Growth failure in children and adolescents with Crohn's disease

Crohn hastalıklı çocuk ve adölesanlarda büyüme geriliği

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Background/aims: *A clinical analysis in children, adolescents and young adults with Crohn´s disease was performed to investigate if growth failure is caused by an impaired growth hormone secretion in these patients.* ***Methods:*** *40 patients with Crohn´s disease (26 male, 14 female) with an average age of 16,7 years (median: 17,0 years, range: 4-29) were included in the study. The observation period varied from 8 months to 16,7 years, patient´s age ranged from 4 years up to 29 years. To examine growth hormone excretion, urinary growth hormone was measured using an in vitro immunoradiometric assay in three morning urine samples. Renal function was obtained by analysing creatinine and α-1-microglobulin in the same samples. Observation period, chronological age, height, growth rate, pubertal stage, localisation, peidatric Crohn disease activitiy index and corticosteroid treatment as well as IGF-1 levels were determined. We found normal urinary growth hormone levels in Crohn´s disease concluding that growth failure in patients with Crohn´s disease is not caused by growth hormone deficiency. Evenly corticosteroid therapy did not appear to be the most responsible factor for growth failure in Crohn´s disease.* ***Conclusions:*** *Disease activity indicated by a high peidatric Crohn disease activitiy index score had an important impact on impaired growth in children and adolescents with Crohn´s disease.*

Key words: Corticosteroid treatment, Crohn´s disease, growth hormone deficiency, inflammation, inflammatory bowel disease, PCDAI, short stature

Amaç: *Crohn Hastalıklı çocuk, adölesan ve genç erişkinlerde görülen büyüme geriliğinin büyüme hormonu salınımındaki yetersizliğe bağlı olup olmadığının değerlendirilmesini amaçlayan bir klinik analiz yapıldı.* ***Yöntem:*** *Crohn hastalıklı, ortalama yaşları 16.7 [Ortanca=17.0 (4 – 29)] olan 40 hasta (26 erkek, 14 kadın) çalışmaya alındı. Hastalar, 8 ayla 16.7 yaş arası değişen süreler boyunca izlendi. Hastaların yaşları 4'ten 29'a kadar değişmekteydi. Büyüme hormonu salınımını değerlendirmesi için, 3 sabah idrar örneğinde in vitro immunoradyometrik ölçüm yöntemiyle büyüme hormonu ölçümü yapıldı. Renal fonksiyonlar, aynı örneklerde kreatinin ve α-1-mikroglobulin analiziyle yapıldı. Gözlem süreleri, kronolojik yaş, boy, büyüme hızı, ergenlik evresi, lokalizasyon, pediatrik Crohn hastalığı aktivite indeksi, kortikosteroid kullanım öyküsü ve bunların yanında IGF-1 seviyeleri tespit edildi.* ***Bulgular:*** *Crohn hastalarında idrar büyüme hormonu seviyeleri normal saptandı ve bu hastalardaki büyüme geriliğinin büyüme hormonu eksikliğine bağlı olmadığı sonucuna varıldı. Hatta, Crohn Hastalığındaki büyüme geriliği için kortikosteroid tedavi de fazla etkili bulunmadı.* ***Sonuç:*** *Yüksek pediatrik Crohn hastalığı aktivite indeksi skoruyla karakterize hastalık aktivitesinin çocuk ve adölesan dönemdeki Crohn hastalarında görülen büyüme geriliğine önemli etkisinin olduğu saptandı.*

Anahtar kelimeler: Crohn Hastalığı, Kortikosteroid tedavisi, büyüme hormonu eksikliği, inflamasyon, iltihabi barsak hastalığı, PCDAİ, kısa boy

INTRODUCTION

Besides various intestinal problems, children and adolescents with Crohn's disease (CD) frequently suffer growth failure like short stature (height below 3rd percentile), growth retardation (growth velocity below 10th percentile or decline in growth rate from a higher to a lower percentile) and reduced growth rate (< 50th percentile) (1).

There are numerous reasons for growth failure in patients with CD, such as inadequate food intake, malabsorption, increased intestinal losses, increased requirements for calories, secondary hypopituitarism, and corticosteroids (2-9).

Especially the influence of hormonal factors such as insulin-like growth factor (IGF)-1 and growth

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hormone (GH) secretion has been broadly discussed [10-15], but the conclusions are not conclusive. However, there have been some approaches to establish GH treatment in Crohn's patients (16, 17). In this context, we investigated whether GH secretion is impaired in children and adolescents with CD.

MATERIALS AND METHODS

Our retrospective study included a total of 40 (26 male, 14 female) patients with CD confirmed by endoscopy, histology or radiology. Tanner's pubertal stage (P1=2, P2=11, P3=2, P4=2 and P5=23 patients) was ascertained and related to the obtained results. The average age at the time of investigation was 16.7 years (median: 17.0 years; range: 4-29). The observation period varied from 8 months to 16.3 years (mean: 5.6 years; median: 4.4 years). Patients' average age at final diagnosis of CD was 11.1 years (median: 11 years, range 2-20). The localization of the disease was ileocolon only (26), colon only (13) and esophagus, stomach and duodenum (1).

