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ACTUAL APPROACHES IN HEALTH SCIENCES

Editor: Prof. Dr. Eray YURTSEVEN

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Chapter 1

Medical Treatments in Pediatric Stone Disease

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1. INTRODUCTION.

Urinary system stones are commonly observed in both adults and children. However, surgical intervention in pediatric patients is generally more complex and challenging compared to that in adults, which underscores the critical importance of medical management for stone disease in younger populations. Research indicates that around 50% of individuals with urinary system stone disease encounter a recurrence of the condition within a decade following their initial treatment(1, 2).

Therefore, regardless of the type of urinary stone or the patient's age, all individuals must receive appropriate medical treatment. Medical management of urinary stones can be broadly classified into two main categories: conservative treatments and specific therapeutic interventions. In the context of pediatric patients, it is particularly important to thoroughly identify and evaluate various factors that may contribute to the development and recurrence of stones. This includes a comprehensive assessment of metabolic risk factors, a detailed evaluation of any anatomical and functional abnormalities, as well as an examination of environmental factors that may influence the condition. Addressing these factors is crucial for the effective management and long-term prevention of urinary stones(1, 3).

2. CONSERVATIVE TREATMENTS

2.1. Lifestyle Changes

Engaging in an active lifestyle constitutes one of the primary preventive measures against the formation of kidney stones. Regular physical activity is crucial for sustaining optimal kidney health and safeguards against many health conditions, including hypertension, coronary artery disease, obesity, and metabolic syndrome. Daily exercise regimens can establish a standard for maintaining an active lifestyle. Notably, there exists a pronounced association between obesity and an elevated risk of kidney stone development.

Obesity and its associated conditions—such as type 2 diabetes mellitus, chronic kidney disease, pathological bone fractures, hyperlipidemia, and an increased body mass index—disrupt calcium metabolism, thereby heightening the risk of kidney stone formation. It is advisable for children with a predisposition to obesity to work towards achieving their ideal weight under the guidance of a pediatric endocrinologist. Therefore, it is imperative to recognize that both preventing obesity and ensuring sufficient physical activity are fundamental in the ultimate prevention of kidney stone disease(4).

2.2. Diet

The relationship between dietary habits and the formation of kidney stones is well-established and warrants a comprehensive examination. Research indicates that individuals adhering to a high-protein diet exhibit a markedly elevated risk of developing kidney stones, with the associated risk potentially increasing by a factor of three to four. This heightened risk is largely attributable to the metabolic processes triggered by protein digestion. Specifically, the digestion of protein leads to increased endogenous acid production and secretion. This, in turn, contributes to metabolic acidosis, which results in a decreased excretion of citrate in the urine. Citrate plays a crucial protective role by binding to oxalate, thereby mitigating the formation of kidney stones. A reduction in citrate levels due to metabolic acidosis compromises this protective effect, making individuals more susceptible to stone formation(5).

Furthermore, a diet high in protein also leads to increased uric acid excretion in the urine. This elevated uric acid concentration is associated with a higher incidence of uric acid stones, a condition known as hyperuricosuria. Empirical studies have consistently demonstrated that individuals with high dietary intake of purine-rich foods are at greater risk for this type of stone formation. Consequently, nutritional recommendations often emphasize the reduction of animal protein consumption to mitigate this risk(6).

Recent advancements in understanding calcium intake among patients with kidney stones have prompted a reevaluation of longstanding dietary guidelines. Historically, it was advised that patients with kidney stones limit their calcium intake to reduce stone formation, particularly in cases of hypercalciuria. However, contemporary guidelines suggest a more nuanced approach. Complete restriction of calcium is now considered counterproductive. A reduction in dietary calcium decreases its availability to bind with oxalate in the gastrointestinal tract, leading to increased intestinal absorption of oxalate. Elevated oxalate levels contribute to a greater propensity for kidney stone formation. Thus, complete calcium restriction is not advisable. Instead, calcium supplementation may be beneficial in managing enteric hyperoxaluria while maintaining a balanced calcium intake, which is recommended in other scenarios.

Additionally, a diet emphasizing plant-based sources of calcium, such as oranges, broccoli, and peppers, rather than animal-derived sources like milk, yoghurt, and cheese, is suggested. This dietary shift aligns with the intention to provide necessary calcium while minimizing the risk of stone formation. It is also crucial to consider the implications for bone development, particularly in pediatric populations, where calcium is essential for proper osteogenesis.

Restricting calcium intake during this critical period could adversely affect bone growth and development. Therefore, a balanced approach to calcium consumption is essential to kidney health and overall skeletal well-being.

Attention should be paid to selecting fibrous foods for fruit and vegetable consumption. Fibers must bind to calcium in the intestine, reducing calcium absorption. Another point to be considered in the diet is salt consumption. Excessive salt intake in the diet will cause natriuresis. Increased sodium absorption increases calcium absorption and causes bicarbonate loss. As a result of the decrease in urine pH, the decreased citrate in urine increases the risk of urate crystal formation. Studies have shown that increasing sodium chloride increases calcium oxalate crystallization.

Restriction of oxalate intake in the diet is beneficial in patients with calcium oxalate stones. In these patients, it is recommended to take calcium and vitamin C in a balanced manner. Restricting foods rich in oxalate, such as nuts, peanuts, almonds, sesame, chocolate, tahini, peanuts, tea, coffee, beer, and snacks in the diet is recommended. Increasing lemon-derived foods rich in citrate will be beneficial. More attention should be paid to these restrictions in cases such as inflammatory bowel disease and small bowel resection, where there is an increase in oxalate absorption.

2.3. Fluid Intake

Increasing fluid intake is a critical dietary intervention for reducing the risk of kidney stone formation. Elevated fluid consumption effectively diminishes the saturation levels of calcium phosphate, calcium oxalate, and monosodium urate in the urine. This reduction in urinary saturation is pivotal, as it mitigates the potential for crystallization, representing the initial and fundamental step in the pathogenesis of kidney stones.

Empirical studies have consistently demonstrated a significant correlation between reduced urine volume and an increased likelihood of stone recurrence. Inadequate fluid intake leads to lower urine volume, exacerbating the concentration of stone-forming substances and promoting crystallization. Consequently, maintaining an optimal hydration level is essential for preventing stone formation and recurrence.

The recommended fluid intake must be individualized, considering factors such as the individual's age and body mass index (BMI). Adjustments in fluid consumption should be tailored to these personal characteristics to ensure adequate hydration and effective dilution of urinary solutes. This personalized approach helps to balance the risk of stone formation with overall health and hydration needs.

