider SM, Hébuterne X, Piche T. Perception of lactose intolerance in irritable bowel syndrome patients. *Eur J Gastroenterol Hepatol* 2014; **26**: 1167-1175 [PMID: 25089542 DOI: 10.1097/MEG.0000000000000089]

130 **Caffarelli C**, Di Mauro D, Garrubba M, Mastrorilli C. Allergy in Children with Functional Constipation and Irritable Bowel Syndrome. *Iran J Pediat* 2016 [DOI: 10.5812/ijp.5206]

131 **Knoflach P**, Park BH, Cunningham R, Weiser MM, Albini B. Serum antibodies to cow's milk proteins in ulcerative colitis and Crohn's disease. *Gastroenterology* 1987; **92**: 479-485 [PMID: 3792784 DOI: 10.1016/0016-5085(87)90145-4]

132 **Virta LJ**, Ashorn M, Kolho KL. Cow's milk allergy, asthma, and pediatric IBD. *J Pediatr Gastroenterol Nutr* 2013; **56**: 649-651 [PMID: 23319082 DOI: 10.1097/MPG.0b013e318285e9d8]

133 **Mishkin S**. Dairy sensitivity, lactose malabsorption, and elimination diets in inflammatory bowel disease. *Am J Clin Nutr* 1997; **65**: 564-567 [PMID: 9022546 DOI: 10.1093/ajcn/65.2.564]

134 **Strisciuglio C**, Giannetti E, Martinelli M, Sciorio E, Staiano A, Miele E. Does cow's milk protein elimination diet have a role on induction and maintenance of remission in children with ulcerative colitis? *Acta Paediatr* 2013; **102**: e273-e278 [PMID: 23445275 DOI: 10.1111/apa.12215]

135 **Ratajczak AE**, Rychter AM, Zawada A, Dobrowolska A, Krela-Kaźmierczak I. Lactose intolerance in patients with inflammatory bowel diseases and dietary management in prevention of osteoporosis. *Nutrition* 2021; **82**: 111043 [PMID: 33316755 DOI: 10.1016/j.nut.2020.111043]

136 **Lim HS**, Kim SK, Hong SJ. Food Elimination Diet and Nutritional Deficiency in Patients with Inflammatory Bowel Disease. *Clin Nutr Res* 2018; **7**: 48-55 [PMID: 29423389 DOI: 10.7762/cnr.2018.7.1.48]

137 **Krela-Kaźmierczak I**, Michalak M, Szymczak-Tomczak A, Czarnywojtek A, Wawrzyniak A, Łykowska-Szuber L, Stawczyk-Eder K, Dobrowolska A, Eder P. Milk and dairy product consumption in patients with inflammatory bowel disease: Helpful or harmful to bone mineral density? *Nutrition* 2020; **79-80**: 110830 [PMID: 32563771 DOI: 10.1016/j.nut.2020.110830]

138 **Sigala-Robles R**, Santiago-López L, Hernández-Mendoza A, Vallejo-Cordoba B, Mata-Haro V, Wall-Medrano A, González-Córdova AF. Peptides, Exopolysaccharides, and Short-Chain Fatty Acids from Fermented Milk and Perspectives on Inflammatory Bowel Diseases. *Dig Dis Sci* 2022 [PMID: 35133532 DOI: 10.1007/s10620-022-07382-2]

139 **Zhang X**, Tong Y, Lyu X, Wang J, Wang Y, Yang R. Prevention and Alleviation of Dextran Sulfate Sodium Salt-Induced Inflammatory Bowel Disease in Mice With *Bacillus subtilis*-Fermented Milk *via* Inhibition of the Inflammatory Responses

and Regulation of the Intestinal Flora. *Front Microbiol* 2020; **11**: 622354 [PMID: 33519783 DOI: 10.3389/fmicb.2020.622354]

140 **Shrier I**, Szilagyi A, Correa JA. Impact of lactose containing foods and the genetics of lactase on diseases: an analytical review of population data. *Nutr Cancer* 2008; **60**: 292-300 [PMID: 18444163 DOI: 10.1080/01635580701745301]

141 **Aune D**, Lau R, Chan DSM, Vieira R, Greenwood DC, Kampman E, Norat T. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. *Ann Oncol* 2012; **23**: 37-45 [PMID: 21617020 DOI: 10.1093/annonc/mdr269]

142 **Wallace K**, Baron JA, Cole BF, Sandler RS, Karagas MR, Beach MA, Haile RW, Burke CA, Pearson LH, Mandel JS, Rothstein R, Snover DC. Effect of calcium supplementation on the risk of large bowel polyps. *J Natl Cancer Inst* 2004; **96**: 921-925 [PMID: 15199111 DOI: 10.1093/jnci/djh165]

143 **Baron JA**, Barry EL, Mott LA, Rees JR, Sandler RS, Snover DC, Bostick RM, Ivanova A, Cole BF, Ahnen DJ, Beck GJ, Bresalier RS, Burke CA, Church TR, Cruz-Correa M, Figueiredo JC, Goodman M, Kim AS, Robertson DJ, Rothstein R, Shaukat A, Seabrook ME, Summers RW. A Trial of Calcium and Vitamin D for the Prevention of Colorectal Adenomas. *N Engl J Med* 2015; **373**: 1519-1530 [PMID: 26465985 DOI: 10.1056/NEJMoa1500409]

144 **Dhanashekar R**, Akkinepalli S, Nellutla A. Milk-borne infections. An analysis of their potential effect on the milk industry. *Germs* 2012; **2**: 101-109 [PMID: 24432270 DOI: 10.11599/germs.2012.1020]

145 **Sharp JC**. Infections associated with milk and dairy products in Europe and North America, 1980-85. *Bull World Health Organ* 1987; **65**: 397-406 [PMID: 3311443]

146 **Tóth AG**, Csabai I, Krikó E, Tőzsér D, Maróti G, Patai ÁV, Makrai L, Szita G, Solymosi N. Antimicrobial resistance genes in raw milk for human consumption. *Sci Rep* 2020; **10**: 7464 [PMID: 32366826 DOI: 10.1038/s41598-020-63675-4]

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OPINION REVIEW

Tangled relationship between insulin resistance and microalbuminuria in children with obesity

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Abstract

Childhood obesity represents a complex disease with a well-known cardio-metabolic burden including fatty liver, type 2 diabetes, metabolic syndrome, and cardiovascular disease. From a pathogenic point of view, insulin resistance (IR) represents the key factor underlying the spectrum of these obesity consequences. As observed in adults, recent data supported the occurrence of microalbuminuria (MA) as marker of early kidney dysfunction and its potential link with cardio-metabolic factors also in children with obesity. In fact, a well-documented pathophysiological hypothesis both in adults and children supported an intimate correlation with the major feature of obesity such as IR through the influence of insulin on renal hemodynamics. Based on the clinical and prognostic relevance of this relationship in daily practice (including an increased risk of chronic kidney disease development overtime), more scientific attention needs to be paid to the evaluation of early kidney damage in children with obesity. In this paper, we attempt to address three debated questions regarding the intriguing liaison between IR and MA in children with obesity: (1) What is the prevalence of pediatric MA? (2) What is the state of art of MA in children with obesity? and (3) Is there a link between IR and MA in children with obesity?

Key Words: Kidney damage; Microalbuminuria; Insulin resistance; Children; Obesity

Core Tip: In addition to the well-known cardiometabolic consequences of obesity (including fatty liver, type 2 diabetes, metabolic syndrome, and cardiovascular disease), early kidney damage has been also demonstrated in children with obesity. As a consequence of the dysmetabolism, the occurrence of microalbuminuria as an early marker of kidney dysfunction has been widely described in these subjects and closely linked to insulin resistance. Given the lack of extensive pediatric data and the prognostic implications of this intriguing association, a better knowledge in this field is needed to counteract the intrinsic increased cardiometabolic risk of children with obesity.

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INTRODUCTION

Microalbuminuria (MA) has been largely recognized as an independent predictive and prognostic marker not only of renal dysfunction but also of cardiovascular morbidity and mortality[1-3] not only in adults with diabetes or obesity but also in healthy subjects[1]. MA is diagnosed when urinary albumin excretion (UAE) is 30-300 mg/24 h in a 24-h urine collection or 20-200 μg/min in a night time collection and ratio of urinary albumin to creatinine concentrations (UACR) is 30-300 mg/g or 3-30 mg/mmol in a first-morning urine sample random urine[2]. Estimates from cross-sectional studies found a prevalence of MA in healthy adult subjects of approximately 4%[3,4] (3.7% in males and 4.6% in females, respectively[4]) with a significant increase up to 6.2% in patients with obesity[4]. In particular, visceral obesity has been linked to MA, since the negative role of visceral adipose tissue on cardiovascular outcomes[5,6]. In this context, MA and obesity had a similar additive effect on the risk of death, independently of other common risk factors (*e.g.*, diabetes, smoking, hypertension)[7].

Owing to its clinical relevance as an early marker of glomerular damage preceding the onset of overt diabetic nephropathy by 10-14 years[8], MA prevalence has been studied also in adults with diabetes, ranging from 7.4% to 11.4%[3,4]. Given the beneficial influence of an optimal glycemic control on the entire spectrum of renal impairments diabetes-related (MA, nephropathy, micro- and macrovascular consequences), MA screening has been recommended in these subjects[9,10].

In contrast to robust evidence supporting the clinical significance of MA in morbid adults, pediatric data in this field are still very limited[1].

WHAT ABOUT PEDIATRIC MA?

The evaluation of MA in healthy children and adolescents represents a pitfall since its potential relationship with strenuous exercise or febrile illness[11].

Based on cross-sectional data from NHANES III[2], MA prevalence in the first years of life has been found to be approximately 5.7%-7.3% in boys and 12.7%-15.1% in girls[1]. The higher percentage of MA in girls than boys could be attributed to the lower muscle mass and urinary creatinine excretion resulting in higher UACR values.

Remarkably, some studies reported an increased prevalence of MA in normal weight adolescents than in those with obesity[12-14]. Higher albumin excretion rate (ACR) levels have been significantly associated with a lower body mass index standard deviation score[15] and a higher height *z*-score[16]. In fact, healthy adolescents with MA are commonly thin and tall[16] and in these subjects MA might be directly related to the increased physical activity of thin children.

More, an increase of MA has been found in small for gestational-age children[1] and in school-age children[13]. In particular, the microalbumin/creatinine ratio in spot urine of healthy children decreased with increasing age[16]. A positive correlation between ACR and pubertal development stage has been also reported[17].

Of note, glucose metabolism impairments [*e.g.*, insulin resistance (IR)], pro-atherosclerotic pathways (*e.g.*, obesity), and haemodynamic load (*e.g.*, hypertension) have been largely accepted as the main cardiometabolic risk factors for the onset of MA in childhood[1,13,18].

Certain pathophysiological mechanisms such as low-grade inflammation, diffuse vascular damage with endothelial dysfunction[19], and increased permeability of the glomerular basement membrane[20] have been implied in urinary albumin loss.

WHAT IS THE STATE OF ART OF MA IN CHILDREN WITH OBESITY?

Although there is a direct association between MA and metabolic syndrome in adults[21,22], no similar consensus has been currently reached in childhood[13,23,24] . As a consequence of pediatric obesity epidemic[21], MA has been described in these children but its relationship with metabolic milieu is still debating[25,26](Table 1).

In cross-sectional studies, MA prevalence in children and adolescents with obesity has been found to be approximately 6.4%[27]. Several clinical and cardiometabolic risk factors linked to MA in children and adolescents with obesity have been studied including age, sex, body mass index, waist circumference, triglycerides, high-density lipoprotein cholesterol, hypertension, and glycated hemoglobin (HbA1c)[28-30].

A large pediatric Korean study[23] demonstrated a significant association of MA with hyperglycemia [odds ratio (OR) 2.62, 95% confidence interval (CI): 1.09-6.30, $P < 0.001$] in normal weight children, while hypertension (OR 14.10, 95%CI: 1.12-177.98, $P < 0.001$) was found to be correlated to MA in children with obesity. Interestingly, HbA1c was associated with MA in both groups (OR 3.34, 95%CI: 1.09-10.17, $P < 0.001$, and OR 6.68, 95%CI: 1.87-23.95, $P < 0.001$, respectively)[21].

Nguyen *et al*[29] showed that overweight adolescents with impaired glucose tolerance, IR, and hypertension had MA, as previously demonstrated in adults[22,23]. From a pathogenic point of view, the increased intraglomerular capillary pressure consequent to the excess weight status might result in glomerular hyperfiltration. Consequently, it may potentially lead to MA through endothelial dysfunction triggered by specific "hits" as hypertension, impaired fasting glucose, diabetes mellitus, or smoking[31].

Lurbe *et al*[32] found that elevated urinary albumin excretion was correlated with higher waist circumference and insulin levels, by emphasizing the role of metabolic derangements in this relationship.

Cho and Kim[24] in a study on 1976 children and adolescents without diabetes mellitus, found a prevalence of MA in subjects with obesity of 3%. More, authors reported an association of HbA1c with MA regardless of weight status. In particular, a significant association of MA with hypertension was demonstrated in these patients, supporting the usefulness of MA as a marker of cardiovascular risk.

Another study[33] examined 105 pediatric patients with obesity divided into three groups as subjects with obesity only, subjects with obesity and metabolic syndrome, and subjects with obesity and type 2 diabetes. MA and increased levels of serum cystatin-C were found in patients with type 2 diabetes. In addition to glomerular damage IR-related, the tubule-interstitial injury might be further aggravated by glucose homeostasis dysregulation in patients with type 2 diabetes.

Burgert *et al*[34] reported a significant correlation of MA with post challenge alterations in glucose metabolism and insulin sensitivity loss in pediatric patients with obesity and normal glucose tolerance. In line with previous evidence[36], no association between metabolic syndrome and MA was reported, but results are affected by the lack of a control group.

Similarly, Bartz *et al*[35], in a study on 58 adolescents described an intriguing link between obesity-related IR (calculated through the euglycemic hyperinsulinemic clamp), and early MA onset. Indeed, insulin enhanced the effects of angiotensin II, contributing to hypertension, raised intraglomerular pressure, exacerbation of proteinuria, production of inflammatory cytokines, and apoptosis[36].

In contrast to the low prevalence of MA in the context of pediatric obesity reported in these studies, data on kidney function from adolescents with severe obesity reported a higher MA prevalence (17.3%) [37], suggesting a greater risk of chronic kidney disease for these patients.

In a study by Martin-Del-Campo *et al*[38] subjects with kidney alterations had higher body fat markers (including body mass index, waist circumference, fat percentage, subscapular skinfold, *etc.*) values and lower high-density lipoprotein cholesterol levels. Commonly, all these factors have been strongly associated with the development of kidney disease in adults[39-41]. In fact, fat deposition in the glomerulus may alter renal production of vasoactive and inflammatory mediators related to glomerular damages[42].

Also, in the study of Sanad and Gharib[43], MA was proposed as a marker of the endothelial dysfunction related to obesity and its metabolic consequences. Indeed, a positive correlation between MA and a worse cardiometabolic profile (including abdominal obesity, dyslipidemia, hypertension, IR, and impaired glucose tolerance) was demonstrated in children with obesity.

Similar evidence was provided by Savino *et al*[44]. Although no clinical evidence of kidney dysfunction was found in youths with obesity compared to healthy controls, MA was confirmed to be associated with hypertension, adiposity, and IR.

Csernus *et al*[45], found that children with obesity and glucose homeostasis abnormalities (including hyperinsulinemia and impaired glucose tolerance) and had a higher urinary albumin/creatinine ratio than normal weight children, supporting the central role of these factors in the development of kidney damage.

On the other hand, there is some contrasting evidence[29] reporting no association between MA and cardiometabolic risk factors in childhood obesity. To explain this, it could be supposed that a longer dysmetabolism (including duration of obesity and IR status) is required for renal dysfunction development.

Table 1 Main studies on microalbuminuria in children with obesity

Ref.	Study design	Population	Main findings
Savino *et al* [44]	Case Control	One hundred seven OB Caucasian prepubertal and pubertal children and adolescents of both sexes (M 52, F 55). Fifty normal weight Caucasian children as control group (M 26, F 24)	A modest significant difference was seen in AER values, which were higher in the OB group, even if mostly within normal range. AER showed a positive correlation with central adiposity, insulin resistance indexes and hypertension
Sanad and Gharib[43]	Cross – Sectional	One hundred fifty prepubertal obese children. Exclusion criteria: fever, infections, renal diseases, LES, endocrine disorders, albuminuria associated with urinary tract infections	There were significant positive correlations between MA and BMI, WC, systolic and diastolic BP, TG and LDL-c levels, insulin resistance and fasting glucose level. In contrast, there was a negative correlation between MA and HDL-c levels ($P < 0.01$). No significant correlations of MA with age and sex were found ($P > 0.05$)
Csernus *et al* [45]	Case-Control	Eighty-six obese children. Seventy-nine normal weight children as a control group. children with secondary obesity were excluded	OB children with obesity had a significantly higher U-ACR and U-BMCR as compared to the normal weight children. OB children with no more than one of cardiovascular risk factors (*e.g.*, hyperinsulinemia, fasting or post-prandial glucose, dyslipidemia and hypertension) had a significantly lower U-ACR than those with two or more features. U-ACR was positively correlated with body weight and with the fasting plasma glucose concentrations measured during the OGTT. U-ACR was increased in OB children with hypercholesterolemia. No association of U-ACR with TG and HDL-c levels was found
Goknar *et al* [30]	Case-Control	Eighty-four OB individuals aged 4-16 yr as study (case) group. Sixty-four normotensive healthy children as control group	No statistically significant differences were found in urine microalbumin/creatinine ($P = 0.740$)
Hirschler *et al* [12]	Retrospective Study	One thousand five hundred sixty-four children aged 5-14 yr, 220/1564 OB (14.1%), 300/1564 OW (19.2%), 1044/1564 (66.7%) normal weight, 318/1564 (20.3%) central OB	U-ACR decreased with increasing z-BMI for boys and girls. Median ACR and urinary albumin levels were significantly higher in normal weight children than in OW/OB children. Median ACR and urinary albumin levels was higher in OB girls than in OB boys
Radhakishun *et al*[28]	Retrospective	Four hundred eight OB children aged 3-19 yr, 50 % males	A low prevalence of MA (2.7%) was found. All subjects with MA were obese
Oz-Sig *et al* [33]	Retrospective	One hundred and five obese children (M 39) aged 4-18 yr. The cohort was divided into three groups as solely obese, with metabolic syndrome and with type 2 diabetes. MA was tested in 24 h collected urine (MA: 30-300 mg)	MA was significantly higher in type 2 diabetic group; statistical significance was reached in the group with metabolic syndrome and type 2 diabetic group. MA was not detected in the solely obese group
Lurbe *et al*[32]	Retrospective	One hundred and thirty-four OB children aged 9-18 yr. Obesity: *z* score > 2, Moderate obesity: *z* score 2-2.5. Severe obesity: *z* score > 2.5. UAE was measured in the first voiding urine of the morning	No differences between different groups of obesity degree were found. Increased UAE was linked to fasting Insulin HOMA Index, higher WC, and TG levels
Cho *et al*[15]	Retrospective	One thousand four hundred and fifty-nine adolescents aged 12-18 yr	MA was detected in 3.6% of subjects (53/1459). The Height *z* score of the MA group was greater than that of the NA group. The Weight z score of the MA group did not differ from that of NA group. The MA group had a lower BMI z score. MA group had higher HDL-c and lower TG levels. No significant differences in BP, fasting glucose, total cholesterol, and LDL levels were reported. UACR was associated with younger age, lower weight *z* score, lower BMI *z* score, lower W/Hr, but not with the height *z* score. UACR was associated with higher HDL level and lower TG values
Burgert *et al* [34]	Cohort Study	Two hundred seventy-seven children and adolescents	MA was found in 10.1 % of subjects (28/277). No significant differences between the two groups (MA e NA) in term of the anthropometrical and common cardiovascular risk factors were reported. Subjects with MA had higher plasma glucose and insulin levels during OGTT
Nguyen *et al* [29]	Cross Sectional	Two thousand five hundred fifteen adolescents aged 12-19 yr. 310/2515 children with BMI > 95 pc.	MA was detected in 8.9% of the study population. UACR girls was significantly higher in girls than in boys. MA was prevalent among NON-OW adolescents. Similarly, MA was prevalent among adolescents without abdominal obesity, and without insulin resistance
Martin-Del-Campo *et al* [38]	Cross Sectional	One hundred seventy-two children and adolescents aged 6-16 yr, 46/172 (27%) normal weight, 55/172 (32%) overweight, 71/172 (41%) obesity	MA was observed in children with OW (3.6%) and with OB (9.9%) more than in normal weight children

AER: Albumin excretion rate; BMI: Body mass index; HDL-c: High-density lipoprotein- cholesterol; LDL-c: Low-density lipoprotein- cholesterol; MA: Microalbuminuria; NA: Normal albuminuria; OB: obese; OGTT: Oral glucose tolerance test; OW: overweight; TG: Triglycerides;U-ACR: Urinary albumin/creatinine ratio; UAE: Urinary albumin excretion; U-BMCR: Urinary beta-2-microglobulin/creatinine ratio; WC: Waist circumference; W/Hr: waist-to-height ratio.

