Effect of Gluten-Free Diet on the Growth and Nutritional Status of Children with Coeliac Disease

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SUMMARY

Introduction Gluten-free diet (GFD) presents the basis of coeliac disease (CD) treatment. If strictly applied, the disorders of the small bowel mucosa and other disease signs rapidly resolve.

Objective The goal of the study was to evaluate the effect of GFD on the growth and nutritional status of children with the classical form of CD. In addition, we analyzed the differences between these parameters with the duration and the patients’ compliance with GFD.

Methods The study goals were achieved on a sample of 90 children, 56 female and 34 male, aged 0.5-7.5 (1.53±1.05) years, with the classic CD diagnosed on the basis of typical pathohistological findings of the small bowel mucosa and clinical recovery of patients on GFD. The duration of the patients’ follow-up was 1.08-8.75 (3.03±1.14) years, i.e. until the age of 2.5-15 (4.59±1.78) years. The initial and control values of body height (BH) in relation to matched values for age and gender were expressed in percentiles, while the deviation in body weight (BW) for the matched values of height and gender was expressed in percentages. The referent haemoglobin (Hb) rate in blood, as a laboratory indicator of nutritional status in children aged up to 5 years was ≥110 g/L, and for those aged above 5 years it was ≥115 g/L. Compliance with GFD was based on the pathohistological findings of the small bowel mucosa or determination of tissue transglutaminase.

Results Over the studied period, the effect of GFD was highly significant, both on the increase of BH percentiles (37.62±26.26 vs. 57.22±25.29; p<0.001), and on the decrease of BW deficit (11.58±10.80 vs. 0.89±8.194; p<0.001). After the treatment period, none of the children showed slowed growth rate or BW deficit above 20%, while BW deviation ranging between 10-20% in relation to the referent values was registered in 17 (18.19%) and the excess of over 20% in 2 patients. In 86 (95.56%) patients, control Hb values in blood were normal, while mild anaemia was registered in 4 patients, all compliant with GFD. The difference between the compliant and non-compliant patients with GFD was not detected either in BH percentiles (p=0.586) or in BW percentage deviation as compared to standard values (p=0.516) or in blood Hb values (p=0.445). In addition, differences between the children on GFD lasting over and below 3 years were not detected either in BH percentiles (p=0.915) or in BW percentage deviation as compared to standard values (p=0.516) or in blood Hb values (p=0.915). After the treatment period, none of the children showed slowed growth rate or BW deficit above 20%, while BW deviation ranging between 10-20% in relation to the referent values was registered in 17 (18.19%) and the excess of over 20% in 2 patients.

Conclusion GFD applied for 1-3 years has a highly significant effect on the growth rate and nutritional status of children with the classical form of CD. Significant differences in these parameters of the disease were not detected between strictly compliant and non-compliant patients on GFD.

Keywords: coeliac disease; gluten-free diet; growth and nutritional status; children

INTRODUCTION

Coeliac disease (CD) belongs to the most frequent chronic human diseases of the modern era [1, 2]. It occurs in genetically predisposed persons exposed to gluten in wheat, rye and barley [1-5]. The basis of the disease and the key finding in its diagnostics lie in the autoimmune inflammation of the small bowel mucosa, which withdraws on a gluten-free diet (GFD) [1, 4, 5, 6]. The disorder of the small bowel mucosa is most prominent in the proximal part of the jejunum progressively descending toward the ileum and duodenum [3, 7]. In addition, disorders of other organs and organic systems are also possible [1-5].