3. MEDICAL TREATMENTS

The incidence of nephrolithiasis in pediatric populations has been observed to be on the rise, a trend that underscores the need for a multifaceted approach to understanding and managing this condition. While genetic predisposition plays a significant role in the formation of kidney stones, it is not the sole determinant. Various other factors, including environmental conditions, climatic factors, fluid intake, and dietary habits, are also critically influential.

Calcium oxalate and calcium phosphate stones are the most prevalent types encountered in children with nephrolithiasis. The primary pathophysiological mechanisms contributing to stone formation include hypercalciuria, characterized by elevated levels of calcium in the urine, and hypocitraturia, marked by insufficient citrate levels in the urine. Citrate is a natural inhibitor of stone formation, and its deficiency can significantly contribute to the risk of developing stones(7).

Given these considerations, the dietary regimen of affected children must be meticulously monitored. This includes increasing fluid intake to ensure adequate hydration and dilution of urinary solutes, crucial for preventing stone formation. Furthermore, patients with identified metabolic disorders should adhere to specific therapeutic interventions designed to address their unique conditions.

In addition to individual management strategies, exploring the history of stone disease in family members is beneficial. This familial investigation can provide valuable insights into potential genetic and environmental factors influencing the child's condition and contribute to a more comprehensive treatment plan. Integrating clinical management and familial considerations can achieve a more practical approach to treating and preventing pediatric stone disease (8).

3.1. Metabolic Risk Factors

Elevated concentrations of calcium, phosphate, oxalate, uric acid, and cystine in the urine are associated with an increased risk of kidney stone formation, particularly in individuals with underlying metabolic disorders. The accumulation of these substances can promote crystallization, a critical precursor to stone development. Conversely, certain substances such as citrate, magnesium, and pyrophosphate act as protective factors by inhibiting stone formation and preventing the growth of crystals(9).

In the assessment of metabolic risk factors, a 24-hour urine collection test provides comprehensive data on urinary excretion levels and is highly valuable for identifying abnormalities associated with stone formation. Nevertheless,

conducting a 24-hour urine collection in pediatric patients may be challenging due to practical considerations. Consequently, spot urine examinations are often emphasized in this demographic. While they may not offer the same level of detail as a 24-hour collection, spot urine tests can still provide valuable insights into metabolic abnormalities and help guide treatment decisions(10).

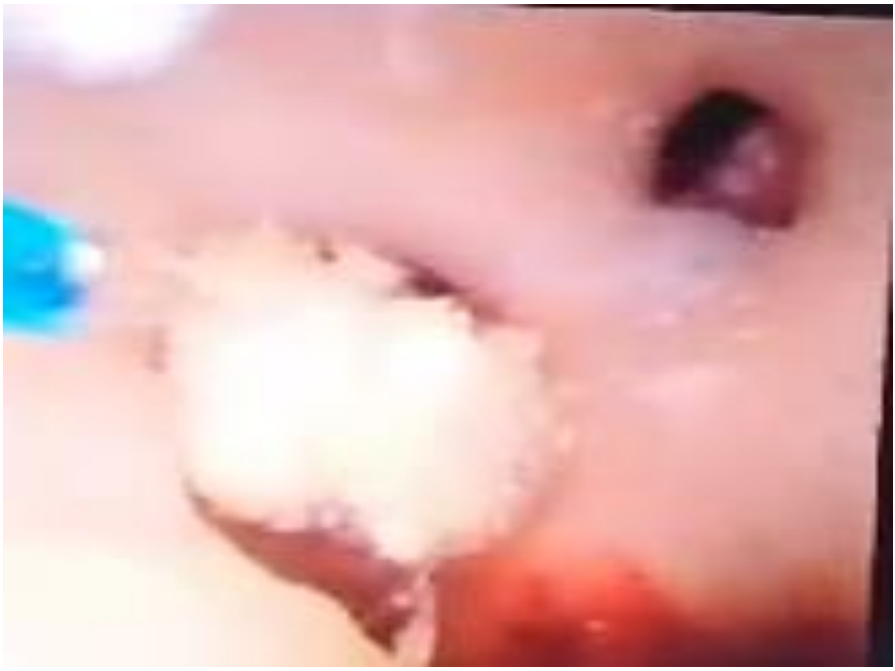

Image-1: Image of a calcium oxalate stone found in the lower calyx during retrograde intrarenal surgery performed in the pediatric age group. (Taken from the author's archive)

3.2. Hyperoxaluria

Oxalate stones are a prevalent type of kidney stone endemic in our country. Oxalate, commonly found in foods such as tea, coffee, nuts, and spinach, can contribute to stone formation in excessive amounts. Hyperoxaluria, an elevated level of oxalate in the urine, may arise from various causes, including excessive dietary intake, short bowel syndrome, pancreatitis, and inflammatory bowel diseases. These conditions can lead to increased absorption or reduced oxalate excretion, heightening the risk of stone formation(11).

3.3. Hypocitraturia

Citrate binds to other minerals and is an essential substance with a protective effect against urinary stone formation. It has a protective role in the formation of calcium stones. Due to reasons such as chronic diarrhoea, intestinal malabsorption, and renal tubular acidosis, hypocitraturia may occur, increasing susceptibility to stone diseases. Since citrate intake increases urine pH, it can protect against uric acid stone formation. Although there is no clear view of the citrate level, a 24-hour urine examination is accepted as the threshold value of 450 mg in men and 550 mg in women.

3.4. Cystinuria

Cystinuria, an autosomal recessive disease, is a disorder of cystine absorption from renal tubules and the intestinal system. It is an essential amino acid such as ornithine, arginine, and lysine. It constitutes approximately 5% of childhood stone diseases. The disease progresses with symptomatic stone attacks starting from the first decade of childhood. Treatments aimed at adjusting urine pH and increasing fluid intake are applied due to the frequent stone formation; rather than open surgery in surgical treatment, percutaneous nephrolithotomy or retrograde intrarenal surgery is often performed(12).

3.5. Hyperuricosuria

Uric acid appears as the end product of purine metabolism. Its solubility decreases in acidic urine. This disease, which occurs due to renal tubular absorption disorder, usually has normal serum uric acid levels. Hematuria and hypercalciuria may accompany. Urine pH is lower than usual. By increasing calcium oxalate crystallization, it also increases the formation of stones.

3.6. Renal Tubular Acidosis

This condition, characterized by metabolic acidosis resulting from the renal loss of protons and bicarbonate, often leads to kidney stone formation in over half of affected patients. Additionally, hypercalciuria can result in renal tubular damage. To manage this condition effectively, monitoring urine pH closely and implementing treatments such as citrate and bicarbonate is crucial. These interventions help to correct the acid-base imbalance and reduce the risk of stone formation(13).