An Italian study[46] involved 901 children and adolescents subdivided according to estimated glomerular filtration (eGFR). Children with mild-low eGFR (< 20th percentile) and high eGFR (> 80th percentile) had an increased presence of cardio-metabolic risk factor. Between these, children with reduced eGFR levels had a worse cardio-metabolic profile. Considering this, authors suggested eGFR as a useful tool to identify children at greater cardiometabolic risk.

Similar findings were reported in another cross-sectional study examining 360 children with obesity [28]. Subjects with eGFR > 1 SD had higher systolic blood pressure, glucose, and insulin levels in response to oral glucose tolerance test. No significant association was demonstrated between MA (reported in 6.4% of subjects) and other cardiometabolic markers in children with obesity, although a lower insulinogenic index in subjects with MA was reported.

IR AND MA IN CHILDHOOD OBESITY: IS THERE A LINK?

As observed adults[7,39], early renal damage (expressed as MA) has been demonstrated as a consequence of obesity in childhood[1,12,26]. Robust evidence has shown that MA represents a close reflection of the systemic vascular endothelial damage status[26,34,35]. In this tangled framework, a pivotal pathogenic role in the development of the underlying renal hemodynamic abnormalities has been widely recognized for IR[26,32,35] (Figure 1). As a consequence of a reduced insulin sensitivity, hyperinsulinemia- through the well-documented conflicting effects of insulin (both antinatriuretic and at tubular and glomerular level, respectively), acts as a key player in the tangled dysregulation of renal hemodynamics (including glomerular hyperperfusion, hyperfiltration, *etc*.) occurring in children with obesity[47,48]. To complicate matter, IR seems to mediate the intertwined relationship of MA with obesity and early renal impairment[35]. Classically, several different signaling pathways are involved in IR development and have been found to act also in the early stages of renal injury[26,34,35]. Therefore, MA represents an early predictive cardiometabolic risk marker as its close relationship with endothelial dysfunction reflecting both renal and systemic endovascular damage[26,34,35]. Although the current paucity of data examining the association of IR with MA in children with obesity, there is some pediatric evidence linking this latter to cardiometabolic risk factors[23,25,26,43]. IR represents a central player in Metabolic syndrome, in turn closely related to obesity, realizing a dangerous vicious circle[26,43,46]. In particular, the adiposity-related IR might lead to endothelial dysfunction with subsequent increased permeability responsible for the loss of albumin and other molecules involved in lipid accumulation and inflammation in the wall of vessels[26,43]. Taken together, these derangements might represent a potential pathophysiological explanation of kidney damage observed in children with obesity[26,43,47].

As the relevant prognostic implications of the relationship between MA and IR on the cardio-metabolic burden of children with obesity[49], this intriguing link deserves to be further strengthen in larger pediatric studies.

CONCLUSION

Within the spectrum of the pediatric obesity-related consequences, recent data have focused on the risk of early kidney damage in these children. Although still contrasting, a large body of evidence supported a complex relationship of MA with IR. Noteworthy, this latter represents an intriguing shared risk factor between obesity and early renal impairment.

Taking into account the adverse prognostic implications of the association of MA with IR not only on renal function but also on the general health status of children with obesity, we believe that MA evaluation should be included in the overall assessment of these patients as subjects with an intrinsic higher cardiometabolic risk.

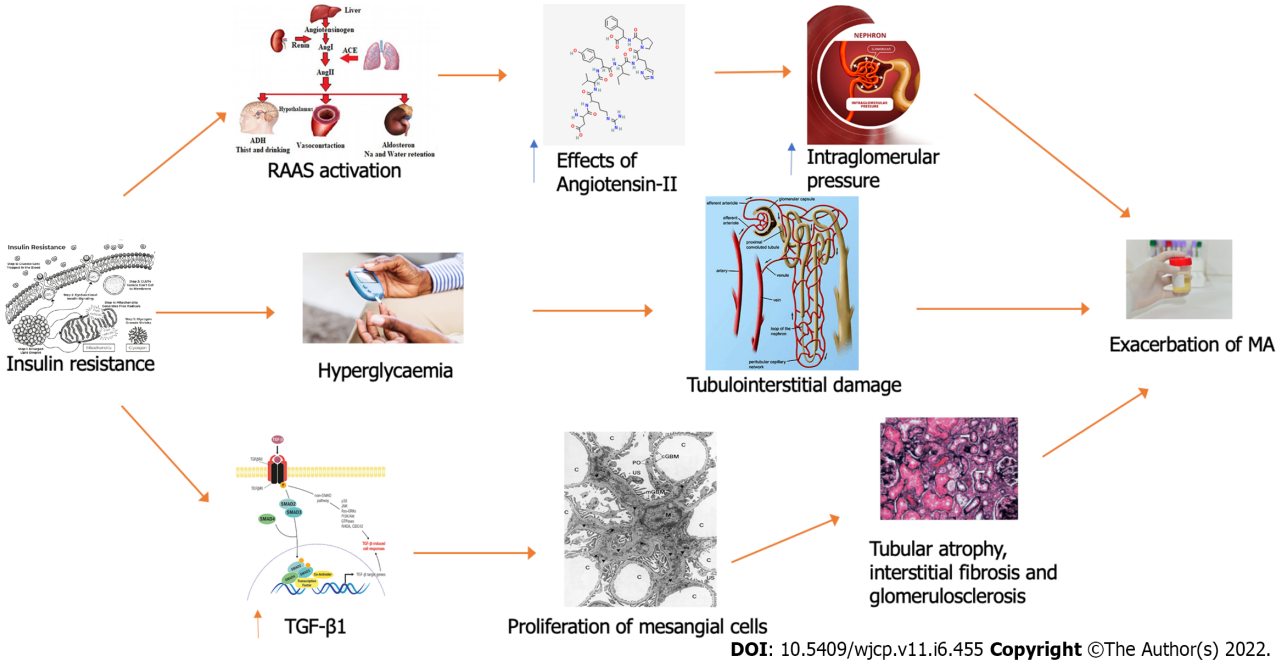

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Figure 1 Pathophysiological link between microalbuminuria and insulin resistance. MA: Microalbuminuria; TGF-β1: Transforming growth factor-β1; RAAS: Renin-angiotensin-aldosterone system.

FOOTNOTES

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REFERENCES

1 **Tsioufis C**, Mazaraki A, Dimitriadis K, Stefanidis CJ, Stefanadis C. Microalbuminuria in the paediatric age: current knowledge and emerging questions. *Acta Paediatr* 2011; **100**: 1180-1184 [PMID: 21443530 DOI: 10.1111/j.1651-2227.2011.02291.x]
2 **Jones CA**, Francis ME, Eberhardt MS, Chavers B, Coresh J, Engelgau M, Kusek JW, Byrd-Holt D, Narayan KM, Herman WH, Jones CP, Salive M, Agodoa LY. Microalbuminuria in the US population: third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2002; **39**: 445-459 [PMID: 11877563 DOI: 10.1053/ajkd.2002.31388]
3 **Tanaka S**, Takase H, Dohi Y, Kimura G. The prevalence and characteristics of microalbuminuria in the general population: a cross-sectional study. *BMC Res Notes* 2013; **6**: 256 [PMID: 23830507 DOI: 10.1186/1756-0500-6-256]
4 **Yan L**, Ma J, Guo X, Tang J, Zhang J, Lu Z, Wang H, Cai X, Wang L. Urinary albumin excretion and prevalence of microalbuminuria in a general Chinese population: a cross-sectional study. *BMC Nephrol* 2014; **15**: 165 [PMID: 25308236

DOI: 10.1186/1471-2369-15-165]
5 **Grundy SM**, Hansen B, Smith SC Jr, Cleeman JI, Kahn RA; American Heart Association; National Heart, Lung, and Blood Institute; American Diabetes Association. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. *Circulation* 2004; **109**: 551-556 [PMID: 14757684 DOI: 10.1161/01.CIR.0000112379.88385.67]
6 **Kim H**, Kim HJ, Shin N, Han M, Park H, Kim M, Kwon H, Choi SY, Heo NJ. Visceral obesity is associated with microalbuminuria in nondiabetic Asians. *Hypertens Res* 2014; **37**: 679-684 [PMID: 24646640 DOI: 10.1038/hr.2014.47]
7 **Klausen KP**, Parving HH, Scharling H, Jensen JS. Microalbuminuria and obesity: impact on cardiovascular disease and mortality. *Clin Endocrinol (Oxf)* 2009; **71**: 40-45 [PMID: 18803675 DOI: 10.1111/j.1365-2265.2008.03427.x]
8 **Correa-Rotter R**, Naicker S, Katz IJ, Agarwal SK, Herrera Valdes R, Kaseje D, Rodriguez-Iturbe B, Shaheen F, Sitthi-Amorn C; ISN-COMGAN Bellagio Study Group 2004. Demographic and epidemiologic transition in the developing world: role of albuminuria in the early diagnosis and prevention of renal and cardiovascular disease. *Kidney Int Suppl* 2004; S32-S37 [PMID: 15485413 DOI: 10.1111/j.1523-1755.2004.09208.x]
9 **American Diabetes Association**. 11. Microvascular Complications and Foot Care: *Standards of Medical Care in Diabetes-2020*. *Diabetes Care* 2020; **43**: S135-S151 [PMID: 31862754 DOI: 10.2337/dc20-S011]
10 **Sherwani SI**, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. *Biomark Insights* 2016; **11**: 95-104 [PMID: 27398023 DOI: 10.4137/BMI.S38440]
11 **Sanchez-Bayle M**, Rodriguez-Cimadevilla C, Asensio C, Ruiz-Jarabo C, Baena J, Arnaiz P, Villa S, Cocho P. Urinary albumin excretion in Spanish children. Niño Jesus Group. *Pediatr Nephrol* 1995; **9**: 428-430 [PMID: 7577402 DOI: 10.1007/BF00866717]
12 **Hirschler V**, Molinari C, Maccallini G, Aranda C. Is albuminuria associated with obesity in school children? *Pediatr Diabetes* 2010; **11**: 322-330 [PMID: 19968814 DOI: 10.1111/j.1399-5448.2009.00599.x]
13 **Mazaraki A**, Tsioufis C, Dimitriadis K, Tsiachris D, Stefanadi E, Zampelas A, Richter D, Mariolis A, Panagiotakos D, Tousoulis D, Stefanadis C. Adherence to the Mediterranean diet and albuminuria levels in Greek adolescents: data from the Leontio Lyceum ALbuminuria (3L study). *Eur J Clin Nutr* 2011; **65**: 219-225 [PMID: 21063428 DOI: 10.1038/ejcn.2010.244]
14 **Tsioufis C**, Tsiachris D, Dimitriadis K, Thomopoulos C, Syrseloudis D, Andrikou E, Chatzis D, Taxiarchou E, Selima M, Mazaraki A, Chararis G, Tolis P, Gennadi A, Andrikou I, Stefanadi E, Fragoulis V, Tzamou V, Panagiotakos D, Tousoulis D, Stefanadis C. Leontio Lyceum ALbuminuria (3L Study) epidemiological study: aims, design and preliminary findings. *Hellenic J Cardiol* 2009; **50**: 476-483 [PMID: 19942561]
15 **Cho MH**, Kim KS, Chung S. Microalbuminuria Is Associated with Lower Weight and Taller Height in Adolescence. *Tohoku J Exp Med* 2017; **243**: 151-157 [PMID: 29129845 DOI: 10.1620/tjem.243.151]
16 **Kwak BO**, Lee ST, Chung S, Kim KS. Microalbuminuria in normal Korean children. *Yonsei Med J* 2011; **52**: 476-481 [PMID: 21488191 DOI: 10.3349/ymj.2011.52.3.476]
17 **Bangstad HJ**, Dahl-Jørgensen K, Kjaersgaard P, Mevold K, Hanssen KF. Urinary albumin excretion rate and puberty in non-diabetic children and adolescents. *Acta Paediatr* 1993; **82**: 857-862 [PMID: 8241647 DOI: 10.1111/j.1651-2227.1993.tb17628.x]
18 **Okpere AN**, Anochie IC, Eke FU. Prevalence of microalbuminuria among secondary school children. *Afr Health Sci* 2012; **12**: 140-147 [PMID: 23056019 DOI: 10.4314/ahs.v12i2.10]
19 **Tsioufis C**, Dimitriadis K, Chatzis D, Vasiliadou C, Tousoulis D, Papademetriou V, Toutouzas P, Stefanadis C, Kallikazaros I. Relation of microalbuminuria to adiponectin and augmented C-reactive protein levels in men with essential hypertension. *Am J Cardiol* 2005; **96**: 946-951 [PMID: 16188522 DOI: 10.1016/j.amjcard.2005.05.052]
20 **Kwak BO**, Chung S, Kim KS. Microalbuminuria in children with urinary tract infection. *Korean J Pediatr* 2010; **53**: 840-844 [PMID: 21189969 DOI: 10.3345/kjp.2010.53.9.840]
21 **Sheng CS**, Hu BC, Fan WX, Zou J, Li Y, Wang JG. Microalbuminuria in relation to the metabolic syndrome and its components in a Chinese population. *Diabetol Metab Syndr* 2011; **3**: 6 [PMID: 21470432 DOI: 10.1186/1758-5996-3-6]
22 **Lee HO**, Bak HJ, Shin JY, Song YM. Association between Metabolic Syndrome and Microalbuminuria in Korean Adults. *Korean J Fam Med* 2015; **36**: 60-71 [PMID: 25802687 DOI: 10.4082/kjfm.2015.36.2.60]
23 **Cho H**, Kim JH. Prevalence of microalbuminuria and its associated cardiometabolic risk factors in Korean youth: Data from the Korea National Health and Nutrition Examination Survey. *PLoS One* 2017; **12**: e0178716 [PMID: 28575100 DOI: 10.1371/journal.pone.0178716]
24 **Lambers Heerspink HJ**, Brantsma AH, de Zeeuw D, Bakker SJ, de Jong PE, Gansevoort RT; PREVEND Study Group. Albuminuria assessed from first-morning-void urine samples *vs* 24-hour urine collections as a predictor of cardiovascular morbidity and mortality. *Am J Epidemiol* 2008; **168**: 897-905 [PMID: 18775924 DOI: 10.1093/aje/kwn209]
25 **Folić N**, Folić M, Marković S, Andjelković M, Janković S. Risk factors for the development of metabolic syndrome in obese children and adolescents. *Srp Arh Celok Lek* 2015; **143**: 146-152 [PMID: 26012122 DOI: 10.2298/sarh1504146f]
26 **Savino A**, Pelliccia P, Chiarelli F, Mohn A. Obesity-related renal injury in childhood. *Horm Res Paediatr* 2010; **73**: 303-311 [PMID: 20389099 DOI: 10.1159/000308161]
27 **Ricotti R**, Genoni G, Giglione E, Monzani A, Nugnes M, Zanetta S, Castagno M, Marolda A, Bellomo G, Bona G, Bellone S, Prodam F. High-normal estimated glomerular filtration rate and hyperuricemia positively correlate with metabolic impairment in pediatric obese patients. *PLoS One* 2018; **13**: e0193755 [PMID: 29505614 DOI: 10.1371/journal.pone.0193755]
28 **Radhakishun NN**, van Vliet M, von Rosenstiel IA, Beijnen JH, Diamant M. Limited value of routine microalbuminuria assessment in multi-ethnic obese children. *Pediatr Nephrol* 2013; **28**: 1145-1149 [PMID: 23503768 DOI: 10.1007/s00467-013-2451-6]
29 **Nguyen S**, McCulloch C, Brakeman P, Portale A, Hsu CY. Being overweight modifies the association between cardiovascular risk factors and microalbuminuria in adolescents. *Pediatrics* 2008; **121**: 37-45 [PMID: 18166555 DOI: 10.1542/peds.2007-3594]
30 **Goknar N**, Oktem F, Ozgen IT, Torun E, Kuçukkoc M, Demir AD, Cesur Y. Determination of early urinary renal injury

