



LEIDS UNIVERSITAIR MEDISCH CENTRUM

FOLLOW-UP IN CHILDREN WITH COELIAC DISEASE

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Rijnstate

Coeliac disease and nutritional deficiencies

Intestinal malabsorption

Study and year published	Study population	No. of patients	Nutrient deficiency** at diagnosis	Nutrient deficiency during follow-up
Bonamico M(39) 1987	Children	80	Iron deficiency (56%)	Not available
Dahele A(40) 2001	Adults	39	Iron deficiency (49%) Vitamin B12 deficiency (41%)	Vitamin B12 deficiency resolved after one year gluten free diet
Kemppainen T(41) 1998	Adults	40	Folate deficiency (35%) Iron deficiency (32.5%)	Folate and iron deficiency 8% and 22.5% after one year gluten free diet respectively
Dickey W(42) 2002	Adults	159	Vitamin B12 deficiency (12%)	Not available
Haapalahti M(18) 2005	Adolescents and young adults	26	Iron deficiency (28%) Folate deficiency (31%) Vitamin B12 deficiency (12%)	Not available
Bergamaschi G(19) 2008	Adults	132	Iron deficiency (34%)	30% "some degree" of iron deficiency after one year with gluten free diet
Fernandez A(43) 2010	Adults	68	Iron deficiency (49%) Folate deficiency (24%)	Not available
Botero-Lopez JE(20) 2011	Children and adults	73	Iron deficiency (45%)	Not available
Wierdsma NJ(21) 2013	Adults	80	Iron deficiency (46%) Folate deficiency (20%) Vitamin B12 deficiency (19%)	Not available
Gokce S(44) 2014	Children	191	Iron deficiency (8%)	Not available

Gluten free diet and nutritional deficiencies

Gluten-containing cereals are important sources of dietary iron, calcium, folate and vitamin B12

Commercially available gluten free products contain less nutrients

Restricted food habits in children, especially while on diet

Link with autoimmune thyroid disease

- 2003 *N. Ansaldi, J Pediatr Gastroenterol Nutr*
 - 26% autoimmunity in children, 8% hypothyroidism and 1% hyperthyroidism
- 2008 *P. Elfstrom, J Clin Endocrinol Metabol*
 - CD and subsequent hypothyroidism: OR 4.4, diagnosis CD during childhood OR 6
 - Hypothyroidism and subsequent CD: OR 3.8

What does this mean in daily practice?

In case of CD diagnosis:

- Nutritional deficiencies to be checked?
- Screening for thyroid disease?

1.1 Offer serological testing for coeliac disease to people with:

- unexplained iron, vitamin B12 or folate deficiency
- autoimmune thyroid disease, at diagnosis
- metabolic bone disorder (reduced bone mineral density or osteomalacia)

1.4 Monitoring in people with coeliac disease

1.4.3 Offer an **annual review** to people with coeliac disease.

During the review:

- measure weight and height
- review symptoms
- consider the need for assessment of diet and adherence to the gluten-free diet
- consider the need for specialist dietetic and **nutritional advice**.