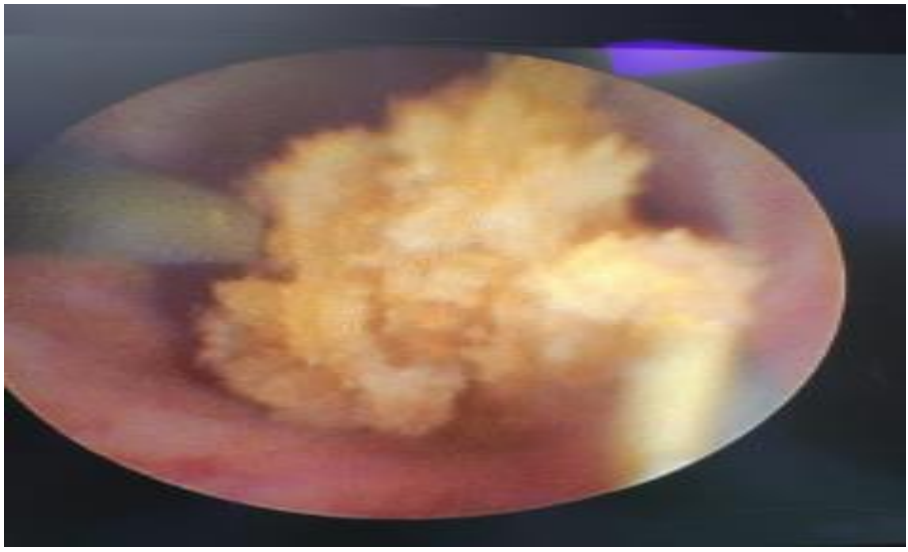

Image-2: Image of a calcium oxalate monohydrate stone found in the upper ureter. (Taken from the author's archive)

3.7. Drugs Used in Pediatric Stone Disease

Thiazide diuretics are a valuable therapeutic intervention for managing hypercalciuria due to their ability to modulate calcium excretion. These diuretics function by enhancing calcium reabsorption within the distal tubules and promoting increased calcium absorption in the proximal tubules, thereby reducing the amount of calcium excreted in the urine. This mechanism is particularly beneficial in patients with elevated urinary calcium levels, helping to mitigate the risk of calcium stone formation. However, thiazide diuretics are not effective in cases of absorptive hypercalciuria, as they do not influence gastrointestinal calcium absorption.

Despite their therapeutic benefits, thiazide diuretics pose several risks, including the potential development of hyperparathyroidism, diabetes, and gout. Additionally, the use of thiazides can lead to hypocitraturia due to potassium loss, which may exacerbate the risk of kidney stone formation. To counteract this effect, potassium citrate is often prescribed. Potassium citrate plays a critical role in preventing the growth and aggregation of calcium oxalate and calcium phosphate crystals. Although citrate is available in various salt forms, including sodium and magnesium salts, potassium citrate is the most commonly used due to its efficacy. Extended-release formulations of potassium citrate are available; however, long-term use may be limited by gastrointestinal side effects(14).

Magnesium, another critical mineral, helps reduce the excretion of magnesium oxalate, decreasing the risk of calcium stone formation. Its role in preventing calcium stones is well established. In cases of primary hyperoxaluria Type 1, particularly in pediatric patients, pyridoxine (vitamin B6) is recommended as it can reduce oxalate absorption by increasing the transamination of glyoxalate, a precursor to oxalate production(15).

For patients with hyperuricosuria, the use of allopurinol is recommended. Allopurinol is effective in preventing the formation of uric acid stones, particularly in individuals with elevated blood uric acid levels. Additionally, allopurinol has demonstrated a 75% success rate in preventing the recurrence of calcium oxalate stones. Pyridoxine can also be introduced at 25 mg/day to decrease oxalate levels in the urine further.

In the management of cystine stone disease, maintaining a urine pH above 7.0 is crucial. This can be achieved through the administration of potassium citrate or potassium carbonate. If these measures are insufficient in reducing citraturia, alternative treatments such as tiopronin, D-penicillamine, and alpha-mercaptopropionylglycine may be utilized. These agents bind to cystine, reducing its concentration and preventing stone formation. In our country, Thiola® (tiopronin) is commonly used to treat cystine stone disease.

4. CONCLUSION

Pediatric nephrolithiasis represents a prevalent health issue within our country, necessitating a comprehensive approach to management. Before proceeding with surgical interventions, it is essential to conduct a thorough metabolic evaluation when feasible. Such an evaluation typically involves a series of diagnostic tests, including a 24-hour urine collection analysis, serum electrolyte and hormone levels assessment, and detailed stone analysis. These diagnostic results provide critical insights that guide the clinician in tailoring a precise treatment strategy.

Rather than concentrating exclusively on surgical approaches, it is paramount to implement prophylactic measures to prevent future stone formation. This preventive strategy includes increasing daily fluid intake to ensure adequate hydration and dilute urinary solutes, thereby reducing the risk of crystallization. Additionally, maintaining urine pH within targeted intervals is crucial, as it can influence the solubility of stone-forming substances. Regular monitoring of urinary electrolytes through spot urine tests also contributes to effective management by identifying imbalances that may predispose to stone formation.

Following these evaluative steps, the possibility of medical management of the stone should be thoroughly considered. If clinical and metabolic assessments indicate that non-surgical treatment is viable, appropriate medical therapies should be initiated. These therapies may include specific medications and dietary modifications aimed at dissolving or preventing the recurrence of stones, thereby offering a conservative alternative to surgical intervention.

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Chapter 2

Multiple Sclerosis Treatment

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Multiple sclerosis (MS) mostly occurs in the relapsing-remitting MS (RRMS) form. It is also seen as less primary progressive MS (PPMS) disease. It is a chronic inflammatory disease (1). In the treatment of MS, highly effective disease-modifying therapies (DMT) have a positive impact on the relapse rate and progression of disability, but they may expose patients to significant risks, such as progressive multifocal leukoencephalopathy (PML) (2).

Drugs used in treatment

Interferons (inferon beta 1a, interferon beta 1b) (IFNB)

Interferons are generally considered safe drugs. The most common side effects include injection site reactions and flu-like symptoms that tend to decrease over time. To a lesser extent, they include leukopenia, anemia, depression, thyroid dysfunction, nephropathy, and thrombotic microangiopathy. Complete blood count, liver, kidney and thyroid functions should be checked periodically during treatment. Patients receiving interferon beta may develop neutralizing antibodies to the drug, which may reduce the effectiveness of the drug. If high titers of neutralizing antibodies occur 12-24 months after starting the drug, treatment should be changed even if disease activity does not occur (3).