markers in obese children. *Pediatr Nephrol* 2015; **30**: 139-144 [PMID: 24801174 DOI: 10.1007/s00467-014-2829-0]
31 **Nenov VD**, Taal MW, Sakharova OV, Brenner BM. Multi-hit nature of chronic renal disease. *Curr Opin Nephrol Hypertens* 2000; **9**: 85-97 [PMID: 10757212 DOI: 10.1097/00041552-200003000-00001]
32 **Lurbe E**, Torro MI, Alvarez J, Aguilar F, Fernandez-Formoso JA, Redon J. Prevalence and factors related to urinary albumin excretion in obese youths. *J Hypertens* 2013; **31**: 2230-6; discussion 2236 [PMID: 24096259 DOI: 10.1097/HJH.0b013e328364bcbf]
33 **Oz-Sig O**, Kara O, Erdogan H. Microalbuminuria and Serum Cystatin C in Prediction of Early-Renal Insufficiency in Children with Obesity. *Indian J Pediatr* 2020; **87**: 1009-1013 [PMID: 32385781 DOI: 10.1007/s12098-020-03294-z]
34 **Burgert TS**, Dziura J, Yeckel C, Taksali SE, Weiss R, Tamborlane W, Caprio S. Microalbuminuria in pediatric obesity: prevalence and relation to other cardiovascular risk factors. *Int J Obes (Lond)* 2006; **30**: 273-280 [PMID: 16231019 DOI: 10.1038/sj.ijo.0803136]
35 **Bartz SK**, Caldas MC, Tomsa A, Krishnamurthy R, Bacha F. Urine Albumin-to-Creatinine Ratio: A Marker of Early Endothelial Dysfunction in Youth. *J Clin Endocrinol Metab* 2015; **100**: 3393-3399 [PMID: 26176802 DOI: 10.1210/JC.2015-2230]
36 **Rüster C**, Wolf G. Renin-angiotensin-aldosterone system and progression of renal disease. *J Am Soc Nephrol* 2006; **17**: 2985-2991 [PMID: 17035613 DOI: 10.1681/ASN.2006040356]
37 **Xiao N**, Jenkins TM, Nehus E, Inge TH, Michalsky MP, Harmon CM, Helmrath MA, Brandt ML, Courcoulas A, Moxey-Mims M, Mitsnefes MM; Teen-LABS Consortium. Kidney function in severely obese adolescents undergoing bariatric surgery. *Obesity (Silver Spring)* 2014; **22**: 2319-2325 [PMID: 25376399 DOI: 10.1002/oby.20870]
38 **Martin-Del-Campo F**, Batis-Ruvalcaba C, Ordaz-Medina SM, Martínez-Ramírez HR, Vizmanos-Lamotte B, Romero-Velarde E, Cortes-Sanabria L, Cueto-Manzano AM. Frequency and Risk Factors of Kidney Alterations in Children and Adolescents who Are Overweight and Obese in a Primary Health-care Setting. *J Ren Nutr* 2019; **29**: 370-376 [PMID: 30679077 DOI: 10.1053/j.jrn.2018.11.005]
39 **Ejerblad E**, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyrén O. Obesity and risk for chronic renal failure. *J Am Soc Nephrol* 2006; **17**: 1695-1702 [PMID: 16641153 DOI: 10.1681/ASN.2005060638]
40 **Hayashi K**, Takayama M, Abe T, Kanda T, Hirose H, Shimizu-Hirota R, Shiomi E, Iwao Y, Itoh H. Investigation of Metabolic Factors Associated with eGFR Decline Over 1 Year in a Japanese Population without CKD. *J Atheroscler Thromb* 2017; **24**: 863-875 [PMID: 28123142 DOI: 10.5551/jat.38612]
41 **Ribstein J**, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. *Hypertension* 1995; **26**: 610-615 [PMID: 7558220 DOI: 10.1161/01.hyp.26.4.610]
42 **Kasiske BL**, O'Donnell MP, Cowardin W, Keane WF. Lipids and the kidney. *Hypertension* 1990; **15**: 443-450 [PMID: 2185148 DOI: 10.1161/01.hyp.15.5.443]
43 **Sanad M**, Gharib A. Evaluation of microalbuminuria in obese children and its relation to metabolic syndrome. *Pediatr Nephrol* 2011; **26**: 2193-2199 [PMID: 21638155 DOI: 10.1007/s00467-011-1931-9]
44 **Savino A**, Pelliccia P, Giannini C, de Giorgis T, Cataldo I, Chiarelli F, Mohn A. Implications for kidney disease in obese children and adolescents. *Pediatr Nephrol* 2011; **26**: 749-758 [PMID: 21308381 DOI: 10.1007/s00467-010-1659-y]
45 **Csernus K**, Lanyi E, Erhardt E, Molnar D. Effect of childhood obesity and obesity-related cardiovascular risk factors on glomerular and tubular protein excretion. *Eur J Pediatr* 2005; **164**: 44-49 [PMID: 15517379 DOI: 10.1007/s00431-004-1546-2]
46 **Di Bonito P**, Sanguigno E, Forziato C, Di Fraia T, Moio N, Cavuto L, Sibilio G, Iardino MR, Di Carluccio C, Capaldo B. Glomerular filtration rate and cardiometabolic risk in an outpatient pediatric population with high prevalence of obesity. *Obesity (Silver Spring)* 2014; **22**: 585-589 [PMID: 23616281 DOI: 10.1002/oby.20497]
47 **Chagnac A**, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U. Glomerular hemodynamics in severe obesity. *Am J Physiol Renal Physiol* 2000; **278**: F817-F822 [PMID: 10807594 DOI: 10.1152/ajprenal.2000.278.5.F817]
48 **DeFronzo RA**, Cooke CR, Andres R, Faloona GR, Davis PJ. The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. *J Clin Invest* 1975; **55**: 845-855 [PMID: 1120786 DOI: 10.1172/JCI107996]
49 **Di Bonito P**, Valerio G, Licenziati MR, Campana G, Del Giudice EM, Di Sessa A, Morandi A, Maffeis C, Chiesa C, Pacifico L, Baroni MG, Manco M. Uric acid, impaired fasting glucose and impaired glucose tolerance in youth with overweight and obesity. *Nutr Metab Cardiovasc Dis* 2021; **31**: 675-680 [PMID: 33272808 DOI: 10.1016/j.numecd.2020.10.007]

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SYSTEMATIC REVIEWS

Insulin pumps in children - a systematic review

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Abstract

BACKGROUND

Insulin pump therapy is a real breakthrough in managing diabetes Mellitus, particularly in children. It can deliver a tiny amount of insulin and decreases the need for frequent needle injections. It also helps to maintain adequate and optimal glycemic control to reduce the risk of metabolic derangements in different tissues. Children are suitable candidates for pump therapy as they need a more freestyle and proper metabolic control to ensure adequate growth and development. Therefore, children and their caregivers should have proper education and training and understand the proper use of insulin pumps to achieve successful pump therapy. The pump therapy continuously improves to enhance its performance and increase its simulation of the human pancreas. Nonetheless, there is yet a long way to reach the desired goal.

AIM
To review discusses the history of pump development, its indications, types, proper use, special conditions that may enface the children and their families while using the pump, its general care, and its advantages and disadvantages.

METHODS
We conducted comprehensive literature searches of electronic databases until June 30, 2022, related to pump therapy in children and published in the English language.

RESULTS
We included 118 articles concerned with insulin pumps, 61 were reviews, systemic reviews, and meta-analyses, 47 were primary research studies with strong design, and ten were guidelines.

CONCLUSION
The insulin pump provides fewer needles and can provide very tiny insulin doses, a convenient and more flexible way to modify the needed insulin physiologically, like the human pancreas, and can offer adequate and optimal glycemic control to reduce the risk of metabolic derangements in different tissues.

Key Words: Insulin pump; Children; Diabetes mellitus; Keto-acidosis; Continuous glucose monitoring; Insulin therapy

Core Tip: The insulin pump is a significant step in proper diabetes management in the way to simulate the human pancreas. Insulin pumps undergo significant daily improvement every day to enhance their performance. The insulin pump is beneficial for children with type I diabetes mellitus. However, proper training and education of the children and their families are mandatory for the appropriate function of the insulin pumps. They should know how to use it properly and overcome the difficulties they may encounter and the different scenarios they may meet. The way still long to achieve our goals.

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INTRODUCTION

The insulin pump is a giant breakthrough in diabetes mellitus (DM) treatment. Treating diabetes with an insulin pump is the method most similar to the normal physiologic function of the pancreas. The pump delivers insulin in 2 different ways simulating the human pancreas. It delivers a continuous small insulin quantity as a "background insulin" to maintain the basal metabolic rate and bolus insulin doses when needed to metabolize the ingested food. The insulin pump is particularly needed in the management of type I DM. The insulin pump is continuously undergoing massive improvement. Nonetheless, there is yet a long way to reach the desired goal[1].

MATERIALS AND METHODS

This review aims to discuss the history of pump development, its indications, types, proper use, special conditions that may enface the children and their families while using the pump, its general care, and its advantages and disadvantages. In this narrative review, we conducted comprehensive literature searches of electronic databases, PubMed, Embase, Cochrane Library, Reference Citation Analysis (RCA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Scopus, Library and Information Science Abstracts (LISA), and the National Library of Medicine (NLM) catalog up until June 30, 2022, related to pump therapy in children. Reference lists were inspected, and citation searches were done on the included studies. We included open access papers for English-language studies concerned with insulin pump therapy and diabetes mellitus in children. We also reviewed many review articles concerned with pump therapy in children. We also reviewed the articles that are

available as abstracts only. We excluded articles with commercial backgrounds.

RESULTS

Figure 1 showed the flow chart of the reviewed articles. We included 118 articles concerned with insulin pumps, 61 were reviews, systemic reviews, and meta-analyses, 47 were primary research studies with strong design, and ten were guidelines.

DISCUSSION

For a long time, there is a need for proper management of children with diabetes. The result of this review showed that despite the many challenges that enface the use of insulin pumps in children, the advantages are far more than the challenges.

HISTORICAL BACKGROUND

Diabetes has been described in the Papyrus Ebers (c. 1550 BC), Ayurvedic medicine (5th/6th century BC), Greek medicine (1st century BC), and medieval Islamic medicine by Avicenna for a long time[2]. Oskar Minkowski and Joseph von Mering first linked diabetes to pancreatic illness in 1889. In 1910, Sir Edward Albert Sharpey-Shafer proposed that the missing pancreatic component be named insulin, after the Latin word Insula (island). Frederick Grant Banting and his colleagues discovered and refined insulin for clinical use in Toronto, Canada, between 1920 and 1922[3].

Leonard Thompson, a fourteen-year-old boy, was the first human to receive an insulin injection, controlling his high blood sugar within 24 h. Shortly after, Eli Lilly's medical company started mass insulin production from cattle and pigs to supply the needs of North America. After about 14 years, Harold Percival Himsworth differentiated type I Diabetes Mellitus from type II in 1936. In the same year, Novo Nordisk Pharmaceuticals developed long-acting insulin. By 1978, genetic engineering enabled the human being to have the first synthetic "human" insulin produced by E. coli bacteria. After four years, Eli Lilly made the human biosynthetic insulin commercially available for the first time with the brand name Humulin in 1982[4,5].

The first insulin pump was invented in 1963 by Arnold Kadish, who developed a prototype backpack pump to deliver insulin and glucagon. However, Dean Kamen developed the first wearable insulin infusion pump in 1973, which started to be produced commercially by AutoSyringe Inc in 1976[6]. In the same year, continuous subcutaneous insulin infusion was started successfully. The glucose-controlled insulin infusion system was developed by BioStar company to be the first step in the development of artificial pancreas development in the 1980s. During the same period, the first blood glucose home-based monitors were available to accurately monitor blood glucose levels at home. A few years later, the prefilled syringe-insulin pen delivery systems appeared, providing a safe and convenient insulin delivery method with accurate dosing[7]. In 1983, MiniMed released the first small-sized programmable insulin pump, followed by the soft-set infusion set in 1987, using a soft, flexible cannula to ensure customer comfort. In 1992, MiniMed redesigned the pump to be programmed to include meal bolus memory and daily insulin totals. Continuous upgrading of the pump continued to prolong blood glucose recording to 3 days in 1999. The same year showed constant upgrading of the pump to enable remote programming abilities to control, administer, and stop insulin delivery and to program multiple delivery patterns and different alert types, including vibration mode and child-block[8].

By 2000, the concept of implantable insulin pumps emerged to help patients with significantly uncontrolled diabetes. In 2003, the wireless "intelligent" insulin pump was introduced, which can automatically transmit a blood glucose value from a glucose meter to the insulin pump, which calculates the proper insulin dosages. In 2004, the pump was upgraded to notify and alarm diabetes patients of potentially severe high or low glucose fluctuations. In 2005, the system was upgraded to display updated real-time blood glucose values every five minutes, plus the alarming system for severe blood glucose fluctuations, which provided significant help to people with diabetes who need better glucose control[9]. In 2006, a real-time insulin pump system with a continuous glucose monitoring system became available, which was a significant step in developing a "closed-loop" insulin delivery system or what is called "artificial pancreas" trying to mimic some human pancreas functions. Updating the pump system continued over the years, so by 2012, the concept of next-generation artificial pancreas systems was elaborated. In 2018, Bekiari *et al*[11] showed that the artificial pancreas is "effective and safe" in treating people with type 1 diabetes[10,11].

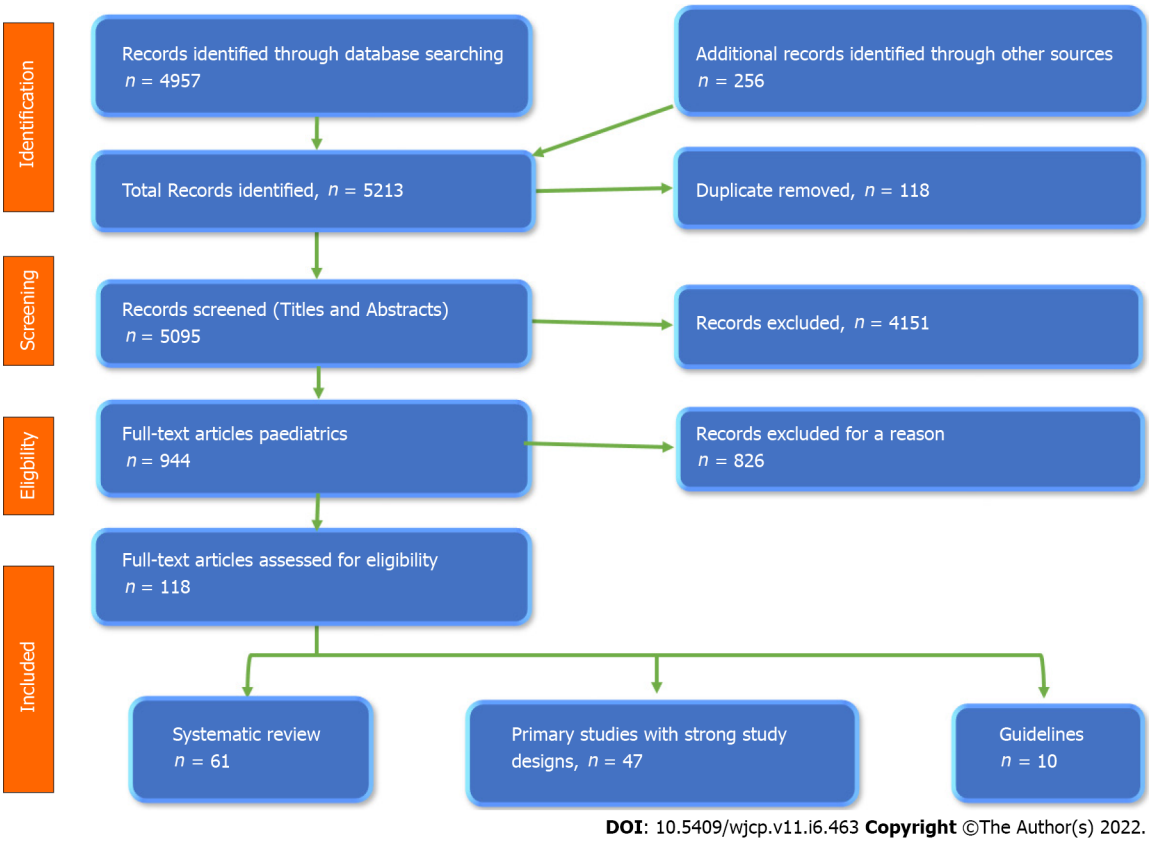

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Figure 1 The flow chart of the study according to PRISMA 2009 guidelines.

INDICATIONS OF INSULIN PUMP

The Key target of diabetes management is to maintain adequate and optimal glycemic control to reduce the risk of metabolic derangements in different tissues. Although it may be a simple goal, it is not always easy to achieve in practice. There are currently two ways to deliver insulin: Multiple daily subcutaneous injections (conventional insulin therapy) or continuous subcutaneous insulin infusion, also identified as insulin pump therapy[12]. There are many difficulties with conventional insulin therapy, including the variable glycemic control with frequent occurrence of hypoglycemia, abnormal weight gain related to the insulin therapy, augmented by improper dosage calculation related to human error, and the lack of adherence to insulin therapy, especially with multidose regimens[13]. Using an insulin pump to manage DM depends on many factors, including the patient's desire, daily life routine, and knowledge and experience with the disease. More than 25% of patients with type I DM are currently using insulin pump therapy. It is especially indicated in the presence of high hemoglobin A1C, poor glycemic control with problematic hypoglycemia such as nocturnal hypoglycemia, recurrent hypoglycemia, activity-induced hypoglycemia, recurrent diabetic ketoacidosis, frequent hospitalization, large total daily dose, presence of progressive complications such as gastroparesis, inability to self-administer insulin (such as in pre-school or grade-school children), the need for more meal time flexibility, or the inability to predict food or meal intake (such as in infants or toddlers)[14]. Baretić *et al* [15] showed that nocturnal hypoglycemia is the main indication for insulin pumps in adults with type I DM, especially with limited affordability. Patients with type 2 Diabetes who fail to have adequate glycemic control with multidose insulin therapy may have better control with pump therapy, improving HbA1c, and limiting weight gain[16]. So, the insulin pump can be sued for type I and II DM in adults and children, especially for those who want more flexibility and proper mealtime adjustment. About 1/1000 of patients with DM are currently using insulin pumps, and their number is increasing; 90% have type I DM, while only 10% have type II. About 6% of adult patients with type I DM use it, while it reaches about 19% in children with type I DM[17].