From the clinical aspect, CD can be symptomatic or asymptomatic [1-5, 7, 8]. The symptomatic form is additionally classified into classic and atypical [1-5, 7, 8]. The classic form of the disease, which mostly occurs in infants and small children, is characterized by chronic diarrhoea followed by developmental disorders [3, 8, 9, 10]. Besides, clinical features also present with anorexia, occasional vomiting, apathy, irritability, anaemia, and in more severe form a marked abdominal flatulence, muscular and osseous mass reduction, and oedema [3, 8, 9, 11]. Occasionally, this form of the disease is also followed by primary and secondary lactose intolerance, and very rarely also by a coeliac crisis [9, 10, 12]. The atypical, i.e. the oligo- or monosymptomatic form of the disease occurs later [2, 3, 9]. Clinical features are more often characterized by constipation than by diarrhoea, while anaemia, body weight (BW) deficit and slowed-down longitudinal growth are predominant and are sometimes the only signs of the disease [3, 4, 5, 9, 11]. In association with the asymptomatic form of the disease, which can be latent or potential, only serological parameters of
gluten intolerance are registered [13, 14]. Pathohistological findings of the small bowel mucosa, contrary to the latent, in the potential form of CD reveal increased intraepithelial lymphocyte infiltration [13, 14].

CD treatment is based on GFD [1-5]. In recently newly discovered patients, it is necessary to correct the deficit of microelements and vitamins, primarily of iron and folates, and occasionally also temporary lactose restriction [2, 15]. However, in the most severe forms of the disease, in addition to the correction of hydroelectrolytic and acid-base disbalance, along with the removal of oedema, it is necessary to apply elementary and/or parenteral nutrition, and exceptionally rarely, a short-term glucocorticoid therapy [10, 12]. Gluten elimination from nutrition must be strict and life-long, which ensures, not only the child's normal growth velocity and weight gain, but also the prevention of numerous and potentially serious complications [1-5, 7, 9, 10, 16].

OBJECTIVE

The objective of the study was to determine the effect of GFD on the growth and nutritional status in children with the classic form of CD. In addition, we analyzed the differences of these parameters according to duration and compliance with GFD.

METHODS

The objectives of the study were achieved on a sample of 90 children, 56 female and 34 male, aged 0.5-7.5 years (1.53±1.05), with the clinically classic form of CD, i.e. the form of the disease followed by chronic diarrhoea (more than 2 weeks) and development disorders. The diagnosis of CD was based on the characteristic pathohistological findings of small bowel mucosa specimens and a complete recovery of patients on GFD [6]. In patients with gluten-sensitive enteropathy verified before the age of 2 years, the definitive CD diagnosis was established based on pathohistological findings obtained during gluten tolerance provocation [6]. At disease diagnosis and outpatients' check-ups, after a detailed talk with parents, all the patients underwent a complete clinical examination and relevant laboratory investigation.

To establish the diagnosis, we requested exact data on the onset, duration and the severity of the basic disease for each patient, while clinical examination involved a precise measurement of body height (BH) and body weight (BW); the obtained values were then matched to the corresponding age and gender [17]. BH values were expressed in percentiles and BW deviation was related to the ideal rates in percentages. Haemoglobin (Hb) in blood, as a laboratory parameter of nutritional status, was determined by the standard laboratory method. Children aged below 5 years were considered anaemic if Hb in blood was <110 g/L, and for those aged above 5 years if Hb was <115 g/L [18, 19]. Hb values ranging from 100-109 g/L were considered as mild anaemia, 70-99 g/L moderate and below 70 g/L severe [19].

Enterobiopsy was performed by endoscopic or aspiration methods. By the former method, the biopsy specimens of the small bowel mucosa were collected from the descending part of the duodenum, and by the latter from the initial part of the jejunum or duodenum. By endoscopic enterobiopsy we obtained three to five specimens of the mucosa and by aspiration two specimens. Immediately after the biopsy and adequate orientation, each mucosal specimen was stereomicroscopically analyzed in detail. After the stereomicroscopical examination and a precise description, the mucosal specimens were immersed in a standard formalin solution and sent for pathohistological analysis. The classification of the degree of the small bowel mucosa damage was made according to the modified Marsh criteria, dividing it into inflammatory damage of infiltrative (I), infiltrative-hyperplastic (II), destructive (III) and hypoplastic (IV) type [19, 20]. Depending on the degree of villous degeneration, destructive enteropathies were additionally differentiated into partial (IIIA), subtotal (IIIB) and total (IIIC) [21, 22].