Glatiramer acetate (GA)

It is indicated in forms of MS including clinically isolated syndrome (CIS), RRMS, and secondary progressive MS (SPMS). Side effects include local injection site reactions and transient systemic post-injection reactions such as chest pain, flushing, dyspnea, palpitations, and anxiety. No specific laboratory parameters need to be checked during GA therapy and no opportunistic infections associated with drug administration have been identified (3).

Dimethyl fumarate (DMF)

DMF is the first-line drug for MS (4). DMF is administered orally, starting with 120 mg twice daily and increasing to 240 mg twice daily after 7 days. The most common side effects of DMF are flushing and gastrointestinal symptoms, including diarrhea, nausea, and abdominal pain. It occurs in more than 25% of patients in the first two months of treatment. DMF should be discontinued if long-term lymphopenia is below 500/mL (3). There is concern about the occurrence of moderate-to-severe and persistent lymphopenia and the associated risk of PML (5). However, DMF has a low risk of progressive multifocal leukoencephalopathy. As with other immunosuppressive treatments, administration of live attenuated vaccines during treatment is not recommended (3). It has a positive safety profile. The onset of clinical efficacy may take up to

8 weeks after initiation of treatment (4). After DMF turns into the active metabolite, it is excreted through breathing. Smaller amounts are eliminated through urine and feces (6). It is not detected in blood (7). Dimethyl fumarate is not metabolized via the cytochrome P450 enzyme or p-glycoprotein systems. No significant drug interactions have been identified in clinical studies. In the treatment of flushing, alternative dosage regimens and extended dose titration may be applied together with acetylsalicylic acid (8).

Teriflunomide

Teriflunomide is taken once a day at a dose of 14 mg. The most common side effects include headache, diarrhea, nausea, and increase in ALT levels. Rare but potentially serious side effects include hepatotoxicity, bone marrow suppression, opportunistic infections, increased blood pressure, peripheral neuropathy, and interstitial lung disease. Live vaccines should not be administered during teriflunomide treatment. Before starting treatment, patients should receive all vaccinations and be screened for latent tuberculosis infection. Transaminase and bilirubin levels should be monitored monthly for the first six months. Blood cell count and renal parameters should be monitored every 6 months during treatment (3).

Fingolimod

It has the highest incidence of PML after natalizumab (2). Patients should be screened for bradycardia, long QT, AV blocks, and other arrhythmic risk factors before initiating treatment and monitored for 6 hours after initial administration. The most common infections during treatment include herpes viruses and cryptococci. With increased transaminase levels the patients, should be closely monitored for liver damage, skin cancers such as basal cell carcinoma, and ocular complications such as macular edema, retinal hemorrhages, and retinal vascular occlusion. Before treatment, immunization should be questioned in terms of varicella zoster (VZV) and if not, vaccination should be given. If lymphocytes drop below 200/mL, fingolimod should be interrupted. In case of increased liver enzymes, fingolimod can also be administered every other day (3). Fingolimod has a washout period of approximately 2 months. It is slowly metabolized mainly by the liver (9).

Siponimod

Washout period is 6-9 days and half-life is 7 hours. It is the first oral medication approved for the treatment of SPMS. Observation and monitoring of the first dose is not mandatory in patients without pre-existing heart disease.

CYP2C9*3 heterozygous carriers should receive half of the maintenance dose, while homozygous carriers are a contraindication to siponimod treatment. Like fingolimod, eye, arrhythmia and serious liver diseases should be investigated and vaccination status should be examined (3). It was approved by the US Food and Drug Administration in March 2019 for the treatment of RRMS and SPMS (10). While fingolimod is mainly used for RRMS, siponimod is recommended for the treatment of SPMS in most countries (11).

Natalizumab (NTZ)

The most important side effect of NTZ is PML (2). The NTZ washout period should not be longer than 3 months (12). In case of presence of JCV antibodies, NTZ treatment should be discontinued and switched to another DMT as soon as possible. NTZ is administered as a 300 mg IV infusion every four weeks. Before starting treatment, leukocyte and neutrophil counts should be within the normal range. NTZ should be stopped at least one month before starting treatment with other DMTs. Approximately 6% of patients develop neutralizing antibodies to NTZ, resulting in poor treatment response. It is not recommended during pregnancy.

Ocrelizumab

Premedication is administered before administering ocrelizumab. Premedication consisting of methylprednisolone, antihistamines and paracetamol is given. Before treatment, the patient should be examined for hepatitis B and C, tuberculosis, VZV and HIV. Mild dermatological side effects are observed. Epilepsy, malignancy and drug-related death have not been reported. The first application is given as 300 mg and 2 weeks later as 300 mg. Then it is administered as 600 mg every 6 months (1). It is the first humanized antibody of this class approved for the treatment of RRMS and also the first drug approved for the treatment of PPMS (3).

Cladribine

Cladribine is the only oral induction therapy. It has side effects such as upper respiratory tract infections, headache and lymphocytopenia. The use of cladribine is contraindicated in patients with malignancy and active chronic infection, during pregnancy and breastfeeding. Infections, malignancy and pregnancy should be excluded before starting treatment. Lymphocyte count should be monitored before, during and after treatment (3).

Alemtuzumab

Alemtuzumab is indicated for the treatment of RRMS. However, it can only be used in patients with very active disease and those who have not responded to other drug treatments. Drug administration requires glucocorticoid, paracetamol and anti-histamine premedication and two hours of observation after each infusion. In the presence of high disease activity, in case of drug intolerance, treatment should be changed to another drug of the same efficacy class but with a different mechanism of action (13).

MS and pregnancy

It has been shown that pregnancy, birth and fetal complications in women with MS are no different from those in women without MS.

Interferons

The prevalence of stillbirth is high. Studies have shown that interferon is excreted in breast milk at very low concentrations and that there are generally no adverse effects associated with interferon exposure on typical development or growth rates. It recommends breastfeeding.

Interferon beta 1a

There is no significant risk from exposure in early pregnancy, so they can be used during pregnancy. The potential benefit for breastfeeding should be evaluated. According to most authors, they can be used during breastfeeding.

GA

The medication is continued before becoming pregnant. Debate continues about whether to continue during pregnancy or what to do in the event of a positive pregnancy test. It passes into milk in very small amounts. Breastfeeding is recommended.

Teriflunomide

It is teratogenic. Strict contraception is recommended for women of reproductive age. Men are advised not to have children during treatment due to the possibility of seminal transmission. Breastfeeding is contraindicated during drug use. Elimination of teriflunomide may take up to two years. To speed up elimination, it is recommended for both women and men to use 8 g of cholestyramine three times a day for 11 days or 50 g of activated charcoal twice a day for 11 days before pregnancy. Pregnancy should be avoided until the serum concentration of teriflunomide is < 0.02 mg/L (3).