TYPES OF INSULIN PUMPS

There are two main types of insulin pumps; the first type is a 'tethered' pump that uses a fine tube connecting the pump with a cannula (Figure 2A). The patient can wear the pump in a pocket or fasten it

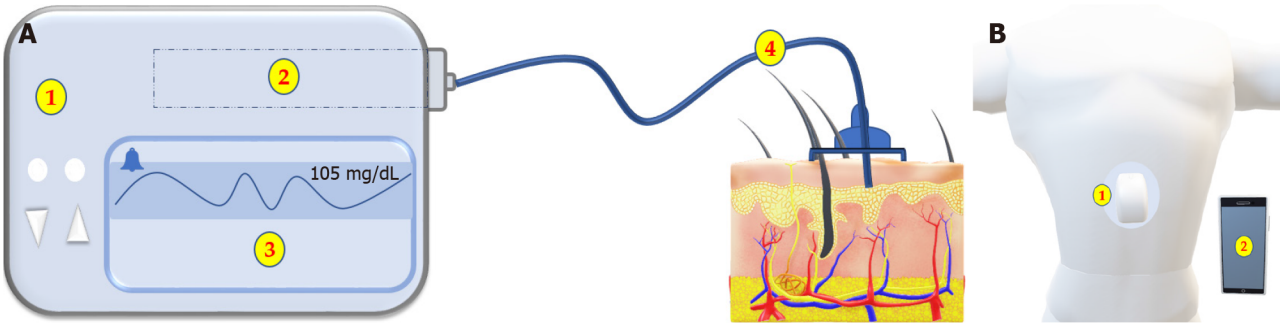

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Figure 2 shows the two main types of Insulin Pumps. A: Tethered pump formed of 1: Main pump. 2: Insulin Reservoir. 3: Monitor. 4: Infusion set; B: The patch pump formed of 1: A pump adherent to the skin with no or very short tube and 2: A wireless control unit.

to a belt and should change the tubing every 2-3 d. The patch pump (micro pump) is another type without tubing or may have a very short flexible plastic tube (cannula) inserted under the skin (Figure 2B). The pump usually adheres to the skin with an adhesive patch and is wirelessly controlled with a handheld controller unit[18]. The insulin pump is generally formed of the central pump unit connected to an insulin reservoir which usually holds between 176-300 units of short-acting insulin. Another new version of the insulin pump has a built-in Continuous Glucose Monitor (CGM). The pump is supplied with an alarm system activated when the blood glucose reaches a predetermined low or high level[19]. A SmartGuard Technology can be added to CGM to stop insulin supply for two hours if the user's blood glucose reaches a predetermined low level pre-settled without activating the alarm system. Some pumps use a hybrid closed-loop technology by using the SmartGuard technology to permit the users to select from increasing the levels of automation that best suit their needs. The auto mode enables automatic adjustment of the basal insulin delivery according to the glucose reading of the user's CGM sensor and recent insulin delivery[20].

There is also a bolus calculator, able to automatically calculate the doses and inform the person if they are too closely set together. However, in this mode, the user should enter the details of carbohydrate intake, confirm the mealtimes, and adjust the correction boluses. Some insulin pumps have an Insulin on board (IOB) feature so that the pump can calculate how much insulin remains active in the patient's body from the previous insulin bolus dose[21]. Some pumps are also waterproof to tolerate up to 12 feet underwater for about 24 h. This feature enables patients with diabetes to enjoy swimming with minimal risk of hypoglycemia. The vast advances in insulin pumps are related to significant software and artificial intelligence progress. For example, some pumps allow choosing an exercise set to change the person's glucose target[22] automatically. Most of the new versions of insulin pumps are compatible *via* Bluetooth with smartphones with different applications such as the Carelink Connect app, which allows family members or caregivers to access the patient's information and show all readings and permits notifications and alarms. People also can deliver insulin remotely using a smartphone-like Personal Diabetes Manager device. The suitable age for the pump use differs according to the pump type and version, in which the manufacturers determine the appropriate age of use according to each pump's features[23].

USE OF THE INSULIN PUMP

The children and their caregivers should understand the proper use of insulin pumps to achieve successful pump therapy. The children and their caregivers should have a comprehensive education program about diabetes management and insulin pump use before starting it. They should be able to adjust the blood glucose levels using multiple daily insulin injections and monitor blood glucose frequency at least four times daily during the last two months before the insulin pump therapy[24]. They should also learn to test ketones when the blood glucose level is more than 13.3 mmol/L (240 mg/dL) and recognize symptoms of ketoacidosis when present. Before using the pump, the children or their caregivers should know the suitable age for using it as predetermined by the manufacturers[25]. They should know whether the pump is waterproof, watertight, water-repellent, water-resistant, or not. If the pump is not, they should remove it before showering or swimming. If the pump is waterproof, they should know how many feet in-depth and how long. The patient also should know the maximum time the pump can be removed without affecting its performance, *e.g.*, one hour for the Aviva Combo insulin pump[26]. The child and his/her caregiver should know the number of insulin units the insulin cartridge can hold. However, they should know that the half-life of the insulin pods may not depend on how much insulin is used. The insulin the pump uses is fast-acting insulin because of its rapid onset and offset. Even fast-acting insulin takes some time for its action onset and offset. We should also note the

presence of significant individual variations in the onset, duration, and offset of the same type of insulin [27].

The patients and their caregivers should be aware of the lowest basal delivery rate the pump can deliver. They should understand the available basal (background) insulin patterns such as daily, weekend, exercise, and night shifts. They also should be aware of the insulin-to-carbohydrate ratio program feature. This mode helps the patient calculate an estimated insulin bolus dose to cover any carbohydrates the patient eats or drinks or improve high blood glucose[20]. The most important thing to properly using the insulin pump is calculating the total daily insulin dose, which equals the basal and the bolus insulin doses delivered each day. Total daily basal insulin is a continuous insulin infusion needed to metabolize hepatic glucose production over 24 h, while the total daily bolus insulin is the insulin units given on needs to control the meal-related glucose peaks over 24 h[28].

The pump's total daily insulin dose is 25% less than the current total daily insulin injection dose. To calculate the pump's total daily insulin dose, we usually take the average of the 25%-reduced current total daily insulin injection dose and the weight-based insulin daily dose, which equals the body weight multiplied by 0.5. The pump's total daily insulin dose is less than the current total daily insulin injection dose as the pump delivers the insulin more efficiently, and the insulin is more regularly absorbed than the intermittent daily injections[26]. 40%-50% of the pump's total daily insulin dose is delivered as a total daily basal insulin, while the other 50%-to-60% will be delivered as bolus doses related to the meal intake (Figure 3). The total daily basal insulin is delivered at an hourly rate. However, it can be programmed at different rates throughout the day according to daily activities and circumstances[29].

Meanwhile, the percentage of the total daily basal insulin from the pump's total daily insulin dose differs according to the age of the patients; 20% to 40% from the pump's total daily insulin dose in prepubertal and pubertal subjects, 30%-40% from puberty to adulthood, and 40% to 50% in adults. The rest of the pump's total daily insulin dose is divided into bolus doses according to the meals. The ratio of basal to bolus insulin is also dependent on the amount of carbohydrate diet, decreasing with a high carbohydrate diet[30].

Basal insulin is the insulin level required to balance gluconeogenesis and peripheral glucose utilization. Basal insulin keeps the blood sugar relatively constant without food intake. The pump delivers the basal insulin in a tiny quantity per hour to control the blood glucose levels over a predetermined period[31]. If a desired change in the basal insulin delivery is required, the adjustment should begin two to three hours before the expected change in the blood glucose to prevent significant fluctuations in its levels; so that the blood glucose level fluctuations are less than 30 mg/dL up or down, either during the day or at night. In the flat basal profile, the total daily basal insulin is divided equally over the day hours (divided by 24)[32]. However, the basal requirements show significant variation within the same person day-on-day, based on circadian rhythm, meal and activity levels, exercise, illness and stress, and the potential changes in the insulin absorption from the cannula. There are various types (4-6) of modified basal profiles. The patient usually starts with a flat basal profile; then, the profile is modified according to the patient's activity[33]. Some patients may need to increase the basal rate in the early morning to neutralize the Dawn phenomenon. Conversely, we may need to reduce the basal rate between mid-morning and mid-afternoon. Meanwhile, some patients may require an increase in the basal rate in the evening (dusk phenomenon) due to a reduction in physical activity later in the day (Figure 4)[34].

Suppose the patient has a fixed period of activity that occurs daily at the same time, such as walking or swimming, when there is a risk of hypoglycemia. In that case, the basal rate can be modified to accommodate these activities by reducing the basal rate 60-90 min before the expected activity. In a situation with an increased likelihood of hyperglycemia, such as during illness, the patients may increase the basal rate 30%-50% above the flat basal rate[35]. It should be noted that Blood insulin levels need 2-3 h to reach a steady state after a basal rate change. Consequently, the changes in the basal rate usually occur in blocks of hours. Most patients need to have multiple basal rates throughout the daytime. Basal rates modified to match the patient's activity are associated with improved outcomes [36]. Some insulin pumps can be programmed to suspend/stop insulin delivery from the pump for a particular time before, during exercise, or in hypoglycemia. To reach the proper basal profile, the patients need to check their blood sugar as frequently as eight times daily during the pump's first month. After getting the target profile, the frequency of checking is about four times daily. However, extra checks may be needed during times of exercise, traveling, illness, or the beeping of the pump alarm[17].

Bolus insulin is an intermittent insulin bolus infusion intended to parallel the rises in blood glucose related to food intake. It depends on personalized carbohydrate-insulin ratios, which are the amount of insulin needed to match the ingested carbohydrate in grams without causing hypo/hyperglycemia[37]. It is calculated by dividing 500 in adults or 300 in children by the total insulin daily dose. For example, if a child needs 45 insulin units as a daily dose, his carbohydrate-insulin ratio is 300/45 = 6.6. This means that the child needs one Insulin unit for every 6.6-gram carbohydrate. For a meal that contains 120 gm of carbohydrates, the child needs 18 insulin units to maintain the blood glucose levels within the normal range[38]. The insulin pump can deliver various forms of insulin bolus. There are three main types of bolus insulin; the typical bolus, the square-wave bolus, and the dual-wave bolus (Figure 5)[39]. In the typical bolus, the pump delivers the insulin immediately on top of the basal rate for three minutes. The

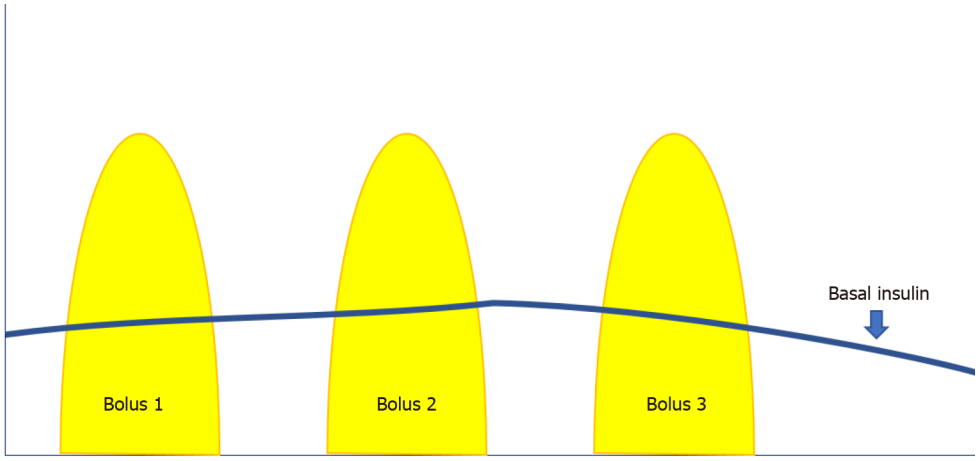

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Figure 3 Basal and bolus insulin. Basal insulin is delivered continuously in a small amount as a background to keep the blood glucose levels within the target between meals. The pump can be programmed to deliver at different rates within 24 h. Bolus insulin is a large amount delivered over a short period, which can be given at any time. The pre-meal bolus is given based on the number of carbohydrates in grams. The bolus can also be given to correct high blood glucose levels.

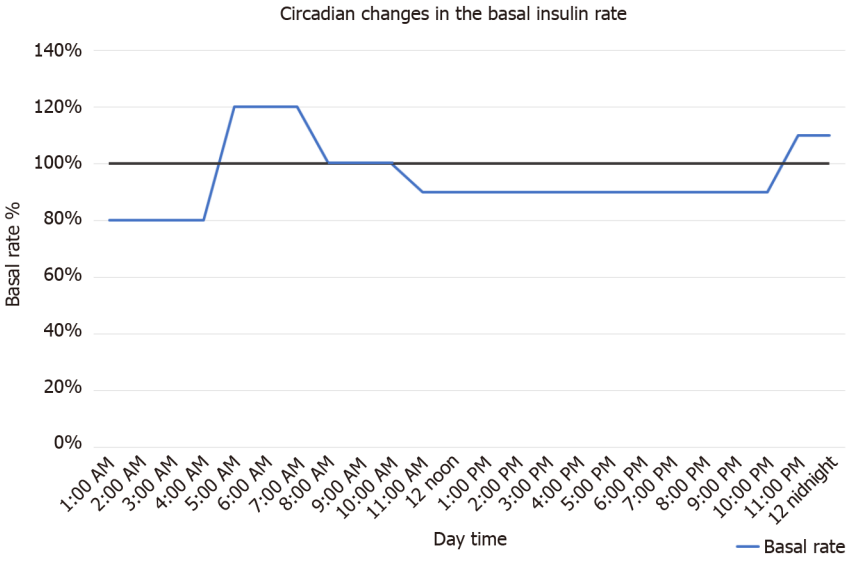

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Figure 4 Circadian changes in the basal insulin profile. An example of the circadian changes in the basal insulin profile. Between 12 midnight to 4:0 am, the basal rate is reduced by 20% to increase 20% between 4:0 am to 7:0 am, then will be 100% between 7:0 am to 10:0 am to be reduced by 10% between 10:0 am to 10:0 pm, then it increases again by 10% between 10:0 pm to 12 midnight.

extended bolus delivers the insulin over a longer period than the typical bolus (the insulin dose is not delivered at once). The square wave bolus is an extended bolus that delivers the insulin over a fixed extended duration (2-4 h)[40]. We usually need it when the food is ingested over a longer time, such as during social events, or delayed digestion, such as in gastroparesis. The dual-wave bolus delivers the insulin in two or more waves (dual or multi-waves], 30%-70% of the insulin bolus is delivered as the typical bolus, and the rest of the bolus is delivered over a predetermined fixed duration, such as 2-4 h (biphasic, dual, or multi-wave). The dual/multi-wave bolus is helpful with meals with high protein or fat content (*e.g.*, pizza, pasta, cheese, or fish) as protein and fat usually take longer to increase blood glucose levels than carbohydrates, which immediately affect blood glucose[41].

In the super bolus (Figure 6), the pump delivers the basal insulin for the next 1-4 h is added to the bolus, followed by temporarily suspending the basal insulin delivery for those hours (basal rate is 0% for the next 1-4 h) without stopping the pump. This super bolus is needed with a diet high in carbohydrates and low in protein and fat, such as white toast, jam, white rice, sugary drinks, jelly sweets, *etc.* However, if the post-meal blood sugar persists to be high after a super-bolus insulin dose, we should revise the insulin: carbohydrate ratio. If the post-meal blood sugar fluctuates, we should revise carbohydrate counting as it often shows a wide range of variations[42]. A comparison between the different types of insulin boluses is shown in Table 1.

Table 1 Comparison between the different types of insulin boluses

Bolus type	Normal	Extended	Dual wave	Super bolus
Indication	With most diets, 10-20 min before the meal	Rarely needed: With lengthy mealtime & gastroparesis	With low carb & high protein & fat (> 25 gm fat) meals	With high carbohydrate meal
Method of insulin delivery	Deliver insulin immediately	Deliver all the insulin in an extended fashion over a chosen duration which may be the meal length.	60%-70% of the bolus is delivered immediately, while 30%-40% is delivered over 2-4 h	The basal insulin units of the next 1-4 h are added to the bolus, followed by a temporary 0% of basal rate for that 1–4 h
When to test blood glucose	Before bolus and after 4 h	Before bolus, after the end of the bolus, & after 4 h	Before bolus, after the end of the bolus, & after 4 h	Before bolus, after one & 4 h after the bolus

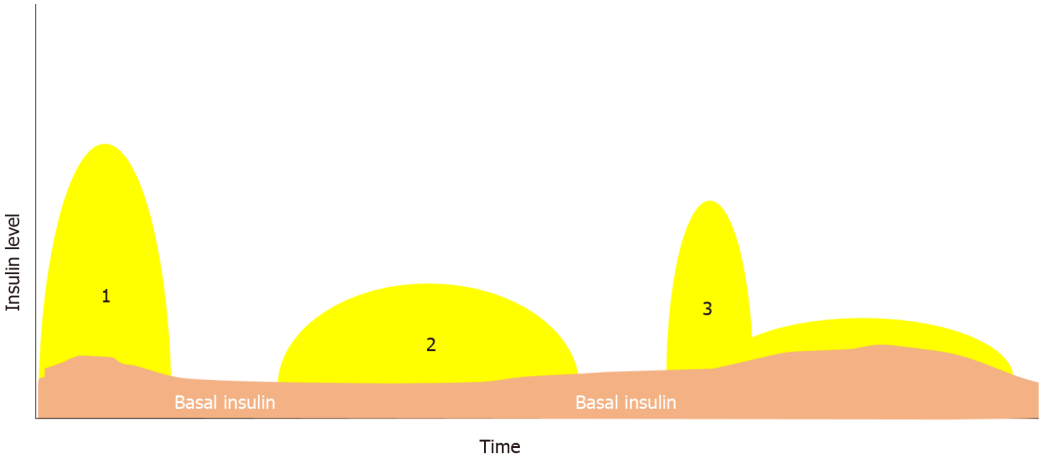

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Figure 5 The different insulin bolus types. 1: The typical bolus, 2: The extended bolus, 3: The dual bolus

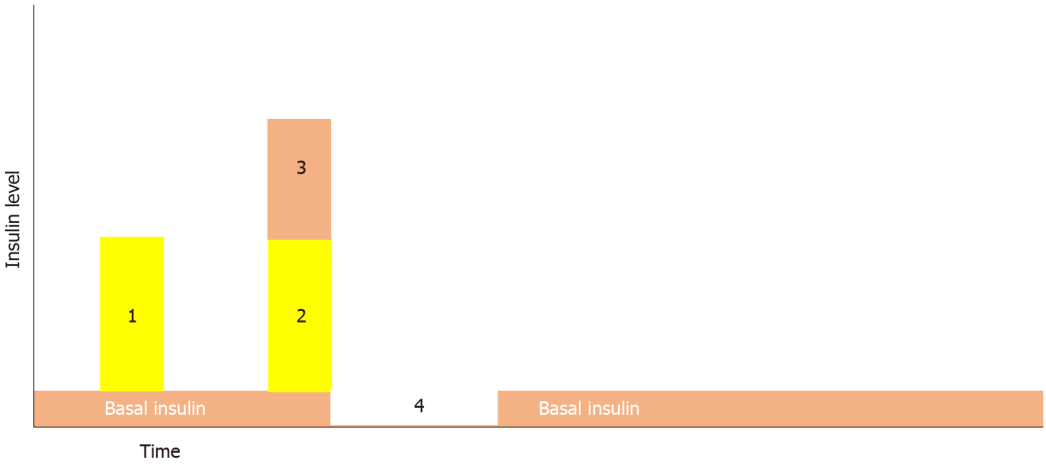

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Figure 6 Different types of insulin bolus. 1: Typical insulin bolus, 2 and 3 super bolus equal to the calculated bolus plus the basal insulin for the coming one to four hours, 4: The basal insulin rate will be 0% for the remaining four hours.