After completed hospitalization, all the children were under follow-up as outpatients. The first control check-up was performed after 2-4 weeks, the second one after 2-3 months, and later after every 3-6 months. The presented follow-up period lasted from 1.08-8.75 (3.03±1.14) years, i.e. until age 2.5-15 (4.59±1.78) years. Check-up examinations involved compliance with GFD, possible presence of difficulties and a complete clinical examination including precise BH and BW measurements; in addition, after every 6-12 months we also determined Hb level in blood in each patient. The compliance with GFD was based on the pathohistological investigation of the small bowel mucosa or determination of IgA and IgG antibodies to tissue transglutaminase (atTG). In accordance with the diagnostic protocol of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition, the first group (78/90) was formed of patients who underwent enterobiopsy prior to gluten tolerance provocation, and the second one (12/90) of those in whom this procedure was unnecessary for the definite confirmation of CD [6]. In 12 of 78 patients who underwent enterobiopsy, we detected asymptomatic enteropathy, in three II, in eight IIIa and in one IIIB, while in the remaining patients the pathohistological findings of the small bowel mucosa or the atTG level were normal. In all the patients with confirmed enteropathy, anamnestic data also indicated noncompliance with GFD lasting for several months prior to the last check-up.

The effect of GFD on the increase of BH and BW, as well as the difference in the control values of BH, BW and Hb level in blood according to the compliance with GFD were tested by the Student's t-test. The differences in BH and BW control values according to the duration of diet were determined by Man-Whitney test.

RESULTS

In our group of patients, the basic characteristics of the disease at the establishment of diagnosis are presented on Table 1. Of total 90 patients, BH was below P50 in 50 (55.56%), of whom it was below P5 in 4. BW deficit above
20% was registered in 20 (22.22%) and anaemia in 47 (52.22%), of whom in 24 it was mild and in 23 moderate.

Within 2 weeks after the diagnosis was established and GFD initiated, all the patients showed stabilization of digestive function and evident clinical recovery. After 1.08-8.75 (3.03±1.14) years of the diet, the patient's BW varied from P10-P95 (57.22±25.29), which was significantly much higher (t=10.704; p<0.001) as related to the percentiles at the time of diagnosis) (Graph 1). After the studied period of treatment, all 4 patients with short stature at the time of diagnosis had normal BH, 3 at P10 and one at P25. In addition, BW was P50 in 42 of 90 or 46.67% of children, of whom in one it was even slightly over P95. After the studied period of treatment, BW deviation in relation to the standard value varied from -18 to +30% (0.89±8.19%). By comparison, we also confirmed a highly significant difference between post- and prior-treatment values (t=10.195; p<0.001) (Graph 2). After the studied period of GFD, most children, 71 (78.89%), had optimal nutritional status. Six children had BW deficit ranging from 10-20%, while the others were overweight; 11 between 10-20% and 2 over 20%. In 86 patients (95.56%), control Hb levels in blood were normal, while in 4 who were GFD compliant we registered mild anaemia. At presentation, these 4 patients also had a moderately severe anaemia and a moderate BW deficit (10-20%). After the studied GFD period, beside mild anaemia, 2 of 4 children still remained slimmer, while the other 2 had a normal nutritional status.

Between the patients on a strict GFD and those who were partially compliant, no differences were detected regarding BH percentiles (t=0.547; p=0.586) or percentages in BW deviation compared to the standard (t=0.653; p=0.516), as well as in HB levels in blood (t=0.771; p=0.445).

In addition, no significant differences were found between the children aged below and above 3 years who were on GFD, both in BH percentiles (Z=-0.107; p=0.915), and in percentages of BW deviation in relation to the ideal rates (Z=-0.713; p=0.476).

**DISCUSSION**

Insufficient weight gain, anaemia and (longitudinal) linear growth failure are considered the basic characteristics of CD [2, 3, 4, 8, 9]. Although, these can be the only signs of CD, which is not rare, such findings are more frequent and marked in the form of the disease with classic clinical presentation [11, 23-26]. Keeping in mind rapid growth and development within the first 2-3 years after birth, it is clear that generally speaking its consequences are most prominent exactly at this early age [3, 11, 27, 28].