DMF

DMF does not accumulate, so patients treated with DMF do not require any washout period for pregnancy (14). It has the highest prevalence of premature births. It may be teratogenic, so it is recommended to discontinue the drug when the pregnancy test is positive. Breastfeeding is not recommended.

Cladribine

It accounts for the majority of ectopic pregnancies. Its use during pregnancy is contraindicated. Pregnancy is not recommended for both male and female patients for 6 months after the last dose. Breastfeeding is contraindicated for 10 days after the last dose.

NTZ

It has the highest prevalence of spontaneous abortion and live birth defects. Congenital malformations are the most common. NTZ is contraindicated in pregnancy.

Fingolimod

It is teratogenic and its use is contraindicated in pregnant women. It is not used during breastfeeding. If pregnancy is considered, washout is recommended for 2 months. Due to the risk of high disease activity 8-16 weeks after discontinuation of the drug, switching to ocrelizumab is recommended before discontinuation.

Siponimod

It is also contraindicated during pregnancy. Due to its shorter bioavailability, only a 10-day washout is required before becoming pregnant.

Ocrelizumab

Pregnancy should not be attempted within six months after the last infusion. It is recommended to discontinue ocrelizumab during pregnancy. Breastfeeding is controversial. However, it is not banned. The drug has an undetectable concentration in breast milk. It has been reported that there was no adverse effect on neonatal development in breastfed babies during treatment.

During pregnancy, oral medications should be discontinued, but first-line injectable medications should be continued. The approach begins before pregnancy, at the time of initial diagnosis. However, it is not recommended to delay DMT treatment due to desire for pregnancy. If pregnancy is planned within five years of diagnosis, it is recommended to avoid DMTs that are not compatible with pregnancy. Plans for breastfeeding should be made early (13). For patients with high disease activity, it is recommended to postpone pregnancy until the

disease is stable. If relapse occurs during pregnancy, prednisolone, which are considered safe, can be used.

The only drugs licensed during pregnancy are interferons and glatiramer acetate. Ocrelizumab, an IgG1-containing monoclonal antibody that acts on B cells, cannot cross the placenta in the first 3 months. The risk of fetal exposure to the drug is low. It carries a low risk of pregnancy toxicity due to its half-life of 2 months after the last drug infusion. They have a very low risk of relapse after discontinuation of treatment. Its protective effects continue for months. It has low teratogenic effects. For these reasons, ocrelizumab treatment has recently been recommended by some authors during pregnancy (3). Corticosteroid use during pregnancy has been shown to be associated with low birth weight. It is also thought to be associated with an increased risk of orofacial abnormalities if applied in the first trimester (15).

Switching medication

Relapse may occur when switching from NTZ to fingolimod. However, this relaps does not increase the risk of permanent disability (12). It is difficult to decide how and when DMTs should be switched. There is no standard criterion for the concept of inadequate treatment response and when a change in DMT should be considered. However, when relapses, increased activity on MRI, and disability progression are observed and at least two of these measurements are detected, it is recommended to switch to a more effective DMT (16).

If inadequate treatment response is considered, another drug with similar efficacy but different mechanism of action is recommended. Switching to a less effective drug may cause relapses (3). Fingolimod and DMF have similar efficacy on disease activity. The effectiveness of teriflunomide is slightly lower than fingolimod and DMF (10). For patients treated with IFNB or GA who continue to show disease activity, switching to more effective drugs is recommended. In patients treated with a highly effective drug, if the drug has to be discontinued for any reason, it is recommended to switch to another highly effective drug (17).

PML

PML symptoms include a wide range of neurological deficits, such as limb and gait ataxia, diplopia, visual field defects, mental status change, hemiparesis, and monoparesis. It is a white matter disease of the brain, so its clinical appearance depends on the anatomical location of the white matter lesions. Immunoglobulin (IVIG), intravenous methylprednisone (IVMP), plasmapheresis, mirtazapine (5HT-2a receptor antagonist) are drugs used in the treatment of PML. The superiority of these treatments over each other has not been demonstrated (2).

Conclusion

It is unclear whether people with MS receiving DMT therapy still benefit from DMT use after years of clinical and radiological stability. Recent studies have concluded that early treatment with highly effective drugs provides stability in long-term EDSS follow-ups, prevention of activation in MRI, and preservation of the integrity of neurons (3). MS drugs associated with lymphopenia are DMF, fingolimod, cladribine, ocrelizumab, and alemtuzumab. Lymphopenia during fingolimod treatment does not affect relapse or progression of disability. It is unclear whether lymphocyte count is related to treatment effectiveness. Some studies support better disease control with lower lymphocytes. There is no generally shared definition for rebound, so the incidence of rebound is not always based on common criteria. During the washout period after discontinuing a DMT, monthly steroid administration should be provided to prevent disease recurrence until the other drug is started. For ocrelizumab, washout of 6 to 9 weeks is effective and safe. If a second drug cannot be started early or there is lymphopenia at week 4, monthly steroid doses are recommended. It is currently unknown when the best time to start a new treatment is after discontinuation of previous treatments associated with specific lymphopenia (18). Although the most commonly used approach to treating MS is from low to high potency, there is evidence that starting early treatment with high potency DMT is beneficial for long-term disease outcomes (19). Mild sensory changes such as numbness, pins and needles sensations, and feelings of fatigue that do not significantly affect the person's activities can usually be left to heal on their own. It has been shown that adequate vitamin D levels may have a protective effect and reduce the risk of developing MS (20). Treatment options for PPMS are currently limited. Ocrelizumab is the only drug with proven efficacy and approval for this indication (9). The transition process from RRMS to SPMS is not yet well defined. There are no criteria considered sufficient for the diagnosis of SPMS. The diagnosis of SPMS is made retrospectively based on the proven course of progression over the past 3-12 months, with or without relapses after diagnosis (21). Maximal control of the early inflammatory phase of RRMS may prevent the development of disability and SPMS (22).

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Chapter 3

Food Safety Management Systems to Prevent Cross-Contamination in Gluten-Free Diets

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Introduction

Grains have been an essential part of the diet of many cultures and civilizations for centuries and are still considered staple foods worldwide. Bread is one of the oldest and most significant foods in human history. Bread is one of the most important foodstuffs consumed in the modern world. It is a highly versatile staple on many kitchen tables worldwide today (Arranz-Otaegui et al., 2018). In our country, bread ranks first in the world regarding consumption. When the nutritional status of societies is examined, gluten in bread is seen as one of the most common components in the diet. Gluten, which means glue in Latin, consists of a combination of two different fractions, gliadin, and glutenin, and constitutes approximately 80% of the total protein content of wheat (Alçay and Ahmetoğlu, 2020). In addition, gluten allows the dough to hold gas during the fermentation. The resulting bread product is an essential protein contributing to the volume and characteristic fluffy mousse-like crumb structure (Qazi and Nunes, 2022). Recent studies have shown that gluten causes various clinical disorders and causes some discomfort. Therefore, the worldwide market share is increasing with the increasing demand for gluten-free products (Alçay and Ahmetoğlu, 2020).