Correction bolus is the number of insulin units delivered by the pump when the blood glucose level is above the target range. It depends on the individual insulin sensitivity factor (ISF), which is the amount of decrease in blood glucose level for every one unit of rapid insulin. It calculates the correction bolus dose, which is the number of insulin units the patient needs to bring the blood glucose into the target range without inducing hypoglycemia[43]. To calculate ISF, we divide 100 by the average total daily insulin dosage over three or four days (TDD) to get the result in mmol/L (100 Rule) or divide 1800 by the average TDD to get the results in mg/dL (1800 Rule). So, when the average TDD is 75 Insulin Units, ISF will be 1.33. Thus, one unit of rapid-acting insulin would reduce the blood sugar by 1.33

mmol/L (24 mg/dL) across the next 2-4 h[43]. The following formula can calculate the correction dose: [(Current Blood Glucose – Target Blood Glucose)/ISF]. However, the Association of British Clinical Diabetologists advises routinely starting with the rule of 130 rather than the 100 rule [ISF = 130/TDD] to achieve the optimal ISF and estimate how much one unit of insulin will decrease the blood glucose level in mmol/L[44]. We should ensure the adequacy of ISF by testing the blood glucose after 4-5 h after the last insulin bolus dose. Carbohydrate was consumed more than three hours ago, and the patient can wait for 4-5 h until the next meal[43].

The caregivers and their child should adequately adjust the pump setting for the IOB and the active insulin time, which is the duration that an insulin dose continues to work after its delivery. Most pumps set this time to be four hours; however, it can be shortened or prolonged in the presence of hypo/hyperglycemia[26]. With short active insulin time, the pump includes the effects of the more recent insulin doses, omitting the impact of the insulin from the previous doses, thus increasing the risk of hypoglycemia[28]. On the other hand, long active insulin time causes overestimation of the insulin on board, and the pump gives smaller boluses which can cause hyperglycemia. Longer active insulin time than four hours is needed in cases with impaired renal functions, as the kidneys clear about 80% of the insulin. Those needing TDD less than or equal to 40 Units/day should reduce active insulin time. In comparison, those receiving a bolus dose of more than 10 Units or TDD of 60 Units/d or more should consider increasing active insulin time[45].

The caregivers and their child should recognize the accepted target blood glucose level, which is individualized according to the child's status and is comfortable with it. Some insulin pumps correct the blood glucose level to a single target level but give the correction bolus when a predefined threshold is reached[46]. Other pumps correct to a higher figure in a predefined target range, while others correct to the mid-target range. The target range usually lies between 4.5-5.5 mmol/L (80-100 mg/dL) (± one mmol/L). However, the target level is modified according to the presence of different factors. Those with high HbA1c need a higher target as the setpoint for hypoglycemic symptoms is higher than for more well-regulated patients with diabetes. They frequently have episodes of pseudohypoglycemia until they are used to lower glucose values[47]. Those with HbA1c > 10% should start with high target blood glucose between 9-10 mmol/L (160-180 mg/dL), then reduce the target level monthly until we reach the normal target blood glucose levels. This gradual decrease of the target is particularly indicated in the presence of diabetic retinopathy, which may deteriorate with the rapid lowering of blood glucose levels. To maintain the target glucose blood level, the caregivers and the children need to frequently test the blood glucose levels, especially in the presence of hypo/hyperglycemia, and to know which insulin doses need to be modified, the basal rate, or the bolus insulin[48].

When there is blood glucose variation (hypo/hyperglycemia) during the night, before breakfast, or when a meal is skipped or delayed, the basal rate of insulin needs to be adjusted. However, the insulin-to-carbohydrate ratio and ISF should be revised when the blood glucose variation (hypo/hyperglycemia) occurs within four hours of the bolus or meal or after giving a correction insulin bolus. To test the basal rate, we should eliminate the influence of other factors that could affect it by dividing the day into windows, testing the basal rate for each window on different days, and ensuring that the tested person follows his/her usual routine without strenuous activity before the test by 24 h and during the test period[49,50]. Hypoglycemia should not present during the last 12 h before testing, and the patients should be fasting for the tested period except for water. We use the standard basal rate during testing, stop testing with hypoglycemia (< 4 mmol/L or 72 mg/dL), and give a corrective bolus with hyperglycemia of more than 14 mmol/L (252 mg/dL). We should record blood glucose levels, basal rate, and carbohydrate intake. There are four main periods to test the basal rate: Morning testing from 7:00 am to 12:00 noon, after noon testing from 12:00 noon to 18:00, evening basal from 18:00 to 22:00, and overnight testing from 21:00 to 7:00 am[51]. Overnight testing is usually done first, followed by the other periods, each on different daily bases. First, we correct hypoglycemia; then, we correct hyperglycemia with a 10%-20% decrease or increase, *i.e.*, 0.025-0.05 unit/ hour one to hours before the expected change, to keep the blood glucose variation less than 1.5 mmol/L (28 mg/dL)[52].

For bolus adjustment, we try to keep the two-hours post-meals to be 1.6-3.2 mmol/L (29-58 mg/dL) higher than the pre-meal blood glucose levels. If the two-hours post-meal blood glucose level increases to less than 1.6 mmol/L (29 mg/dL), decrease the total bolus by 10%-20%. If the two-hour post-meal blood glucose level increases to more than 3.2 mmol/L (58 mg/dL), increase the total bolus by 10%-20%. Slattery *et al*[53] suggested that insulin administration 15-20 min before the meal will provide optimum postprandial glucose control. To adjust the correction bolus dose, adjust the insulin sensitivity factor by a 10%-20% increase or decrease to make the two-hours post-meal blood glucose level halfway to the target and reach the target by four-hours post-meal. If the patient uses continuous glucose monitoring (CGM), a retrospective analysis of the time associated with blood sugar fluctuations can help modify the basal rate[54]. Some pumps have a wizard to change the basal rate according to the blood sugar levels. However, CGM should be associated with an event diary to document the meal timing and the carbohydrate intake for accurate assessment. CGM is indicated with frequent or severe hypoglycemia, hypoglycemia unawareness such as in young children, suboptimal glycemic control, or monitoring of young children or beloved ones by family members or friends[55,56].

Suppose the patient needs to change the insulin pump therapy to subcutaneous insulin for any reason. In that case, we need to calculate the total daily basal insulin given by the pump and increase it by 20% for the first few days and by 30% in the following days to calculate how much long-acting basal subcutaneous insulin is needed. This dose can be administered as a single or divided dose depending on the type of long-acting insulin used[57,58]. The bolus pre-meal insulin and the corrective insulin doses are given as usual. The pump should continue working for two hours after starting the first long-acting insulin dose. Doing this shifting in the morning is recommended to avoid troubleshooting at night[59]. Alternatively, if we need to resume the pump therapy after subcutaneous therapy, we resume it two hours before the next long-acting insulin dose. Again, we need to reprogram the pump setting and temporarily reduce the basal insulin rate by about 30% for the next 24 h. Blood glucose levels should be checked one to two hours after starting pump therapy[18]. So this shift is better to be in the morning for easy monitoring. Suppose we want to shift the insulin therapy from continuous intravenous infusion to pump therapy. In that case, we can shift without waiting for the coming meal and discontinue the intravenous insulin infusion only 60 min after starting the pump therapy[60].

PUMP THERAPY IN SPECIAL SITUATIONS

Sports and exercise

Exercise has a long-term beneficial effect on blood glucose regulation regardless of the type of exercise. However, it has a short-term modification on the blood glucose level to be considered during the pump therapy—two significant difficulties enface children with type I diabetes who are willing to exercise regularly. The first problem is controlling the blood glucose level, and the second is the possible occurrence of hypoglycemia during or following exercise[61]. Aerobic exercise reduces blood glucose levels and enhances insulin sensitivity for 16 h following the exercise. On the other side, high-intensity aerobic exercise or that associated with high adrenaline could cause hyperglycemia. Resistance training or anaerobic exercise increases blood glucose levels and insulin resistance, which persist 6-8 h after exercise. Brief periods of anaerobic exercise activity (*e.g.*, short sprints or weight lifting) during moderate-intensity aerobic exercise may decrease the risk of hypoglycemia[62]. However, all types of physical exercises may increase the risk of nighttime and even the next day hypoglycemia, mainly when performed in the afternoon, independent of sex[63].

We can prevent the development of exercise-induced hypoglycemia by reducing the bolus or basal insulin, increasing carbohydrate intake, or adjusting the exercise regimen. The basal insulin can temporarily be reduced one to two hours before and throughout the exercise. The degree of basal rate reduction depends on the intensity of exercise, 30% in low-intensity, 50% in moderate-intensity, and up to 100% reduction in high-intensity exercise. If modification of the basal insulin is not feasible, a fast-acting carbohydrate (15-20 gm without bolus insulin dose) can be given immediately before the short, intense exercise. For more extended, moderately intense exercise, a solid snack with slow-release carbohydrates can be given. If an exercise is planned within two hours after a meal, the premeal-bolus insulin dose can be reduced by 25%-75% according to the exercise intensity[64]. If we are anticipating anaerobic exercise-induced hyperglycemia, we can give a 50% extra bolus dose 30-60 min before the exercise to antagonize the expected increase in the blood sugar. Alternatively, we can increase the basal rate by 10%-20%, 30-90 min before the exercise, and continue at this rate when post-exercise hypoglycemia persists. In the case of combined aerobic and anaerobic exercise, hypoglycemia is more frequent but less than pure aerobic exercise. Hypoglycemia can be prevented with a reduction of basal insulin by up to 50%. If these changes are impossible, we should consider the artificial pancreas. The artificial pancreas system appeared to get efficient and secure control of blood glucose levels during exercise and four hours later[65].

Troubleshooting hypoglycemia

If severe hypoglycemia is present, the patient should not stop the pump but keep it running and check blood glucose levels. When confirmed, the patient is advised to take 15 gm of fast-acting carbohydrates and to recheck blood glucose after 10-15 min. If hypoglycemia persists, another dose of fast-acting carbohydrates is given, and the basal insulin could be temporarily reduced by 10%-20%. As the insulin type used in pump therapy is short-acting, long-acting carbohydrate is not a valid option to treat hypoglycemia with pump therapy. Patients with type I DM on pump therapy should be well trained to recognize and manage the episodes of hypoglycemia they may encounter. The patients should not rely on the hypoglycemia symptoms. Pseudohypoglycemia may occur in patients with diabetes with the typical symptoms of hypoglycemia with blood glucose levels of more than 3.9 mmol/L (70 mg/dL)[66].

Disabling hypoglycemia occurs when repeated episodes of hypoglycemia result in persistent anxiety and impaired quality of life. It usually occurs with tight DM control and with an increasing duration of diabetes. Severe hypoglycemia is that associated with the patient's inability to self-treat with marked impairment of cognitive functions, contrary to non-severe hypoglycemia in which the patient can self-treat and mild cognitive function impairment. Therefore, all children and adolescents with type I DM should have annual screening for impaired hypoglycemia awareness using a valid screening tool such

as Gold Score or Clarke Score[67]. These tools can identify the increased risk of severe hypoglycemic events. CGM can detect when more than 10% of the reading is less than four mmol/L (72 mg/dL) or when there are more than three readings with less than three mmol/L (54 mg/dL) per week, which increases the risk of severe hypoglycemic events[68]. It is crucial to investigate the underlying cause of disabling hypoglycemia, such as cortisol, a Growth Hormone, Coeliac disease, insulin Antibodies, *etc*. If no reason is detected, we should start an intensive education program for the family and the child. Then we can update the pump to sensor augment pump {SAP} without low glucose suspend (LGS). If not improved, we can shift to SAP with LGS. Islet cell or pancreas transplant could be the last option[69]. The child should be reassessed every 3-6 mo.

Sick child

Children with diabetes and adequate metabolic control should not encounter more infections or illnesses than children without diabetes. However, when a child with type I DM gets sick, we should rule out the presence of uncontrolled or symptomatic hyperglycemia, ketoacidosis, dehydration, and hypoglycemia[70]. The most crucial point to be emphasized is never to stop insulin; it is a prevalent mistake that leads to the development of ketoacidosis. When a child with diabetes has vomiting, we should consider insulin deficiency till proven otherwise. Consequently, the insulin dose may need to be increased or decreased according to the blood glucose level and the presence or absence of ketosis. The blood glucose should be monitored more frequently, at least every 3–4 h, particularly during the night and occasionally every 1–2 h. we also need to monitor for ketosis[70]. We should not depend on urinary ketones' presence to diagnose ketoacidosis as there is a long time lag between the pump stoppage and appearance of the ketone bodies in the urine and the lack of association between the ketones in the urine and the ketones in the blood. Blood beta-hydroxybutyrate monitoring is beneficial in too young children or when urine collection is hard to get[71].

In the presence of hyperglycemia, we need to check for ketosis. If the urine ketones are absent or small or the blood ketones are less than 0.6 mmol/L (11 mg/dL), we give a pump correction bolus by drinking extra low-carbohydrate fluids and hourly checking of the blood glucose. If the blood glucose starts to decrease, then continue monitoring and accordingly decide to give another bolus dose or not. If the blood glucose fails to decrease after one hour from the corrective dose, then we supplement with a syringe or pen injection. Suppose the urine ketones are moderately or severely increased, or the blood ketones are equal to or more than 0.6 mmol/L (11 mg/dL). In that case, we should check for a pump delivery failure or a significant medical problem, *e.g*., severe infection. Accordingly, we can shift to insulin therapy by pen or syringe according to the severity of hyperglycemia and degree of ketonuria/ketonemia[70]. The pump should be checked for mechanical or catheter difficulties by replacing the insulin in the pump, the infusion set, and the cannula while continuing to give bolus doses with a pen or syringe until the hyperglycemia is controlled. Then, we must resume the pump therapy with a temporary basal rate of 120%, hourly blood glucose monitoring, and extra low-carbohydrate diet fluids[72].

If the child exhibits signs of diabetic ketoacidosis (DKA), the pump therapy should be discontinued due to the altered tissue perfusion in DKA, which impairs insulin absorption and affects the reliability of the pump therapy. The pump should be temporarily discontinued; the cannula should be removed, then follow the standard protocol to manage DKA. Once DKA is fixed, pump therapy is resumed at the patient's standard basal rate, but the patient should maintain intravenous insulin infusion till he receives a meal bolus[73]. Wang *et al*[74] showed that using nano-insulin pumps in children with DKA can quickly correct children's blood glucose and ketone body levels. If there is ketosis with low blood glucose, the child should drink extra high-carbohydrate fluids with continuous blood glucose monitoring. In case of persistent vomiting or failure of the previous attempt to control the disorder, the child should be hospitalized[75].

Insulin pump use in a hospitalized child

When hospitalized with a severe medical condition, children with type I DM need aggressive management of diabetes. Adequate and meticulous control of diabetes is associated with significant morbidity and mortality improvement in children and adults with diabetes[76]. However, intensive insulin therapy is associated with an increased hypoglycemia rate and complications without a significant mortality reduction. Therefore, continuous monitoring of the blood glucose level is crucial to prevent hypo/hyperglycemia[77]. Non-critically ill children hospitalized for elective and non-acute hospitalizations who can operate their insulin pumps are allowed to continue using them. Fasting prior to elective surgical procedure is allowed with proper adjustment of the basal insulin rate to prevent the development of hypoglycemia. However, if the children cannot operate their pump, they can transition to the basal-bolus regimen[78]. If the child is expected to go into a minor procedure with general anesthesia for less than two hours and is expected to eat or drink within 2-3 h, check the blood glucose levels hourly and adjust the insulin pump accordingly (Figure 7)[79].

It is acceptable that hospitalized patients continue to self-control their DM using an insulin pump except if they are unconscious, confused, or have severe pain, undergo major surgery or procedure under general anesthesia lasting more than two hours, or develop DKA. However, if children are hospitalized due to a critically ill condition or surgery that needs anesthesia for more than two hours

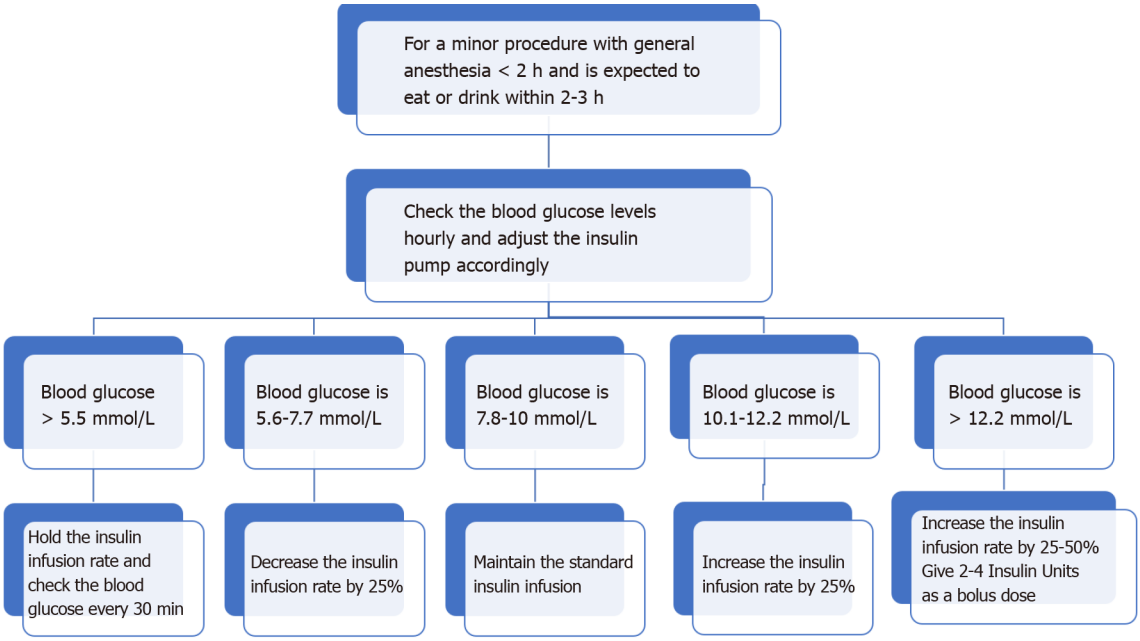

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Figure 7 A flow chart for a minor procedure with general anesthesia for less than two hours.

and will miss more than one meal, they need to shift to intravenous insulin therapy. The patients should remove the insulin pump and keep it safe to be resumed once the procedure finishes unless being critically ill. Frequent blood glucose monitoring (or CGM) offers safe insulin delivery control[80]. Care should be taken while doing specific procedures in the hospital to avoid damage to the insulin pump. The insulin pump should be covered by a lead apron while doing an X-ray, computerized tomography scan, cardiac catheterization, or insertion of a pacemaker/automatic implantable defibrillator. Ultrasonography can be done when needed, but the operator should avoid direct pointing the transducer to the pump. On the other hand, the pump should be removed while doing magnetic resonance imaging. Upper or lower gastrointestinal endoscopies do not require the removal of the pump[81].