NICE guideline on coeliac disease

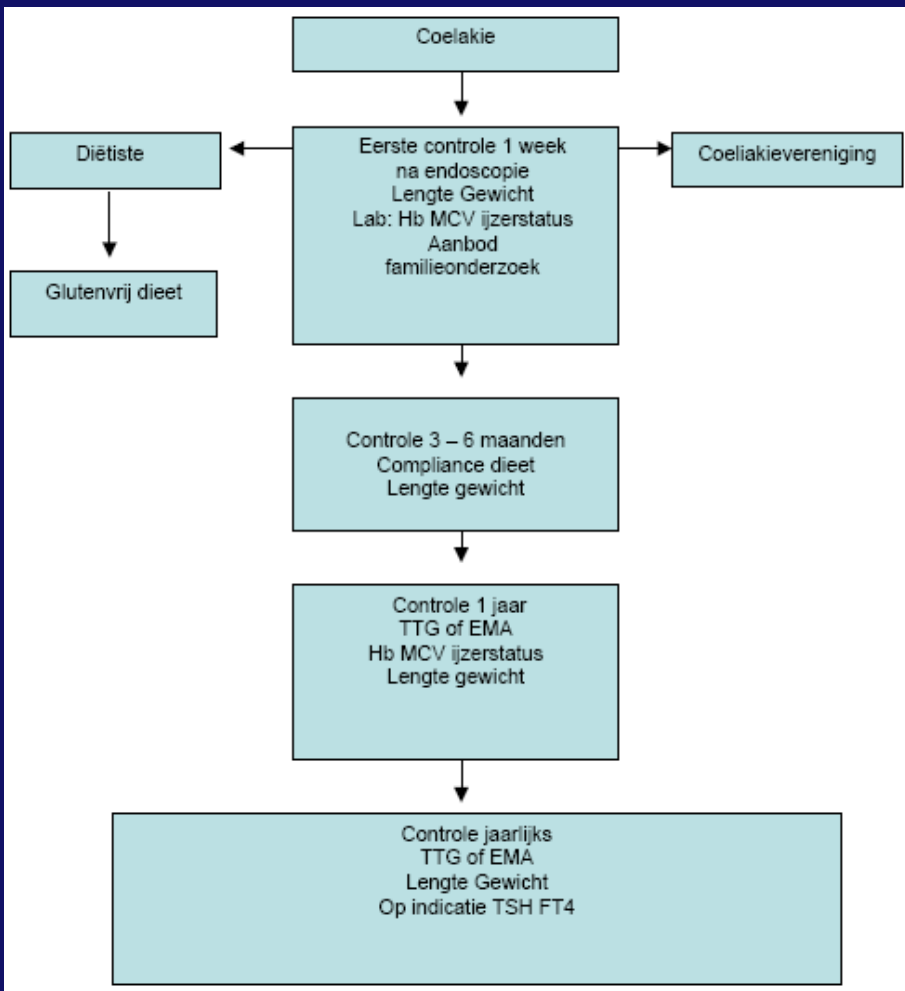
1.4.4 **Refer the person to a GP or consultant if concerns are raised** in the annual review. The GP or consultant should assess all of the following:

- the need for a dual-energy X-ray absorptiometry (DEXA) scan (in line with the NICE guideline on osteoporosis: assessing the risk of fragility fracture) or active treatment of bone disease
- **the need for specific blood tests**
- **the risk of long-term complications and comorbidities**
- the need for specialist referral

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease

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Coeliac Disease Diagnosis, on behalf of the ESPGHAN Gastroenterology Committee*

No remarks on blood tests at diagnosis or during follow-up
Revision of guidelines in progress



- Intestinal and extraintestinal complaints
- Glutenfree diet assessment
- **Associated diseases**
- **Complications**
- QOL

Main objective: determination of the frequency of nutritional deficiencies and thyroid dysfunction in CD children at diagnosis and during follow-up after initiation of a gluten free diet

Methods:

- 2009-2014
- Children visiting pediatric gastroenterology department LUMC
- Characteristics:
 - Age
 - CD antibodies
 - Marsh classification
 - HLA-type

Biochemical parameter	Limit of abnormal value
Hemoglobin, age <7 years	< 6.9 mmol/L (< 11.0 g/dL)
Hemoglobin, age 7-15 years	< 6.5 mmol/L (< 10.4 g/dL)
Hemoglobin, age >15 years	< 6 mmol/L (<9.6 g/dL)
Ferritin, age <5 years	< 12 ug/L
Ferritin, age ≥5 years	< 15 ug/L
Folate	< 10 nmol/L (< 4.45 ng/mL)
Vitamin B12	< 150 pmol/L (203 pg/mL)
Calcium	< 2.15 mmol/L
Vitamin D-25-OH	< 50 nmol/L (< 20.8 ng/mL)
Thyroid Stimulating Hormone	< 0.3 mU/L > 4.8 mU/L
Free Thyroxin	< 10 pmol/L (< 0.78 ng/dL) > 24 pmol/L (< 1.86 ng/dL)