Different standards apply in all countries for a food to be considered "gluten-free." Gluten content, according to the codex standard accepted by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), should not exceed 20 ppm in gluten-free foods that do not contain wheat, rye, barley, oats, or their hybrids; it should not exceed 100 ppm in foods containing these components but with reduced gluten content. According to the Turkish Food Codex Regulation "Communiqué on foods suitable for individuals with gluten intolerance," In food produced for individuals with gluten intolerance, containing or consisting of a substitute for wheat, barley, oats, or rye, including their hybrids, the amount of gluten should not exceed 20 ppm. The gluten content should not exceed 100 ppm in food with reduced gluten content that contains or consists of a component obtained from wheat, barley, oats, rye, or hybrids specially processed to reduce the gluten level. In the labeling, advertisement, and promotion of the specified products, the phrase "contains very low gluten" is used. The term "gluten-free" may be used if the gluten level in the food offered to the end consumer does not exceed 20 mg/kg when the declaration is made (Anonymous, 2012).

Allergen Foods and Their Effects on Health

With the importance given to healthy and balanced nutrition, individuals prefer food. Non-allergenic and therapeutic foods that meet the body's essential

nutrients, protect it from diseases, and prevent disease formation are used (Saçkesen and Ocak, 2019). The body shows specific and reproducible hypersensitivity reactions when consuming allergen foods (Özcan et al., 2015). These foods are also defined as foods containing nutritional proteins that cause abnormal immune system reactions (e.g., serum albumin, ovalbumin, and profilin). The most common food allergens are milk, egg, soy, shellfish, tree nuts (e.g., walnuts, hazelnuts), peanuts, and wheat proteins (Tercanlı and Atasever, 2021). Allergens in foods are an essential danger threatening food safety and, more importantly, human health. Food allergies are becoming more common worldwide. Both children and adults may have genetic origins, and their dietary habits are also highly influential (Özcan et al., 2015). A food allergen can cause different symptoms in the same person, at various times, at different doses, or cause completely different reactions in other people. When allergens, known as antigens, cause allergic reactions, antibodies are formed against these antigens in the body. Antibodies are proteins that specifically bind to an antigen and destroy it to counteract the effect of that antigen. Although initial exposure to the allergen does not give rise to an immune reaction, subsequent exposure causes a group of antibodies known as predefined immunoglobulin E (IgE) to recognize the allergen. This antibody binds to allergens and enters a reaction involving mast cells and basophils, a blood cell. At the end of the reaction, an allergic reaction occurs in the body with the secretion of histamine, prostaglandins, and leukotrienes from mast cells (Eren, 2008). Food allergy can cause dermatological, gastrointestinal, and adverse respiratory reactions such as abdominal pain, diarrhea, skin rash, and respiratory distress, as well as severe health problems such as anaphylaxis. Therefore, the most effective method in its treatment is elimination diets and safe food practices (Çakır and Dokumacıoğlu, 2021).

Gluten sensitivity was first described in 1980 and is known as one of the manifestations of celiac disease. Gluten-related diseases are classified as celiac disease, non-celiac gluten sensitivity, and wheat allergy (Sümer et al., 2015). In celiac disease, T cell-mediated immunity develops with the intake of gliadin, which is in the gluten structure, and as a result, gastrointestinal and extraintestinal symptoms are observed. Classical adaptive immune responses (acquired immunity) are absent in non-celiac gluten sensitivity. In wheat allergy, proteins in the structure of albumin/globulin and IgE-mediated immune response against gluten occur (Tercanlı and Atasever, 2021).

Celiac Disease

Celiac disease is a food intolerance developed by immunological mechanisms against gluten protein found in wheat, barley, and rye in people carrying human

leukocyte antigen DQ2 or DQ8. In celiac disease, dietary gluten intake causes T-cell-mediated inflammation in the small intestine (Şaşihüyeyinoğlu et al., 2021). There is a lifelong intolerance to gluten. In celiac disease, gliadin peptide, one of the essential components of gluten, increases intestinal permeability by triggering zonulin secretion. This protein regulates the permeability of tight bonds between the intestinal wall cells. As a result of increased intestinal permeability, antigens in the intestine pass into the submucosa, and the continuation of this situation causes intestinal system and liver damage. Autoimmune diseases occur when the body produces antibodies to create a robust immune response—revealing that it makes clinical and histopathological conditions and may cause complications such as infertility, osteoporosis, intestinal lymphoma, and cancer (Çalışır, 2019).

Despite the latest developments in the field, a gluten-free diet remains the only efficient tool for normalizing serum autoantibodies, which are indicators of disease activity, and improvement of the histological structure of the intestine (Farage et al., 2018). Therefore, a lifelong gluten-free diet is the most essential treatment method for celiac disease (Türksoy and Özkaya, 2006). Full compliance with the diet is necessary for the prognosis of the disease (Catassi et al., 2005). Today, bakery products, defined as 'gluten-free foods,' are produced for these patients. They are prepared from gluten-free grain products such as rice, soy flour, corn, guar, and amaranth. When such products prepared for celiac patients are enriched with some B vitamins, iron, and dietary fiber, they will enable them to lead a healthy life without nutritional deficiency (Türksoy and Özkaya, 2006).

Non-Celiac Gluten Sensitivity

Non-celiac gluten sensitivity is a clinical condition unrelated to allergy, in which enteropathy caused by gluten consumption disappears with gluten removal from the diet, and celiac-specific antibodies and villous atrophy are absent (Danış and Vardar, 2018). This picture, first described in 1980, is also known as gluten sensitivity or gluten intolerance (Ermiş and Koç, 2014). The scientific world has recently started to give importance to non-celiac gluten sensitivity. This disease is characterized by gastrointestinal or extraintestinal symptoms occurring in susceptible individuals who do not meet the diagnostic criteria for celiac or wheat allergy but present with prominent symptoms like irritable bowel syndrome. Its prevalence is thought to be more common than celiac disease. Consumption of gluten-free or gluten-reduced foods reduces sensitivity (Sürmeli and Karabudak, 2019).