Use of corticosteroid with pump therapy

As DM type I is an autoimmune disease, it is frequently associated with other autoimmune disorders, such as autoimmune thyroid disease[82]. Corticosteroids are frequently used in high doses to treat these autoimmune disorders such as asthma and inflammatory bowel diseases. Steroids usually increase insulin resistance, insulin requirement, and the risk of hyperglycemia. Hyperglycemia is predicted to occur approximately four to eight hours following oral steroids administration and sooner following intravenous steroids[83]. On the contrary, blood glucose levels may return to pre-steroid levels 24 h following intravenous steroids discontinuation. If oral steroids are withdrawn gradually over many weeks, glucose levels may decrease dose-dependently[84,85].

Interestingly, the daily timing of steroid-induced hyperglycemia depends on the type of steroid use. For example, prednisolone, usually given in the morning, induces hyperglycemia in the late morning and persists into the evening with a gradual fall of blood glucose back overnight, often reaching baseline levels the following morning[86]. Therefore, children on pump therapy need to increase the basal insulin rate to 130%-150% during the expected times of maximal hyperglycemia. However, we may occasionally need to increase the basal insulin rate to 200%-300% of the standard rate. Other management options are adjusting ICR or giving corrective insulin bolus when needed. Frequent blood glucose monitoring every 4 h should be done. Once steroid therapy is reduced or stopped, the insulin requirement can be decreased back to pre-steroid levels; therefore, readjusting insulin rates may be needed[87].

Improving insulin absorption at the insertion sites

Warming the injection site increases the blood flow, increasing the subcutaneous insulin absorption rate. Warming can be done by massaging or using special warming devices, which is particularly helpful in managing postprandial hyperglycemia[88,89]. Local application of recombinant human hyaluronidase increases the subcutaneous insulin dispersion and absorption rate at the injection site, conferring both ultrafast insulin absorption and action[90]. Using silicon microneedles integrated within the insulin pump trans-dermally delivers insulin efficiently, safely, and painlessly. It also helps decrease the insulin

pump size[91].

Insulin pump and school days

School life occupies an integral part of children's daily life. Consequently, children using an insulin pump should be able to manage it and have a good education about the proper use of the pump and the management of different problems that they may enface. This awareness is crucial for young children who may need continuous supervision of the pump data and settings, especially for carbohydrate intake, blood glucose monitoring, and insulin administration. The responsible teachers or the school healthcare worker should be well trained in the different scenarios the child using an insulin pump may encounter to allow rapid interference when needed. A clear school health plan to manage students with Type I DM should be available and practiced in recognizing and managing specific acute emergencies such as hypo/hyperglycemia with/without ketonemia[87].

Puberty in children using an insulin pump

Puberty is associated with increased sex hormone levels which increase the degree of insulin resistance and, consequently, increase the insulin requirement during puberty. Puberty is associated with higher hemoglobin A1c levels and rates of diabetes complications[92]. Adolescence is also associated with an increased risk of alcohol consumption and considerably increases the diabetes risk in young adulthood and makes diabetes control more difficult. Alcohol consumption in the evening increases the risk of hypoglycemia, especially at night and after the next breakfast, which needs frequent blood glucose monitoring, particularly at night and early morning[93,94].

Menstrual cycle in an adolescent female with Type I DM

Menses is associated with high fluctuations of the glycaemic control with an increased risk of hyperglycemia and increased insulin resistance during periovulation and early luteal phases (premenstrual period), possibly due to the rising oestradiol levels that occur before ovulation, which may need a temporary increase in the basal insulin rate[95]. On the contrary, when menses start, the progesterone level begins to drop, causing a sharp decline in the insulin requirement, which may increase the hypoglycemia risk steeply[96]. If the adolescent girl has a disturbed menstrual cycle and needs to use contraceptive pills to regulate the cycle, care should be taken while using them as an increase in the basal insulin requirement may occur, especially with high-dose contraceptive pills or with long-acting progesterone injections[97].

Traveling with an insulin pump

Despite traveling being a welcome retreat from our everyday life difficulties, it is associated with an extraordinary increase in daily activity, which could increase the risk of hypoglycemia and becomes a real challenge in patients with diabetes. It is particularly challenging in the presence of time zone differences > 3 h, significant variations in the basal rates, such as the marked Dawn phenomenon, recurrent or severe episodes of hypoglycemia, or reduced hypoglycemia awareness. The pump basal rate is reduced by 10%-20% during traveling for the first 24 h and gradually changes the pump timing setting to the new local time upon arrival at the destination by 2-3 h each day. This change should be associated with frequent blood glucose monitoring. Disconnecting the pump during take-off and landing is also essential to avoid pressure effects on the pump delivery mechanism[98].

GENERAL CARE FOR CHILDREN WITH DM WHO REQUIRE INSULIN PUMP THERAPY

Skin care and prevention of insertion site infection

Skin changes occur in one-third of patients with diabetes. Children with high glucose levels tend to have dry skin[99]. Therefore, they need adequate blood sugar control and proper skin hydration with specific lotions for diabetes following site change, especially in pump care. Itching is frequent at the insertion site; the child is advised to gently rub and avoid scratching the affected area to avoid skin breakage [100]. The insertion set should be applied to dry, unwet, non-broken skin. The insertion site should be rotated ideally every three days, over 6-10 sites, to long-term preserve skin integrity. Certain areas are advised more than others due to their superior insulin-absorptive capabilities, more comfort, and better convenience. The most common sites suitable for insertion are the abdomen (two-centimetre radius around and away from the navel), upper buttocks, upper thigh (medial and lateral areas, at least 5 cm away from hip or knee joints), upper buttocks (flank), upper arm, and rarely forearm (Figure 8A). The area with the least hair should be chosen as the hair decreases the longevity of the insertion site. Every site should take at least one week for recovery and should be away from the next site by at least one to two inches. Different patterns of insertion site rotations are demonstrated in Figure 8B[101].

Vaccination

Patients with DM, especially those requiring insulin pump therapy, need intense vaccination programs.

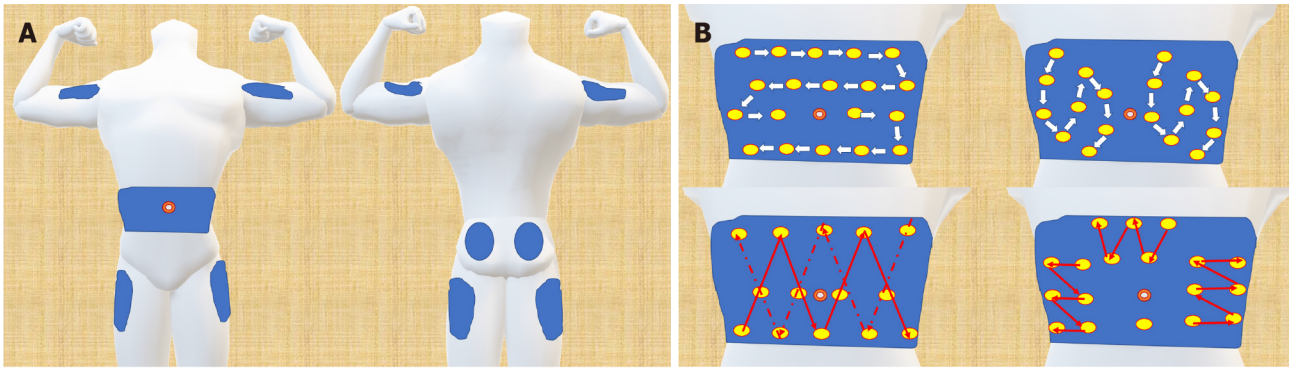

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Figure 8 Approved insertion sites and different types of insertion site rotation. A: There are four approved sites for the subcutaneous injection of insulin: Insulin Absorption Rate Fluctuation Depending on Injection Site; B: shows different types of insertion site rotation. Note that all the rotation patterns keep away from the umbilicus by at least one inch.

They should receive an annual flu vaccination. They also should consider having Streptococcus pneumoniae vaccines, and the coronavirus disease 2019 (COVID-19) vaccination is strongly recommended[102].

The use of insulin pumps in special situations such as traveling, swimming, bathing, imaging, and other procedures is summarized in Table 2.

ADVANTAGES OF INSULIN PUMP THERAPY

The insulin pump provides fewer needle injections as there is no need to inject insulin every time needed. It also can provide small insulin doses down to ten times less (0.05-0.1 Units) than an insulin pen or syringe, which is particularly useful in insulin-sensitive young children. Meanwhile, the insulin pump provides a convenient and more flexible way to modify the needed insulin more physiologically, relatively similar to the human pancreas[103]. Hence basal insulin can be programmed to match the person's activity, the changing daily requirement, hormonal changes, pubertal spurts, stress, illness, traveling, and any other situations. At the same time, insulin bolus can be delivered in different ways considering various conditions such as gastroparesis, malabsorption, or even to match the ingested foods. On the other hand, insulin delivery can be temporarily reduced or suspended in certain situations, such as hypoglycemia[32].

This incredible flexibility in the insulin delivery system and the marked less in blood glucose fluctuations allow a better quality of life. Using rapid-acting insulin delivered in a low volume tailored to the individual needs allows the insulin pump to overcome the variation in insulin absorption that is usually observed with long-acting insulin, resulting in more consistent and reliable insulin absorption and consequently less fluctuation of both insulin profile and blood glucose level[104]. This feature also helps to decrease the need for snacks, especially before exercise, consequently decreasing the rate of weight gain[105]. However, Boucher-Berry *et al*[106] found that lower bolus to basal insulin ratios increases the risk of excess weight gain. Hence, proper bolus and basal insulin dose adjustments are mandatory during insulin therapy. Pump therapy also improves the patient experience and satisfaction due to technology motivation and improved self-management. Pumps can also integrate easily with the new technology, so they can link easily with blood glucose measuring technology, bolus advisors, and wizards for diabetes management, forming a closed-loop system similar to an artificial pancreas which significantly improves the patient's quality of life[107].

DISADVANTAGES OF INSULIN PUMP THERAPY

There are some disadvantages to insulin pump therapy that may limit its use. Being worn all the time (24 h a day/7 days a week), even during sleep, showering, and sports, with continuous reminders of being diabetic, can influence body image and self-confidence. Luckily, numerous accessories are accessible to make wearing the pump hidden and convenient[108]. Because insulin pumps use only rapid-acting insulin without a long-acting insulin depot, there is a high risk of rapid development of DKA with technical failure or interruption of insulin flow such as air in the tubing, a damaged infusion set, or infection at the insertion site. Therefore, the patient should monitor blood glucose levels more frequently, at least four times daily, and a specialized well-trained interdisciplinary care team should be accessible in case of emergency. The pump also should not be disconnected for a long time (short-acting

Table 2 Special situations with insulin pumps

Situation		Management
Air travel		The patient should have a note from the physician about the need for the pump before traveling
		The patient should inform the security about the pump before passing through the security checkpoint with an X-ray detector
		All the suppliers and the accessories should be carried in a separate bag for easy inspection
		The metal detectors and whole-body scanners do not damage the device
Shower and bathing		A warm shower is associated with more rapid insulin absorption than usual, increasing the risk of hypoglycemia
		A warm bath (*e.g.*, hot tub or sauna) can expose insulin to high temperatures, which could be spoiled when exposed for an extended period
		High temperatures can also damage the pump, so it is crucial to check the owner manual for temperature specifications about ideal operating temperatures for the pump
		Knowing the type of the pump as waterproof, watertight, water-repellent, and water-resistant is essential
		If the insulin pump is not water waterproof, it is better to disconnect the pump and keep it in a dry place
Swimming		Knowing the type of the pump as waterproof, watertight, water-repellent, and water-resistant is essential
		If the pump is waterproof, they should know how many feet in-depth and how long
		The patient also should know the maximum time the pump can be removed without affecting its performance, *e.g.*, one hour for the Aviva Combo insulin pump
		Some pumps can be worn while swimming. It will be adjusted to deliver a specific basal rate throughout the swimming
		If the pump is not compatible with swimming according to the manufacturer's guidelines, the pump can be removed, leaving the cannula attached in place and covered with a dressing and a cap
		If the pump is removed for more than one hour, testing the blood glucose using a glucometer is advised with the recommended amount of carbohydrates and insulin intake, and continue swimming
Contact sports		All types of sports, including martial arts and those with possible body contact, are permitted if there are no other systemic contraindications
		Contact sports may increase the risk of dislodgement of the pump cannula
		Ensure adequate hydration during any exercise
		The pump can be removed for up to one hour
		After one hour, testing the blood sugar using a glucometer is advised with the recommended amount of carbohydrates and insulin intake, and continue sports
Imaging	**X-ray**	Radiation can provoke electrical currents in the electric circuit, impairing the pump function
		The pump should be removed when possible
		Safe to keep on an insulin pump in position if the x-ray beam is less than 3 seconds at a time and if a lead apron protects the pump
	Dental X-ray	The patient should ensure that the pump is covered by the lead apron he wears
	Ultrasound	The ultrasound beam should not directly point at the pump or the insertion site
	CT-scan and Fluoroscopy	The pump should be removed when possible
		If unable to remove the pump, relocate it to another area away from the anatomic examination site and cover it with a lead apron
		Switch off the pump during the examination and set a reminder timer to reoperate the pump just after finishing the radiological procedure
		After finishing the procedure, the pump should be checked for any possible malfunction with frequent blood glucose monitoring
	MRI	The MRI magnetic field is strong enough to magnetize the pump's motor and thus damage it
		The pump should be removed and kept outside the MRI room whenever possible
		If it is impossible to remove the pump and the patient uses a metal cannula or an Omnipod, he/she must remove it before entering the room and insert a new cannula after finishing the test
		If the pump is accidentally exposed to an MRI field, it should be stopped and disconnected immediately and checked by the maintenance team for any malfunction before resuming its use

Insulin pump renewal	The pump is renewed if there is evidence of clinical benefits over the past four years
	The pump is renewed after warranty expiration to obtain the safest result. However, it can still be used but with an increased risk of malfunction
The transition from Pediatric to the adult pump user	The child pump users can shift to MDT between 12-18 yr of age. However, they can continue using the pump as an adult
	They need at least three monthly follow-up appointments to ensure the adequacy of MDT with a smooth transition to the adult clinic
	Pediatric pump users can take a holiday off from the pump therapy. During this holiday, they can receive MDT as a training period and are not considered as a pump therapy failure
	Strong cooperation between the pediatric and the adult pump therapy clinic is needed to ensure a smooth transition of the adolescent to an adult pump or MDT user

CT: Computed tomography; MDT: Multidose therapy; MRI: Magnetic resonance imaging.

insulin). This limitation could affect the child's daily activities, such as swimming. However, many pump types are waterproof and fit for swimming[109].

Insulin pump setup occasionally is complicated and difficult to proceed with compared to pen or syringe use. Therefore, adequate training and education are mandatory for both the child and the caregiver. It also needs a high level of motivation, understanding, and education to achieve the best benefit of the pump and avoid complications. In addition, the insertion set, including the infusion set and cannula, requires to be replaced every 2-3 d. In addition, the infusion set may be prone to incorrect priming, air bubbles, tubing breakdown, and kinking or slippage of the cannula, which can interrupt insulin delivery[110].

Infection of the insertion site occurs in 17% of patients on insulin pumps over a period of three years, especially when the infusion set is left for longer than it should[111]. Risk factors for insertion site infections include large insulin doses, poor patient selection, inadequate patient education, lack of hygienic measures, infrequent changes of the infusion set as requested by the manufacturer, and incorrect cannula insertion[112]. Staphylococcal or streptococcal bacterial infections are the most common infection at the insertion site, followed by *Rhizomucor pusillus* fungal cellulitis[113]. Occasionally the infection may progress to cellulitis or collect into an abscess requiring surgical drainage. Primary tuberculous infection of the insulin injection site is rare but reported complications of insulin therapy[114]. Changing the insertion set should be done according to the manufacturer's guidelines or pump educator to diminish the chance of infection. It is also imperative that the patient follow proper hygienic measures, especially washing the hands and periodically changing the site to decrease infection chances. The cost of the pump is not only limited to the device but also running costs for accessories, cartridge syringes, batteries, skin preparation items, cannulas, and infusion sets, which are significantly higher than the regular insulin pens and syringes. Because insulin is a lifesaving essential medicine, every effort should be made to minimize the cost to the patient and his family[115].

DISCONTINUATION OF INSULIN PUMP THERAPY

About 3% of the pump user discontinue pump therapy within one year. The most frequent causes, according to Wong *et al*[116], include difficulties in pump insertion/adhesive (60%), interference with sports activities (42%), discomfort with wearing the pump (38%), interference with intimacy (34%), pump dysfunction (28%), and problematic hyperglycemia (28%). Beato-Víbora *et al*[117] 2015 showed that pump therapy improves glycaemic control and hypoglycemia awareness, decreases hypoglycemia frequency, and can be sustained for many years. However, 5% of the users discontinued the pump therapy due to a lack of clinical advantage, technical problems, safety issues, or user choice.

The pump therapy should be discontinued for recurrent DKA as it affects the local absorption of insulin due to altered tissue perfusion. It should also be discontinued when there is a pump failure or mismanagement, inadequate blood glucose monitoring (less than four times/day), recurrent injection site infection, intentional overdosing, failure to meet the objective of pump therapy, or with the parents' or the child's wishes. Pump therapy should be discontinued if the patient becomes unconscious, confused, and unable to self-management, such as severe pain or illness. It should also be discontinued if the patient goes for major surgery with general anesthesia for more than two hours[118]. Limitation of the study: some of the included articles were in favor of using insulin pumps which may carry the risk of bias. However, we tried to include most of the available studies to minimize the risk of bias.