Impaired linear growth, poor weight gain and anaemia form the basis of the negative nutritional status due to malabsorption [2, 3, 8, 28, 29]. A significant participation in its development has anorexia, which is almost regularly present in infants and small children with the classic form of the disease [2, 3, 8, 11]. In addition, a considerable number of children of the youngest age with gluten tolerance disorder also suffer from vomiting [3, 10, 11]. The negative effect of energy-protein deficiency on the linear growth is manifested indirectly, but to a significant level directly as well, i.e. by a decrease the rate of growth-hormone receptors and the inhibition of the synthesis and activity of insulin-like growth factor I (IGF-I), as well as its transport protein (IGFBP-I) – the factor of key significance in cell proliferation and differentiation [30-33]. According to recent studies, an additional negative effect on the IGF-I, and IGFBP-I expression is also manifested by proinflammatory cytokines, interleukin-6 (IL-6) and tumour necrotic factor-α (TNF-α), which are also present in the acute phase of the disease [30, 33, 34, 35]. In addition, IL-6 also induces the synthesis of hepcidin in the liver, which by its expression, blocks intestinal iron absorption and its mobilization from storage [34]. The disappearance of these pathogenic factors after the introduction of GFD results in a complete recovery of the patient, followed by the corrected deficiency.

| Table 1. Basic data on 90 patients with coeliac disease at diagnosis |
| Data | Values |
| Duration of problems (months) | 1-8 (X=2.21±1.48) |
| Body height (percentiles)* | P5-P90 (X=37.62±26.26) |
| Body weight (% from ideal) | From +9 till -33 (X=11.58±10.80) |
| Haemoglobin in blood (g/L) | 71-128 (X=109.29±16.13) |
| Enteropathy (IIIa:IIIb:IIIc) | 7:41:22 |

* in four patients below P5

Graph 1. Body height in children with coeliac disease before and after the studied gluten-free diet

Graph 2. Body weight in children with coeliac disease before and after the studied gluten-free diet
of BW and iron, as well as by accelerated linear growth [29, 32, 34-39]. The positive effect of GFD on the nutritional status of a child with CD can be already seen within the first few weeks after its introduction, and growth acceleration considerably later [10]. According to authors studying the recovery of children with CD, a complete restoration of BW deficit is achieved after 6-12 months and of BH as long as after 2-3 years [27, 29, 37, 40, 41].

The group of our patients was composed of 90 children aged 0.5-7.5 (1.53±1.05) years with the classic clinical form of the disease. The duration of problems until the establishment of the diagnosis lasted for over two months, a relatively long period, particularly at that age. In all the patients, we registered destructive enteropathy, of which in 81 (92.22%) it was subtotal or total. Half of the patients had BH below P50, of whom in four it was P5. In most, BW deficit as related to the ideal value was also above 10%, of who in 20 it was over 20%. In addition, 47/90 patients also had syderopenic anaemia, of whom in 24 it was mild and in 23 moderate.

Gluten elimination from nutrition resulted in a rapid stabilization of digestive functions and complete clinical recovery of all our patients. The positive effect of a three-year long GFD was highly significant, both regarding the rapid rate of longitudinal growth and correction of BW deficit. Following the treatment period, none of the patients had short stature, while almost in half BW was slightly over P50 for the matched age and gender. After 3-year GFD, four-fifth of our patients was optimally nourished. None of the children had BW deficit over 20%, while only 6 were slimmer, 11 were pre-obese and two obese. Additionally, the conducted dietary-therapeutic measures resulted in the decrease rate of anaemia registered in 4 children only. All 4 children with mild anaemia adhered to GFD and were without any difficulties, indicating at the independence of its nutritive nature from CD. In our sample of patients, the prevalence of obesity and syderopenic anaemia was much lower, while the rate of moderate malnutrition was equivalent to that of the general population of children in our surroundings [42]. Beside GFD, as clearly understood, the explanation for such good parameters of nutritional status in children with CD should be certainly searched for in increased healthcare supervision provided both by doctors and parents.