Patient characteristics n=182

Sex, % female	65
Ethnicity, %	
European	93
(North) African and Turkish	4
Asian	2
Unknown	1
Age at diagnosis, mean in years (SD)	6.3 (\pm 4.3)
Duration of follow-up, mean in years (SD)	3.1 (\pm 3.1)
Diagnosis without biopsies (ESPGHAN criteria), nr	28
Biopsies confirmed CD, nr	154
Histology small bowel biopsies at diagnosis, %	
Biopsies performed in another center without report available	1
Marsh 2	4 [^]
Marsh 3a	25
Marsh 3b	49
Marsh 3c	21
HLA-typing result, %	
DQ2 or DQ8 positive	94
Unknown	6
IgA level, %	
>0.2 g/l	96
<0.2 g/l	4
CD specific antibodies at diagnosis, %	
EMA and/or TG2A positive	97
EMA and TG2A negative*	1
EMA and TG2A unknown†	2

Variable assessed between January 2009 and December 2014	Diagnosis n=119* (%)	1st Year n=83* (%)	2nd Year n=79* (%)	3rd Year n=57* (%)	4th Year n=50* (%)	5th Year n=48* (%)
Iron deficiency [†]	29/104 (28)	4/79 (5)	4/77 (5)	4/57 (7)	4/48 (8)	2/48 (4)
Iron deficiency anemia ^{**}	10/110 (9)	2/81 (2)	1/78 (1)	1/57 (2)	0/49	0/47
Folate deficiency [^]	12/84 (14)	0/73	2/71 (3)	0/55	0/40	0/44
Vitamin B12 deficiency ^{^^}	1/85 (1)	1 ^{**} /73 (1)	1 ^{**} /71 (1)	0/55	0/40	0/44
Elevated Thyroid Stimulating Hormone (TSH) [†]	12/99 (12)	10/76 (13)	7/71 (10)	3/55 (5)	3/46 (7)	9/47 (19)
Hypo ^{**} /hyperthyroidism ^{***}	0/99	0/79	0/73	0/54	0/46	0/47
Variable assessed between January 2012 and December 2014	Diagnosis n=71* (%)	1st Year n=50* (%)	2nd Year n=43* (%)	3rd Year n=36* (%)	4th Year n=26* (%)	5th Year n=31* (%)
Hypocalcemia [‡]	0/65	0/37	0/34	0/25	0/14	0/31
Vitamin D deficiency ^{‡‡}	8/30 (27)	9/48 (19)	7/42 (17)	4/34 (12)	3/22 (14)	7/28 (25)

Iron deficiency:

- IDA children younger (mean 2.6 yrs vs 6.5 yrs, $p < 0.001$)
- Normalization of IDA during first year without supplements, expect for 1 girl
- 3 girls with IDA in first 3 yrs on GFD

Important to acknowledge due to important role of iron in development/immune system

Folate deficiency:

- At diagnosis 12 patients, normalization in first year, 40% with supplements
- During follow-up 2 patients with mild folate deficiency (8.7-9.5 nmol/l)

Vitamin B12 deficiency:

- At diagnosis 1 girl who also had folate deficiency (reason to check CD)
- During follow-up low level in 1 girl (normal methylmalonic acid)

Vitamin D deficiency:

- In up to 25% of the children (mean 38.5 nmol/l)
- No consistent prescription
- Older children (mean 7.6 yrs vs 5.9 yrs, $p=0.03$)
- Normalization in all but 2 adolescents without supplements

Important to acknowledge since association coeliac disease and osteoporosis

DEXA scan in adults with CD, no such recommendation in children.

High level of thyroid auto-immunity (elevated TSH up to 19%, no decline after treatment with GFD)

Prevalence thyroid disease 3.8% (6 children hypothyroidism, 1 hyperthyroidism)

- Diagnosis prior to CD diagnosis
- Diagnosis > 5 yrs after CD diagnosis
 - All children had complaints

At diagnosis frequent occurrence of iron deficiency (anemia) and folate deficiency

While on gluten free diet, complementary investigations only when indicated

Awareness of vitamin D status



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