CONCLUSION

The insulin pump is a giant breakthrough in DM management, especially in the pediatric age. The insulin pump provides fewer needles and can provide very tiny insulin doses. It provides a convenient and more flexible way to modify the needed insulin physiologically, like the human pancreas. It can offer adequate and optimal glycemic control to reduce the risk of metabolic derangements in different tissues. However, there are some disadvantages to insulin pump therapy that do not necessarily prevent its use. It should be discontinued with recurrent diabetic ketoacidosis.

ARTICLE HIGHLIGHTS

Research background

The insulin pump is a giant breakthrough in diabetes mellitus (DM) treatment. Treating diabetes with an insulin pump is the method most similar to the normal physiologic function of the pancreas.

Research Motivation

We are motivated to write this manuscript to decrease the gap in understanding of insulin pump use among children health care professionals, parents, and children with diabetes mellitus who need intensive insulin therapy.

Research objectives

To identify all the existing evidence-based research for the proper use of insulin pumps among children with diabetes Mellitus and to increase awareness among these patients and their families.

Research Methods

We conducted comprehensive literature searches of electronic databases until June 30, 2022, related to pump therapy in children and published in the English language. The selected articles were subsequently explored to identify the most recent evidence-based research and existing guidelines for the proper use of insulin pumps in children.

Research Results

We identified 118 articles concerned with insulin pumps, 61 were reviews, systemic reviews, and meta-analyses, 47 were primary research studies with strong design, and ten were guidelines. These articles covered the different aspects of insulin pump use in children with diabetes mellitus.

Research conclusions

The insulin pump is a giant breakthrough in pediatric DM management. It provides fewer needles and can provide very tiny insulin doses with a convenient and flexible way to modify the needed insulin physiologically, like the human pancreas. It can offer adequate and optimal glycemic control to reduce the risk of metabolic derangements in different tissues.

Research perspectives

Continuous modification and upgrading of the insulin pump are expected to proceed. These modifications will probably help to make insulin pumps more physiologic and similar to the human pancreas.

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REFERENCES

1 **McAdams BH**, Rizvi AA. An Overview of Insulin Pumps and Glucose Sensors for the Generalist. *J Clin Med* 2016; **5** [PMID: 26742082 DOI: 10.3390/jcm5010005]
2 **Karamanou M**, Protogerou A, Tsoucalas G, Androutsos G, Poulakou-Rebelakou E. Milestones in the history of diabetes mellitus: The main contributors. *World J Diabetes* 2016; **7**: 1-7 [PMID: 26788261 DOI: 10.4239/wjd.v7.i1.1]
3 **Lee J**, Sanders DPM. From Thebes to Toronto and the 21st Century: An Incredible Journey. *Diabetes Spectr* 2002; **15**: 56-60 [DOI: 10.2337/diaspect.15.1.56]
4 **Lewis GF**, Brubaker PL. The discovery of insulin revisited: lessons for the modern era. *J Clin Invest* 2021; **131** [PMID: 33393501 DOI: 10.1172/JCI142239]
5 **Fralick M**, Zinman B. The discovery of insulin in Toronto: beginning a 100 year journey of research and clinical achievement. *Diabetologia* 2021; **64**: 947-953 [PMID: 33492422 DOI: 10.1007/s00125-020-05371-6]
6 **Thomas LJ**, Bessman SP. Prototype for an implantable insulin delivery pump. *Proc West Pharmacol Soc* 1975; **18**: 393-398 [PMID: 1178703]
7 **Riley WJ**, Silverstein JH, Rosenbloom AL, Spillar R, McCallum MH. Ambulatory diabetes management with pulsed subcutaneous insulin using a portable pump. *Clin Pediatr (Phila)* 1980; **19**: 609-614 [PMID: 6996894 DOI: 10.1177/000992288001900907]
8 **Kaufman FR**, Halvorson M, Miller D, Mackenzie M, Fisher LK, Pitukcheewanont P. Insulin pump therapy in type 1 pediatric patients: now and into the year 2000. *Diabetes Metab Res Rev* 1999; **15**: 338-352 [PMID: 10585620 DOI: 10.1002/(sici)1520-7560(199909/10)15:5<338::aid-dmrr57>3.0.co;2-y]
9 **Marcus A**. Diabetes care - insulin delivery in a changing world. *Medscape J Med* 2008; **10**: 120 [PMID: 18596953]
10 **Kesavadev J**, Saboo B, Krishna MB, Krishnan G. Evolution of Insulin Delivery Devices: From Syringes, Pens, and Pumps to DIY Artificial Pancreas. *Diabetes Ther* 2020; **11**: 1251-1269 [PMID: 32410184 DOI: 10.1007/s13300-020-00831-z]
11 **Bekiari E**, Kitsios K, Thabit H, Tauschmann M, Athanasiadou E, Karagiannis T, Haidich AB, Hovorka R, Tsapas A. Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. *BMJ* 2018; **361**: k1310 [PMID: 29669716 DOI: 10.1136/bmj.k1310]
12 **Sherr J**, Tamborlane WV. Past, present, and future of insulin pump therapy: better shot at diabetes control. *Mt Sinai J Med* 2008; **75**: 352-361 [PMID: 18729180 DOI: 10.1002/msj.20055]
13 **Pickup JC**. Insulin-pump therapy for type 1 diabetes mellitus. *N Engl J Med* 2012; **366**: 1616-1624 [PMID: 22533577 DOI: 10.1056/NEJMct1113948]
14 **Mbundu Ilunga R**, Camponovo C, Le Dizès O, Wojtusciszyn A. [Insulin pump treatment: For whom and how to set it up on an outpatient? *Rev Med Suisse* 2020; **16**: 1191-1196 [PMID: 32520457]
15 **Baretić M**, Kraljević I, Renar IP. NOCTURNAL HYPOGLYCEMIA--THE MAIN INDICATION FOR INSULIN PUMP THERAPY IN ADULTHOOD. *Acta Clin Croat* 2016; **55**: 93-99 [PMID: 27333724 DOI: 10.20471/acc.2016.55.01.14]
16 **Cengiz E**, Bode B, Van Name M, Tamborlane WV. Moving toward the ideal insulin for insulin pumps. *Expert Rev Med Devices* 2016; **13**: 57-69 [PMID: 26560137 DOI: 10.1586/17434440.2016.1109442]
17 **Berget C**, Messer LH, Forlenza GP. A Clinical Overview of Insulin Pump Therapy for the Management of Diabetes: Past, Present, and Future of Intensive Therapy. *Diabetes Spectr* 2019; **32**: 194-204 [PMID: 31462873 DOI: 10.2337/ds18-0091]
18 **Yen PM**, Young AS. Review of Modern Insulin Pumps and the Perioperative Management of the Type 1 Diabetic Patient for Ambulatory Dental Surgery. *Anesth Prog* 2021; **68**: 180-187 [PMID: 34606570 DOI: 10.2344/anpr-68-03-16]
19 **Paul N**, Kohno T, Klonoff DC. A review of the security of insulin pump infusion systems. *J Diabetes Sci Technol* 2011; **5**: 1557-1562 [PMID: 22226278 DOI: 10.1177/193229681100500632]
20 **Biester T**, Kordonouri O, Holder M, Remus K, Kieninger-Baum D, Wadien T, Danne T. "Let the Algorithm Do the Work": Reduction of Hypoglycemia Using Sensor-Augmented Pump Therapy with Predictive Insulin Suspension (SmartGuard) in Pediatric Type 1 Diabetes Patients. *Diabetes Technol Ther* 2017; **19**: 173-182 [PMID: 28099035 DOI: 10.1089/dia.2016.0349]
21 **Sussman A**, Taylor EJ, Patel M, Ward J, Alva S, Lawrence A, Ng R. Performance of a glucose meter with a built-in automated bolus calculator versus manual bolus calculation in insulin-using subjects. *J Diabetes Sci Technol* 2012; **6**: 339-344 [PMID: 22538144 DOI: 10.1177/193229681200600218]
22 **Vettoretti M**, Cappon G, Facchinetti A, Sparacino G. Advanced Diabetes Management Using Artificial Intelligence and

Continuous Glucose Monitoring Sensors. *Sensors (Basel)* 2020; **20** [PMID: 32664432 DOI: 10.3390/s20143870]
23 **Doyle-Delgado K**, Chamberlain JJ. Use of Diabetes-Related Applications and Digital Health Tools by People With Diabetes and Their Health Care Providers. *Clin Diabetes* 2020; **38**: 449-461 [PMID: 33384470 DOI: 10.2337/cd20-0046]
24 **Kesavadev J**, Das AK, Unnikrishnan R 1st, Joshi SR, Ramachandran A, Shamsudeen J, Krishnan G, Jothydev S, Mohan V. Use of insulin pumps in India: suggested guidelines based on experience and cultural differences. *Diabetes Technol Ther* 2010; **12**: 823-831 [PMID: 20807118 DOI: 10.1089/dia.2010.0027]
25 **Dhatariya K**. Blood Ketones: Measurement, Interpretation, Limitations, and Utility in the Management of Diabetic Ketoacidosis. *Rev Diabet Stud* 2016; **13**: 217-225 [PMID: 28278308 DOI: 10.1900/RDS.2016.13.217]
26 **Paldus B**, Lee MH, O'Neal DN. Insulin pumps in general practice. *Aust Prescr* 2018; **41**: 186-190 [PMID: 30670886 DOI: 10.18773/austprescr.2018.056]
27 **Zisser H**, Jovanovic L. OmniPod Insulin Management System: patient perceptions, preference, and glycemic control. *Diabetes Care* 2006; **29**: 2175 [PMID: 16936173 DOI: 10.2337/dc06-0986]
28 **King AB**. Continuous glucose monitoring-guided insulin dosing in pump-treated patients with type 1 diabetes: a clinical guide. *J Diabetes Sci Technol* 2012; **6**: 191-203 [PMID: 22401339 DOI: 10.1177/193229681200600124]
29 **Kuroda A**, Kaneto H, Yasuda T, Matsuhisa M, Miyashita K, Fujiki N, Fujisawa K, Yamamoto T, Takahara M, Sakamoto F, Matsuoka TA, Shimomura I. Basal insulin requirement is ~30% of the total daily insulin dose in type 1 diabetic patients who use the insulin pump. *Diabetes Care* 2011; **34**: 1089-1090 [PMID: 21430086 DOI: 10.2337/dc10-2149]
30 **Demir G**, Atik Altınok Y, Özen S, Darcan Ş, Gökşen D. Initial Basal and Bolus Rates and Basal Rate Variability During Pump Treatment in Children and Adolescents. *J Clin Res Pediatr Endocrinol* 2021; **13**: 198-203 [PMID: 33374094 DOI: 10.4274/jcrpe.galenos.2020.2020.0171]
31 **Silver B**, Ramaiya K, Andrew SB, Fredrick O, Bajaj S, Kalra S, Charlotte BM, Claudine K, Makhoba A. EADSG Guidelines: Insulin Therapy in Diabetes. *Diabetes Ther* 2018; **9**: 449-492 [PMID: 29508275 DOI: 10.1007/s13300-018-0384-6]
32 **McCall AL**, Farhy LS. Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control. *Minerva Endocrinol* 2013; **38**: 145-163 [PMID: 23732369]
33 **Heden TD**, Kanaley JA. Syncing Exercise With Meals and Circadian Clocks. *Exerc Sport Sci Rev* 2019; **47**: 22-28 [PMID: 30334851 DOI: 10.1249/JES.0000000000000172]
34 **Chawla R**, Madhu SV, Makkar BM, Ghosh S, Saboo B, Kalra S; RSSDI-ESI Consensus Group. RSSDI-ESI Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2020. *Indian J Endocrinol Metab* 2020; **24**: 1-122 [PMID: 32699774 DOI: 10.4103/ijem.IJEM_225_20]
35 **Chetty T**, Shetty V, Fournier PA, Adolfsson P, Jones TW, Davis EA. Exercise Management for Young People With Type 1 Diabetes: A Structured Approach to the Exercise Consultation. *Front Endocrinol (Lausanne)* 2019; **10**: 326 [PMID: 31258513 DOI: 10.3389/fendo.2019.00326]
36 **Elleri D**, Allen JM, Kumareswaran K, Leelarathna L, Nodale M, Caldwell K, Cheng P, Kollman C, Haidar A, Murphy HR, Wilinska ME, Acerini CL, Dunger DB, Hovorka R. Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: randomized clinical trial. *Diabetes Care* 2013; **36**: 838-844 [PMID: 23193217 DOI: 10.2337/dc12-0816]
37 **Howard JY**, Watts SA. Bolus Insulin Prescribing Recommendations for Patients With Type 2 Diabetes Mellitus. *Fed Pract* 2017; **34**: S26-S31 [PMID: 30766313]
38 **King AB**, Kuroda A, Matsuhisa M, Hobbs T. A Review of Insulin-Dosing Formulas for Continuous Subcutaneous Insulin Infusion (CSII) for Adults with Type 1 Diabetes. *Curr Diab Rep* 2016; **16**: 83 [PMID: 27457238 DOI: 10.1007/s11892-016-0772-0]
39 **Heinemann L**. Insulin pump therapy: what is the evidence for using different types of boluses for coverage of prandial insulin requirements? *J Diabetes Sci Technol* 2009; **3**: 1490-1500 [PMID: 20144405 DOI: 10.1177/193229680900300631]
40 **Lukka M**, Tillmann V, Peet A. Decreased Need for Correction Boluses with Universal Utilisation of Dual-Wave Boluses in Children with Type 1 Diabetes. *J Clin Med* 2022; **11** [PMID: 35330014 DOI: 10.3390/jcm11061689]
41 **Lee SW**, Cao M, Sajid S, Hayes M, Choi L, Rother C, de León R. The dual-wave bolus feature in continuous subcutaneous insulin infusion pumps controls prolonged post-prandial hyperglycaemia better than standard bolus in Type 1 diabetes. *Diabetes Nutr Metab* 2004; **17**: 211-216 [PMID: 15575341]
42 **Kowalczyk E**, Dżygało K, Szypowska A. Super Bolus: a remedy for a high glycemic index meal in children with type 1 diabetes on insulin pump therapy? *Trials* 2022; **23**: 240 [PMID: 35351180 DOI: 10.1186/s13063-022-06173-4]
43 **Hanas R**, Adolfsson P. Bolus Calculator Settings in Well-Controlled Prepubertal Children Using Insulin Pumps Are Characterized by Low Insulin to Carbohydrate Ratios and Short Duration of Insulin Action Time. *J Diabetes Sci Technol* 2017; **11**: 247-252 [PMID: 27470666 DOI: 10.1177/1932296816661348]
44 **Davidson PC**, Hebblewhite HR, Steed RD, Bode BW. Analysis of guidelines for basal-bolus insulin dosing: basal insulin, correction factor, and carbohydrate-to-insulin ratio. *Endocr Pract* 2008; **14**: 1095-1101 [PMID: 19158048 DOI: 10.4158/EP.14.9.1095]
45 **Berián J**, Bravo I, Gardel-Vicente A, Lázaro-Galilea JL, Rigla M. Dynamic Insulin Basal Needs Estimation and Parameters Adjustment in Type 1 Diabetes. *Sensors (Basel)* 2021; **21** [PMID: 34372462 DOI: 10.3390/s21155226]
46 **Silverstein J**, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, Deeb L, Grey M, Anderson B, Holzmeister LA, Clark N; American Diabetes Association. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care* 2005; **28**: 186-212 [PMID: 15616254 DOI: 10.2337/diacare.28.1.186]
47 **Pozzilli P**, Battelino T, Danne T, Hovorka R, Jarosz-Chobot P, Renard E. Continuous subcutaneous insulin infusion in diabetes: patient populations, safety, efficacy, and pharmacoeconomics. *Diabetes Metab Res Rev* 2016; **32**: 21-39 [PMID: 25865292 DOI: 10.1002/dmrr.2653]
48 **Ceriello A**, Prattichizzo F, Phillip M, Hirsch IB, Mathieu C, Battelino T. Glycaemic management in diabetes: old and new approaches. *Lancet Diabetes Endocrinol* 2022; **10**: 75-84 [PMID: 34793722 DOI: 10.1016/S2213-8587(21)00245-X]
49 **Boronat M**, Sánchez-Hernández RM, Rodríguez-Cordero J, Jiménez-Ortega A, Nóvoa FJ. Suspension of basal insulin to

avoid hypoglycemia in type 1 diabetes treated with insulin pump. *Endocrinol Diabetes Metab Case Rep* 2015; **2015**: 140081 [PMID: 25614824 DOI: 10.1530/EDM-14-0081]

50 **Ogiso K**, Koriyama N, Obo T, Tokito A, Nishio Y. Basal insulin ameliorates post-breakfast hyperglycemia *via* suppression of post-breakfast proinsulin/C-peptide ratio and fasting serum free fatty acid levels in patients with type 2 diabetes. *Diabetol Int* 2021; **12**: 161-170 [PMID: 33786271 DOI: 10.1007/s13340-020-00457-3]

51 **Nauck MA**, Lindmeyer AM, Mathieu C, Meier JJ. Twenty-Four Hour Fasting (Basal Rate) Tests to Achieve Custom-Tailored, Hour-by-Hour Basal Insulin Infusion Rates in Patients With Type 1 Diabetes Using Insulin Pumps (CSII). *J Diabetes Sci Technol* 2021; **15**: 360-370 [PMID: 31633384 DOI: 10.1177/1932296819882752]

52 **Trief PM**, Cibula D, Rodriguez E, Akel B, Weinstock RS. Incorrect Insulin Administration: A Problem That Warrants Attention. *Clin Diabetes* 2016; **34**: 25-33 [PMID: 26807006 DOI: 10.2337/diaclin.34.1.25]

53 **Slattery D**, Amiel SA, Choudhary P. Optimal prandial timing of bolus insulin in diabetes management: a review. *Diabet Med* 2018; **35**: 306-316 [PMID: 29044708 DOI: 10.1111/dme.13525]

54 **King AB**, Armstrong DU. A prospective evaluation of insulin dosing recommendations in patients with type 1 diabetes at near normal glucose control: bolus dosing. *J Diabetes Sci Technol* 2007; **1**: 42-46 [PMID: 19888378 DOI: 10.1177/193229680700100107]

55 **De Ridder F**, den Brinker M, De Block C. The road from intermittently scanned glucose monitoring to hybrid closed-loop systems: Part A. Keys to success: subject profiles, choice of systems, education. *Ther Adv Endocrinol Metab* 2019; **10**: 2042018819865399 [PMID: 31384420 DOI: 10.1177/2042018819865399]