Most patients, 78/90 or 13.13%, strictly adhered to GFD, while the remaining children did not fully adhere to such a dietary regime. In all non-compliant patients, we verified a mild to moderate asymptomatic damage of the small bowel mucosa, i.e. a silent CD. However, the absence of significant difference in the BH percentiles and parameters of the nutritional status parameters in comparison to the GFD compliant group showed that the non-compliance in the diet of these patients was neither substantial nor long lasting. In addition, this fact also indicated the significance of TG determination in the verification of compliance to GFD [2].

It is well known that within 2-3 years children on GFD restore previous both longitudinal growth failure and BW deficit [27, 29, 37, 40, 41]. Our results are a contribution to the findings that point at the absence of differences in the anthropometric parameters between the children who are on GFD for up to and over three years.

CONCLUSION

Our findings indicate the high significance of GFD effects on the growth and weight of children with the classic form of CD. Longitudinal growth failure is fully corrected within 1-3 years of treatment, while after this period any marked deficiency of body weight and Hb level in blood as compared to normal values are relatively rare and occur independently from the basic disorder. Minor and short-term non-compliance with a diet in such patients are not followed by either subjective difficulties or longitudinal growth failure and weight deficiency, which, unless serological markers of the disease are used, may create an outstanding obstacle in their prompt recognition and rapid resolution.

REFERENCES

17. Needelman RD. Growth and development. In: Bermaasen RE, Kleigman


Утицај дијете без глутена на раст и исхраненост деце с целијачном болешћу

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Увод Дијета без глутена је основа лечења целијачне болесте. Њеном доследном применом ичезавају промене на слузници танког црвца и други знаци болести. Циљ рада Циљ рада је био да се утврди утицај дијете без глутена на раст и исхраненост деце с класичним обликом целијачне болести. Метође рада Истраживање је обухватило 90 деце (56 девојчица и 34 дечака) узраста од шест месеци до седам и по година (посебно 1,53±0,05 година) код које је на основу типичног патохистолошког наплаза на слузници танког црвца дијагностиковани класичан облик целијачке болести и која су била на дијети без глутена. Испитивање је трајало од 1,08 до 8,75 година (посебно 3,03±1,14 година), односно до узраста од две и по године до петнаест година (посебно 4,59±1,78 година). Почетне и контролне вредности телесне висине (TB) су изражаване у проценетима за огледајући узраст и пол, док су одступања у телесној тежини (TV) у односу на референтну вредност за одговарајућу висину и пол изражаване у проценетима. Референтна вредност хемоглобина крви, лабораторијског показатеља исхранености, за децу до пет година била је ≥110 г/л, а за старју децу ≥115 г/л. Доследност примене дијете без глутена је заснована на патохистолошком прегледу слузнице танког црвца или одређивању антитела на тиквени трансплутаминазу.

РЕЗУЛТАТИ Утицај дијете без глутена био је статистички високо значајан и на повећање перцептила TB (37,62±26,26 према 57,22±25,29; p<0,001), а на смањење дефицијета TV (-11,58±10,80 према 0,89±8,194; p<0,001). Након периода лечења ниједно дете није заостајало у TB, нити је имало дефицитет TV већи од 20%, док је одступање TV између 10% и 20% у односу на референтне вредности установљено код 17 болесника (18,89%), а преко 20% код два испитања. Контролна вредност хемоглобина у крви је код 86 испитања (95,56%) била нормална, док је код четири болесника (сви на доследној дијети без глутена) уочена анемија. Разлике између болесника на стриктној дијети без глутена и оних који су примали грешке у исхраненим нису нађене ни у перцептилу TB (p=0,586), ни у проценету одступања TT у односу на стандардну (p=0,516), нити у вредности хемоглобина у крви (p=0,445). Разлике нису забележене ни између деце која су била на дијети без глутена до три године и дуже од овог периода, како у перцептилу TB (p=0,915), тако и у проценету одступања TT у односу на оптималну вредност (p=0,476).

ЗАКЉУЧАЧ Успена глутена током 12-36 месеци има статистички високо значајан утицај на раст и исхраненост деце с класичним обликом целијачне болести. Значајне разлике у овим показатељима болести између болесника на стриктној дијети без глутена и оних који је нису доследно примењивали нису запажене.

КЛУЧНЕ РЕЧИ: целијачка болест; дијета без глутена; раст и исхраненост; деца