Wheat Allergy

Wheat allergy is defined as an autoimmune reaction against the proteins found in wheat. In other words, it is an IgE-mediated reaction against gliadins, especially omega-5 gliadins, which are insoluble in water and salt. The reaction that develops in wheat allergy is not only against gluten. Other non-gluten proteins, such as lipid transfer protein, peroxidase, alpha-amylase, and trypsin inhibitors, which cause respiratory and gastrointestinal distress, also cause reactions in the body against wheat. In addition, it does not cause permanent damage to organs, as in celiac disease. Wheat food allergy is a condition that starts in early childhood, primarily moderately severe atopic dermatitis and sensitivity to other foods such as eggs and milk (Parlak, 2018).

Gluten-Free Diets

Gluten-free diets are currently the only treatment method for individuals with gluten-related disorders. People must avoid gluten-containing products such as wheat, barley, and oats (Alçay and Ahmetoğlu, 2020). Instead of grains, they can eat grain-like products such as rice, corn, psyllium, chickpeas, potatoes, lupine, quinoa, soy, teff flour, amaranth, or legumes (Aydar et al., 2019).

People need help to adhere to a gluten-free diet when they consume gluten-free food. First, there are food and beverage restrictions, particularly the fact that cereals, a significant source of nutrition, are not included in the diet; many types of processed foods contain gluten-based products; and the products in the diet are exceptionally high in B group vitamins and vitamin D, magnesium, zinc, iron, and dietary fiber. Low nutritional value causes significant issues in gluten-free patients with balanced and adequate nutrition (Arendt et al., 2008). A gluten-free diet can have many complications, depending on the disease and the individual, including metabolic syndrome, increased cardiovascular risk, and often severe constipation. In addition, due to the negative aspects of gluten-free products, such as less pulp and more oil, they are more expensive, difficult to find, and create a heavy burden on the family budget. Many studies have been carried out in recent years to eliminate the deficiency related to the subject (Yıldırım, 2020). In gluten-free diets, as an alternative to gluten-free cereals, flours obtained from legumes such as beans, chickpeas, and soybeans, as well as flours obtained from starch, chestnut, coconut, flaxseed, and banana, are used as additives. Chickpea protein has good emulsifying properties that increase the volume of gluten-free bread. Compared to rice flour, chickpea flour has been demonstrated by some studies where the blends exhibit high protein and fat content, a low propensity to spoil, and a higher foaming capacity and stability, which may benefit their use. It has been reported that chickpea flour increases the viscous and elastic properties of rice-based doughs, providing an excellent shape (Alçay and Ahmetoğlu, 2020).

Cross-Contamination on Gluten-Free Diets

While cross-contamination is expressed through direct or indirect contamination of bacteria or viruses from a contaminated product to another non-contaminated product, it is also defined as the contamination of any substance that is not desired within the food. Transfer generally occurs from air to food, from surface to food in liquids, and through contact (Pérez-Rodríguez, 2008). Cross-contamination for allergens is expressed as the involuntary, residual, or trace amount of the allergen in the composition of the food mixed with another food (Özcan et al., 2015). Cross-contamination is common in foods that do not naturally contain gluten but are added or accidentally contaminated with gluten (grain yogurt, sausage, meatball mortar, instant soups, breakfast products, etc.). In the food sector, gluten and its products are added to some products as a thickener and structure improver. In addition, when considering the use in other areas such as toothpaste, cosmetics, and drugs, good labeling practices must be made. Cross-contamination is also frequently seen in institutions that provide mass nutrition and packaged products. Cross-contamination can occur at any stage of the food production chain, and its leading cause is hidden gluten in foods, especially in institutions that provide mass nutrition, kitchen tools and equipment, business facilities, storage areas, etc.—creating adequate hygienic conditions in places (Yıldırım, 2020).

Cross-contamination in institutions providing mass nutrition services occurs with the contact of the same work surfaces and kitchen equipment, such as fryers, grills, mixers, and pans, to prepare and serve foods containing allergenic components, especially in kitchens where food preparation areas are limited, and special equipment is insufficient (Parlak, 2018).

The Association of European Celiac Societies (AOECS) uses the cross-grain symbol (Figure 1) to label gluten-free foods. This symbol indicates that the product contains less than 20 ppm of gluten and is gluten-free. Some gluten-free food manufacturers in Turkey also use this symbol. It is essential to control raw materials during gluten-free food production, take necessary precautions to prevent cross-contamination at every step of production, verify that the final product is gluten-free through periodic analyses, and indicate on the label (Atasoy, 2017).

Figure 1. Licensed cross grain symbol of AOECS (AOECS 2017)

Food Safety Management Systems in Gluten-Free Diets

Due to the increase in the world population and the related problems in accessing food resources, food safety has become an increasingly important issue in recent years (Çetin and Şahin, 2017). Today, the increase in immigration and rapid developments in communication have significantly increased the use of unprocessed and/or processed food products. Foods meet many substances and materials and are subjected to different processes in these stages, called the food chain, starting from the source they are supplied to for consumption. For this reason, it has direct effects on human health. Most foodborne diseases can be prevented by meticulously and systematically controlling the stages from farm to table (İnce Palamutoğlu and Palamutoğlu, 2021). Food safety is defined as producing foodstuffs suitable for consumption due to their physical, chemical, and biological properties and that have not lost their nutritional value when prepared as intended (Bosi, 2003). According to the Veterinary Services, Phytosanitary, Food, and Feed Law, Food Safety Is "the whole of the measures taken to eliminate physical, chemical, biological and all kinds of harm that may occur in food." According to the Food Codex Commission (CAC), "to ensure healthy and perfect food production It is defined as following the necessary rules and taking precautions during production, processing, storage, and distribution" (Artık et al., 2013; Artık et al., 2017). In other words, food safety is expressed as the sustainable and improvable realization of studies to prevent contamination and foodborne diseases in all production stages of food products with the principle of farm-to-fork (Eren, 2020).

Organizations that produce, process, supply, or distribute food products need management systems to provide standardized control of food safety, as ensuring food safety is a complex, specialized, demanding, and costly business. To ensure the food safety of food businesses, Framework programs with proven effectiveness for managing and continuously improving principles, procedures, and activities are called Food Safety Management Systems (İnce Palamutoğlu and Palamutoğlu, 2021). To ensure food safety, the International Organization for Standardization (ISO) has established total quality systems such as ISO 9000:

Quality Management System and ISO 22000 Food Safety Management System (Erkmen, 2010). Two international practices have emerged in forming food safety and quality infrastructure. The first of these is "Hazard Analysis and Critical Control Points (HACCP)," which is a quality security system, and the other is "Traceability," which is aimed at ensuring the control of food in all areas (Eren, 2020). HACCP is a food safety concept that systematically defines all production process stages from farm to fork and takes preventive measures with critical control points (Çetin and Şahin, 2017). At this stage, information businesses provide about food products is essential for consumer protection, decision-making processes, and business competition.