56 **Aye T**, Block J, Buckingham B. Toward closing the loop: an update on insulin pumps and continuous glucose monitoring systems. *Endocrinol Metab Clin North Am* 2010; **39**: 609-624 [PMID: 20723823 DOI: 10.1016/j.ecl.2010.05.005]

57 **Nicolajsen T**, Samuelsson A, Hanas R. Insulin doses before and one year after pump start: children have a reversed dawn phenomenon. *J Diabetes Sci Technol* 2012; **6**: 589-594 [PMID: 22768890 DOI: 10.1177/193229681200600314]

58 **Cope JU**, Samuels-Reid JH, Morrison AE. Pediatric use of insulin pump technology: a retrospective study of adverse events in children ages 1-12 years. *J Diabetes Sci Technol* 2012; **6**: 1053-1059 [PMID: 23063031 DOI: 10.1177/193229681200600509]

59 **Davidson MB**. Insulin Therapy: A Personal Approach. *Clin Diabetes* 2015; **33**: 123-135 [PMID: 26203205 DOI: 10.2337/diaclin.33.3.123]

60 **Kelly JL**. Continuous Insulin Infusion: When, Where, and How? *Diabetes Spectr* 2014; **27**: 218-223 [PMID: 26246783 DOI: 10.2337/diaspect.27.3.218]

61 **Codella R**, Terruzzi I, Luzi L. Why should people with type 1 diabetes exercise regularly? *Acta Diabetol* 2017; **54**: 615-630 [PMID: 28289908 DOI: 10.1007/s00592-017-0978-x]

62 **Yardley JE**, Sigal RJ, Perkins BA, Riddell MC, Kenny GP. Resistance exercise in type 1 diabetes. *Can J Diabetes* 2013; **37**: 420-426 [PMID: 24321724 DOI: 10.1016/j.jcjd.2013.07.020]

63 **Metcalf KM**, Singhvi A, Tsalikian E, Tansey MJ, Zimmerman MB, Esliger DW, Janz KF. Effects of moderate-to-vigorous intensity physical activity on overnight and next-day hypoglycemia in active adolescents with type 1 diabetes. *Diabetes Care* 2014; **37**: 1272-1278 [PMID: 24574352 DOI: 10.2337/dc13-1973]

64 **Buoite Stella A**, Assaloni R, Tonutti L, Manca E, Tortul C, Candido R, Francescato MP. Strategies used by Patients with Type 1 Diabetes to Avoid Hypoglycemia in a 24×1-Hour Marathon: Comparison with the Amounts of Carbohydrates Estimated by a Customizable Algorithm. *Can J Diabetes* 2017; **41**: 184-189 [PMID: 27939876 DOI: 10.1016/j.jcjd.2016.09.007]

65 **Quirós C**, Bertachi A, Giménez M, Biagi L, Viaplana J, Viñals C, Vehí J, Conget I, Bondia J. Blood glucose monitoring during aerobic and anaerobic physical exercise using a new artificial pancreas system. *Endocrinol Diabetes Nutr (Engl Ed)* 2018; **65**: 342-347 [PMID: 29483036 DOI: 10.1016/j.endinu.2017.12.012]

66 **Seaquist ER**, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R; American Diabetes Association; Endocrine Society. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *J Clin Endocrinol Metab* 2013; **98**: 1845-1859 [PMID: 23589524 DOI: 10.1210/jc.2012-4127]

67 **Xie X**, Guo J, Bremner KE, Wang M, Shah BR, Volodin A. Review and estimation of disutility for joint health states of severe and nonsevere hypoglycemic events in diabetes. *J Comp Eff Res* 2021; **10**: 961-974 [PMID: 34287017 DOI: 10.2217/cer-2021-0059]

68 **Farrell CM**, McCrimmon RJ. Clinical approaches to treat impaired awareness of hypoglycaemia. *Ther Adv Endocrinol Metab* 2021; **12**: 20420188211000248 [PMID: 33796253 DOI: 10.1177/20420188211000248]

69 **Choudhary P**, Olsen BS, Conget I, Welsh JB, Vorrink L, Shin JJ. Hypoglycemia Prevention and User Acceptance of an Insulin Pump System with Predictive Low Glucose Management. *Diabetes Technol Ther* 2016; **18**: 288-291 [PMID: 26907513 DOI: 10.1089/dia.2015.0324]

70 **Brink S**, Joel D, Laffel L, Lee WW, Olsen B, Phelan H, Hanas R; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Sick day management in children and adolescents with diabetes. *Pediatr Diabetes* 2014; **15** Suppl 20: 193-202 [PMID: 25182314 DOI: 10.1111/pedi.12193]

71 **Laffel L**. Sick-day management in type 1 diabetes. *Endocrinol Metab Clin North Am* 2000; **29**: 707-723 [PMID: 11149158 DOI: 10.1016/s0889-8529(05)70160-2]

72 **Cescon M**, DeSalvo DJ, Ly TT, Maahs DM, Messer LH, Buckingham BA, Doyle FJ 3rd, Dassau E. Early Detection of Infusion Set Failure During Insulin Pump Therapy in Type 1 Diabetes. *J Diabetes Sci Technol* 2016; **10**: 1268-1276 [PMID: 27621142 DOI: 10.1177/1932296816663962]

73 **Evans K**. Diabetic ketoacidosis: update on management. *Clin Med (Lond)* 2019; **19**: 396-398 [PMID: 31530688 DOI: 10.7861/clinmed.2019-0284]

74 **Wang J**, Zhang L, Wang X, Dong J, Chen X, Yang S. Application of Nano-Insulin Pump in Children with Diabetic Ketoacidosis. *J Nanosci Nanotechnol* 2021; **21**: 5051-5056 [PMID: 33875090 DOI: 10.1166/jnn.2021.19356]

75 **Choudhary A**. Sick Day Management in Children and Adolescents with Type 1 Diabetes. *J Ark Med Soc* 2016; **112**: 284-286 [PMID: 27434984]

76 **van den Berghe G**, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359-1367 [PMID: 11794168 DOI: 10.1056/NEJMoa011300]

77 **Griesdale DE**, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 2009; **180**: 821-827 [PMID: 19318387 DOI: 10.1503/cmaj.090206]

78 **Partridge H**, Perkins B, Mathieu S, Nicholls A, Adeniji K. Clinical recommendations in the management of the patient with type 1 diabetes on insulin pump therapy in the perioperative period: a primer for the anaesthetist. *Br J Anaesth* 2016; **116**: 18-26 [PMID: 26675948 DOI: 10.1093/bja/aev347]

79 **Chase HP**. Don't take away my pump! *Diabetes Forecast* 2005; **58**: 55-56 [PMID: 16187438]

80 **Pasquel FJ**, Lansang MC, Dhatariya K, Umpierrez GE. Management of diabetes and hyperglycaemia in the hospital. *Lancet Diabetes Endocrinol* 2021; **9**: 174-188 [PMID: 33515493 DOI: 10.1016/S2213-8587(20)30381-8]

81 **Umpierrez GE**, Klonoff DC. Diabetes Technology Update: Use of Insulin Pumps and Continuous Glucose Monitoring in the Hospital. *Diabetes Care* 2018; **41**: 1579-1589 [PMID: 29936424 DOI: 10.2337/dci18-0002]

82 **Kawasaki E**. Type 1 diabetes and autoimmunity. *Clin Pediatr Endocrinol* 2014; **23**: 99-105 [PMID: 25374439 DOI: 10.1297/cpe.23.99]

83 **Amusan O**, Armeni E, Raichura H. Audit of the identification and management of steroid-induced hyperglycaemia and steroidinduced diabetes. *Journal of Diabetes Nursing* 2019; **23**: JDN093, 1-7

84 **Beaupere C**, Liboz A, Fève B, Blondeau B, Guillemain G. Molecular Mechanisms of Glucocorticoid-Induced Insulin Resistance. *Int J Mol Sci* 2021; **22** [PMID: 33435513 DOI: 10.3390/ijms22020623]

85 **Tamez-Pérez HE**, Quintanilla-Flores DL, Rodríguez-Gutiérrez R, González-González JG, Tamez-Peña AL. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World J Diabetes* 2015; **6**: 1073-1081 [PMID: 26240704 DOI: 10.4239/wjd.v6.i8.1073]

86 **Shah P**, Kalra S, Yadav Y, Deka N, Lathia T, Jacob JJ, Kota SK, Bhattacharya S, Gadve SS, Subramanium KAV, George J, Iyer V, Chandratreya S, Aggrawal PK, Singh SK, Joshi A, Selvan C, Priya G, Dhingra A, Das S. Management of Glucocorticoid-Induced Hyperglycemia. *Diabetes Metab Syndr Obes* 2022; **15**: 1577-1588 [PMID: 35637859 DOI: 10.2147/DMSO.S330253]

87 **Maahs DM**, Horton LA, Chase HP. The use of insulin pumps in youth with type 1 diabetes. *Diabetes Technol Ther* 2010; **12** Suppl 1: S59-S65 [PMID: 20515309 DOI: 10.1089/dia.2009.0161]

88 **Freckmann G**, Pleus S, Haug C, Bitton G, Nagar R. Increasing local blood flow by warming the application site: beneficial effects on postprandial glycemic excursions. *J Diabetes Sci Technol* 2012; **6**: 780-785 [PMID: 22920802 DOI: 10.1177/193229681200600407]

89 **Cengiz E**, Weinzimer SA, Sherr JL, Tichy EM, Carria L, Cappiello D, Steffen A, Tamborlane WV. Faster in and faster out: accelerating insulin absorption and action by insulin infusion site warming. *Diabetes Technol Ther* 2014; **16**: 20-25 [PMID: 24367934 DOI: 10.1089/dia.2013.0187]

90 **Muchmore DB**, Vaughn DE. Accelerating and improving the consistency of rapid-acting analog insulin absorption and action for both subcutaneous injection and continuous subcutaneous infusion using recombinant human hyaluronidase. *J Diabetes Sci Technol* 2012; **6**: 764-772 [PMID: 22920800 DOI: 10.1177/193229681200600405]

91 **Hultström M**, Roxhed N, Nordquist L. Intradermal insulin delivery: a promising future for diabetes management. *J Diabetes Sci Technol* 2014; **8**: 453-457 [PMID: 24876605 DOI: 10.1177/1932296814530060]

92 **Cho YH**, Craig ME, Donaghue KC. Puberty as an accelerator for diabetes complications. *Pediatr Diabetes* 2014; **15**: 18-26 [PMID: 24443957 DOI: 10.1111/pedi.12112]

93 **Liang W**, Chikritzhs T. Alcohol consumption during adolescence and risk of diabetes in young adulthood. *Biomed Res Int* 2014; **2014**: 795741 [PMID: 24757678 DOI: 10.1155/2014/795741]

94 **Turner BC**, Jenkins E, Kerr D, Sherwin RS, Cavan DA. The effect of evening alcohol consumption on next-morning glucose control in type 1 diabetes. *Diabetes Care* 2001; **24**: 1888-1893 [PMID: 11679452 DOI: 10.2337/diacare.24.11.1888]

95 **Brown SA**, Jiang B, McElwee-Malloy M, Wakeman C, Breton MD. Fluctuations of Hyperglycemia and Insulin Sensitivity Are Linked to Menstrual Cycle Phases in Women With T1D. *J Diabetes Sci Technol* 2015; **9**: 1192-1199 [PMID: 26468135 DOI: 10.1177/1932296815608400]

96 **Trout KK**, Rickels MR, Schutta MH, Petrova M, Freeman EW, Tkacs NC, Teff KL. Menstrual cycle effects on insulin sensitivity in women with type 1 diabetes: a pilot study. *Diabetes Technol Ther* 2007; **9**: 176-182 [PMID: 17425444 DOI: 10.1089/dia.2006.0004]

97 **Cursino K**, Sider M, Pavin EJ, dos Santos Pde N, Bahamondes L, Zantut-Wittmann DE, Fernandes A. Insulin resistance parameters in users of the injectable contraceptive depot medroxyprogesterone acetate during one year of use. *Eur J Contracept Reprod Health Care* 2016; **21**: 22-29 [PMID: 26140543 DOI: 10.3109/13625187.2015.1059415]

98 **MacNeill G**, Fredericks C. Vacation ease: travelling with an insulin pump. *Can J Diabetes* 2015; **39**: 178-182 [PMID: 26004904 DOI: 10.1016/j.jcjd.2015.02.004]

99 **Pathania YS**, Budania A. Diabetic Stiff Hand Syndrome in a Child. *J Paediatr Child Health* 2021; **57**: 1347 [PMID: 34169601 DOI: 10.1111/jpc.15629]

100 **Heinemann L**, Kamann S. Adhesives Used for Diabetes Medical Devices: A Neglected Risk With Serious Consequences? *J Diabetes Sci Technol* 2016; **10**: 1211-1215 [PMID: 27566734 DOI: 10.1177/1932296816662949]

101 **Messer LH**, Berget C, Beatson C, Polsky S, Forlenza GP. Preserving Skin Integrity with Chronic Device Use in Diabetes. *Diabetes Technol Ther* 2018; **20**: S254-S264 [PMID: 29916740 DOI: 10.1089/dia.2018.0080]

102 **Hingorani A**, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, Driver VR, Frykberg R, Carman TL, Marston W, Mills JL Sr, Murad MH. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg* 2016; **63**: 3S-21S [PMID: 26804367 DOI: 10.1016/j.jvs.2015.10.003]

103 **Pisano M**. Overview of insulin and non-insulin delivery devices in the treatment of diabetes. *P T* 2014; **39**: 866-876

[PMID: 25516696]

104 **Bruttomesso D**, Crazzolara D, Maran A, Costa S, Dal Pos M, Girelli A, Lepore G, Aragona M, Iori E, Valentini U, Del Prato S, Tiengo A, Buhr A, Trevisan R, Baritussio A. In Type 1 diabetic patients with good glycaemic control, blood glucose variability is lower during continuous subcutaneous insulin infusion than during multiple daily injections with insulin glargine. *Diabet Med* 2008; **25**: 326-332 [PMID: 18307459 DOI: 10.1111/j.1464-5491.2007.02365.x]

105 **Andersen HU**, Hangaard S, Hommel E, Ridderstråle M. Six-Year Follow-Up After Insulin Pump Initiation: HbA1c Is Significantly Reduced Without Weight Gain. *J Diabetes Sci Technol* 2018; **12**: 535-536 [PMID: 28927286 DOI: 10.1177/1932296817731424]

106 **Boucher-Berry C**, Parton EA, Alemzadeh R. Excess weight gain during insulin pump therapy is associated with higher basal insulin doses. *J Diabetes Metab Disord* 2016; **15**: 47 [PMID: 27777901 DOI: 10.1186/s40200-016-0271-5]

107 **Breton MD**, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, Schoelwer M, Ruedy KJ, Jost E, Carria L, Emory E, Hsu LJ, Oliveri M, Kollman CC, Dokken BB, Weinzimer SA, DeBoer MD, Buckingham BA, Cherñavvsky D, Wadwa RP; iDCL Trial Research Group. A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. *N Engl J Med* 2020; **383**: 836-845 [PMID: 32846062 DOI: 10.1056/NEJMoa2004736]

108 **Ghazanfar H**, Rizvi SW, Khurram A, Orooj F, Qaiser I. Impact of insulin pump on quality of life of diabetic patients. *Indian J Endocrinol Metab* 2016; **20**: 506-511 [PMID: 27366717 DOI: 10.4103/2230-8210.183472]

109 **Alshami A**, Purewal T, Douedi S, Alazzawi M, Hossain MA, Ong R, Sen S, Cheng J, Patel S. Effect of Insulin Pump Use on Diabetic Ketoacidosis in Type 1 Diabetes Mellitus: A Matched Cohort Study. *J Clin Med* 2021; **10** [PMID: 33668749 DOI: 10.3390/jcm10050898]

110 **AbdulAziz YH**, Al-Sallami HS, Wiltshire E, Rayns J, Willis J, McClintock J, Medlicott N, Wheeler BJ; Paediatric Society of New Zealand Diabetes Clinical Network. Insulin pump initiation and education for children and adolescents - a qualitative study of current practice in New Zealand. *J Diabetes Metab Disord* 2019; **18**: 59-64 [PMID: 31275875 DOI: 10.1007/s40200-019-00390-6]

111 **Pickup JC**, Yemane N, Brackenridge A, Pender S. Nonmetabolic complications of continuous subcutaneous insulin infusion: a patient survey. *Diabetes Technol Ther* 2014; **16**: 145-149 [PMID: 24180294 DOI: 10.1089/dia.2013.0192]

112 **Patel B**, Priefer R. Infections associated with diabetic-care devices. *Diabetes Metab Syndr* 2021; **15**: 519-524 [PMID: 33668001 DOI: 10.1016/j.dsx.2021.02.023]

113 **Wickline CL**, Cornitius TG, Butler T. Cellulitis caused by Rhizomucor pusillus in a diabetic patient receiving continuous insulin infusion pump therapy. *South Med J* 1989; **82**: 1432-1434 [PMID: 2814631 DOI: 10.1097/00007611-198911000-00024]

114 **Chakraborty PP**, Chakraborty M, Dasgupta S. Primary Mycobacterium tuberculosis infection over insulin injection site. *BMJ Case Rep* 2016; **2016** [PMID: 27873753 DOI: 10.1136/bcr-2016-218054]

115 **Brown-Georgi J**, Chhabra H, Vigersky RA. The Rising Cost of Insulin for Pump Users: How Policy Drives Prices. *J Diabetes Sci Technol* 2021; **15**: 1177-1180 [PMID: 32757774 DOI: 10.1177/1932296820947100]

116 **Wong JC**, Boyle C, DiMeglio LA, Mastrandrea LD, Abel KL, Cengiz E, Cemeroglu PA, Aleppo G, Largay JF, Foster NC, Beck RW, Adi S; T1D Exchange Clinic Network. Evaluation of Pump Discontinuation and Associated Factors in the T1D Exchange Clinic Registry. *J Diabetes Sci Technol* 2017; **11**: 224-232 [PMID: 27595711 DOI: 10.1177/1932296816663963]

117 **Beato-Víbora P**, Yeoh E, Rogers H, Hopkins D, Amiel SA, Choudhary P. Sustained benefit of continuous subcutaneous insulin infusion on glycaemic control and hypoglycaemia in adults with Type 1 diabetes. *Diabet Med* 2015; **32**: 1453-1459 [PMID: 26213236 DOI: 10.1111/dme.12869]

118 **Jarosz-Chobot P**. [The use of continuous subcutaneous insulin infusion (CSII) with personal insulin pumps in the treatment of children and adolescents with diabetes type 1]. *Wiad Lek* 2004; **57**: 263-266 [PMID: 15518073]

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