Food labels, the most common and essential form of this information transfer, make it easier for consumers to make healthy and conscious choices because they carry valuable information about the composition, expiration date, origin, and nutritional value. Since food allergy treatment is still unavailable, it is essential to include food allergens on food labels in their information (İnce Palamutoğlu et al., 2021). Grains containing gluten are among the most significant foods that must be reported as allergens. Wheat, rye, oat, barley, or their hybrid species and products contain gluten protein. Besides cereals, food products such as processed meats, ketchup, soy sauce, beer, and ice cream may contain gluten (Akay and Yılmaz, 2020). The presence of allergens in foods poses an essential problem for individuals sensitive to allergen foods. Depending on other variables, notably the allergen dose, these individuals may react to these components, and even grave scenarios that result in death may occur. Allergens can be a component of the food formulation and the cross-contamination with allergen compounds during the food production and manufacturing stages. Cross-contamination is the primary source of hidden allergens in foods and can occur at every stage of the food chain (Parlak, 2018). Food safety should be guaranteed with proper labeling and prescribing techniques because allergen items should be recognized in risk analysis, and allergy processes should be designed to prevent contamination. (Akay and Yılmaz, 2020).

People with at least one of the gluten-related diseases, such as celiac disease, dermatitis herpetiformis, gluten intolerance, or gluten ataxia, cannot tolerate gluten. Consuming gluten-free food in one's diet is mandatory to lead a healthy life (Atasoy et al., 2020). In recent years, the number of voluntary gluten-free consumers who prefer gluten-free food consumption as a lifestyle without any reason has been increasing (Gökhisar and Turhan, 2019). There are two types of gluten-free foods: naturally occurring and artificially produced. Produced gluten-free foods are made for those who consume gluten-free food and are advertised on the market as such (Atasoy et al., 2020). In adequate procedures from the field

to the milling and production steps, including in communal production areas, improper sanitation, practices, and storage conditions of industry/restaurant personnel may be responsible for cross-contamination of foods with gluten (Anonymous, 2009). For this reason, the contamination of foods with gluten is a leading problem worldwide for mandatory and voluntary gluten-free food consumers (Atasoy et al., 2020). Gluten detection requires compassionate, analytical tools. Several analyses are currently used in food safety inspection, assessment of gluten in foodstuffs, and regulatory compliance testing. These methods, Enzyme-linked immunosorbent assays (ELISA), mass spectrometry, chromatography, polymerase chain reaction (PCR) techniques, and new approaches such as aptamer, microarray, and multi-analyte profiling are being developed (Bustamante, 2017).

There are many studies examining gluten contamination in gluten-free products. Gluten-free grains or flours produced during harvesting, transportation, or processing are contaminated with gluten-containing grains or flours (Demirkesen and Özkaya, 2020). In a study to evaluate the gluten content of beans served in self-service restaurants, 16% of the samples were found to have gluten contamination. It has been determined that the main reason for cross-contamination is the lack of standardization. It was emphasized how necessary public health measures are to increase access to safe gluten-free products, thereby improving the quality of life of celiac patients (Oliveira et al., 2014).

The systematic review study evaluated the prevalence of gluten contamination in gluten-free industrial and non-industrial products. While the contamination level was determined as 13.2% in industrial food products, the contamination level in non-industrial food products was 41.5% higher than in industrial products. It has been determined that these products are labeled as gluten-free due to the low level of gluten contamination in industrial products. However, the difference in contamination levels between industrial and non-industrial products is negligible. For this reason, it has been emphasized that foods labeled "gluten-free" should not be considered safe (Falconer et al., 2020).

In a study, the ELISA test was applied to some foods that do not contain gluten on the label, and it was determined that 62.5% of breakfast cereals, 37.5% of bread, 23.1% of pasta, 13.3% of snacks and 11.1% of flour mixes contain gluten above the limit. It was determined that 20.2% of them exceeded the limit of 20 ppm. According to the data, 43.8% of gluten-contaminated foods are rice, 18.8% are corn, and 37.5% are rice-based foods from a mixture of grains. According to the study, the claim on the label that a product is gluten-free does not guarantee that it is gluten-free; tests must verify that claim and that cross-contamination is a significant concern (Lee et al., 2014).

Atasoy (2017) used the ELISA method to analyze the gluten content of 170 gluten-free meals sold in Turkey. Price and gluten research were also conducted. He determined that 68% of the foods with gluten contamination (>20ppm) were buckwheat-based, 6% corn, and 3% rice-based. The study emphasized the high prices of gluten-free foods and stated that gluten analysis should be mandatory in the final product. Another study aimed to establish the ideal separation between the food preparation area containing wheat flour and the impact of the exposure time of gluten-free food to wheat flour on contamination to assess the level of gluten contamination that may arise due to cross-contamination in gluten-free products in the preparation area of gluten-containing bakery products and the preparation area. Petri dishes containing gluten-free food at different distances in 2 different directions from the food preparation area containing wheat flour were placed 1 m from the ground. Petri dishes were collected at various periods. As a result of the ELISA test analysis, the samples' gluten levels were found below the legal limit (<20 ppm). Gluten contamination levels of the samples exposed to wheat flour were significantly different from the gluten level of the control sample ($p<0.05$). According to the study's results, the maximum transfer distance was 0.5 m, and the transfer exposure time was 1 hour. Even if the results are below the legal limit, it has been stated that manufacturers should be careful about this issue, mainly because it poses a risk for celiac patients (Parlak, 2018).

The most essential step in preventing cross-contamination is separating gluten-free product production areas from those of gluten-containing product production areas. In other words, the equipment used in all production stages of gluten-containing and non-gluten products from the field to the storage stage should be separate. Good Manufacturing Practices (GMP) should be adopted to ensure the safety of products, and frequent checks should be made that standard manufacturing procedures are being followed. To reduce the risk of gluten contamination, effective strategies such as taking regulation and control measures regarding the training of employees should be adopted to prevent cross-contamination (Demirkesen and Özkaya, 2020).

Conclusion

In the food industry, studies on allergens are critical to ensure food safety. In addition, it is essential to understand the difference between immune-related food allergy and non-immune-related food intolerance to assess food-related diseases accurately. A detailed understanding of the characterization and functions of food allergens at the molecular level will contribute to developing approaches to diagnosing and treating food allergies. Raising producers' and consumers' awareness of food allergies is necessary. In addition, producers must take the

required hygiene measures against cross-contamination throughout the entire production chain and indicate the allergenic components that can be found in foods on the label, especially for people with allergies. These measures will positively contribute to preventing food allergies and increasing people's quality of life.

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