Pediatric Crohn's Disease Activity Index (PCDAI) was determined according to Harms et al. and defined as low with a PCDAI <150, moderate from 150-220 and high >220 (18). Parameters such as appetite, stool frequency per week, alpha-2-microglobulin, iron, blood sedimentation rate, and numbers of rod nuclear cells were included (see Table 1).

In 22 patients PCDAI could be ascertained at the time of diagnosis and revealed a moderate activity (PCDAI: median 165.5; range 106-382) (18).

The dosage of corticosteroid therapy and the application mode (alternate versus daily corticosteroid treatment) were obtained.

Bone age was assessed in 35 patients (in 5 patients before start of corticosteroid therapy, in 24 cases under treatment and in 1 patient after application of corticosteroids) and followed up in 24 cases. Bone age retardation was defined as "retarded" when showing a difference with chronological age > -1.5 years.

Table 1. PCDAI according to Harms

Index =	49.7 + 20.2 x appetite (1, 2, 3)*
	+ 2.4 x stool frequency per week
	+ 0.8 x blood sedimentation rate (mm/h)
	- 0.3 x iron (mg/dl)
	+ 4.1 x alpha-2-microglobulin (%)
	+ 1.3 x rod nuclear cells (%)

*1 = good; 2 = moderate; 3 = little.
PCDAI defined as: low < 150; moderate 150-220; high > 220.

The concentration of urinary GH (uGH) was measured with an in vitro immunoradiometric assay (125 I-hGH U COATRIA, bio Mérieux; France) in three successive morning urine samples. The sensitivity of the kit is approximately 0.5 pg/ml, and the specificity is ≤0.2 µIU/ml. Within- and between-run reproducibility varies from <6.6 and 8.1%, respectively. Validation shows a significant correlation between the test and serum GH values in 24-hour measurements, as well as in day and night measurements. Each patient registered urine volume (in ml) and clock times for the last micturition in the evening, alternate night, and the first morning micturition for calculation of the collection period showing a significant correlation to uGH excretion (19).

To investigate the renal function, we used creatinine as a parameter of glomerular filtration and alpha-1-microglobulin as a parameter of tubular function. Creatinine was measured with an enzymatic *in vitro* test (CREAplus, Boehringer Mannheim Systems; Germany), and alpha-1-microglobulin was determined with a kinetic nephelometry test (Beckman A1M-Test; Germany).

The ratio of uGH and creatinine was calculated and compared with standard values for hGH Urine Coatria of bio Mérieux. The reference values of uGH excretion in relation to creatinine correspond to age and pubertal stage.

Statistical analysis was done using chi-square test.

All patients provided their informed written consent, and in the case of minors, informed written consent was given by the parents; patient anonymity was preserved.

The study is in full accordance with the ethical standards of the Declaration of Helsinki (1995).

RESULTS

The median observation period was 4.4 years (mean: 5.6 years; range: 8 months – 16.3 years). Within the observation period, 33 (82.5%) patients showed normal height within 3rd and 97th percentile, 2 patients (5%) had increased height over the 97th percentile (in the following, subsumed in patients with normal growth), whereas 5 patients (12.5%) showed short stature below the 3rd percentile. Bone age was equivalent to chronological age in 11 patients of the observed patient group, while bone age was retarded in 24 patients (the retardation varied from 1.5 to 6.5 years); in 5 patients bone age was not obtained. Analysis of the detailed growth curves of the patients with normal height

showed growth retardation in 25 patients, defined as growth velocity below the 10th percentile or decline in growth velocity from a higher to a lower percentile. Decline in growth velocity ranged from 10-94 percentile (mean: 40; median: 40). Growth failure was defined as short stature (height below 3rd percentile) and growth retardation as growth velocity below the 10th percentile or decline in growth rate from a higher to a lower percentile) (1).

Subsuming the 5 patients with short stature and 25 patients with normal height but growth retardation, 30 patients (75%) had growth failure.

There was no significant relation between growth failure and sex or between growth failure and localization of disease.

The concentration of uGH in correlation to creatinine was normal in 4 patients with short stature. However, uGH/creatinine was below –2 SDS in 3 patients with normal growth and 5 patients with growth retardation. These results were not significant. One patient with short stature had to be excluded from the study because of additional renal insufficiency.

PCDAI could be determined in 35 patients within the disease period. The mean value was 153 (median: 145.5; range: 107-219). Average PCDAIs were higher in patients with growth failure than in patients with normal growth (Table 2).

Patients with short stature (height below 3rd percentile) showed higher PCDAIs compared to patients with growth retardation (decline in growth rate, but height above 3rd percentile) and patients with normal growth (Figure 1). The differences were not significant.

Thirty-four patients were treated with corticosteroids, either as a continuous treatment (13 patients) or an intermittent treatment (21 patients) (Figure 2). All patients treated with corticosteroids received prednisolone, respectively prednisone; in addition, 2 male patients were treated with methylprednisolone intermittently. The duration of treatment varied from 6 months to 16.3 years

Table 2. Relation between growth failure and average PCDAI

	Mean average PCDAI	Median	Range
Short stature	179.5	175	169-199
Growth retardation	153	141.5	113-219
Normal growth	141	142.5	107-178

These differences were not significant.

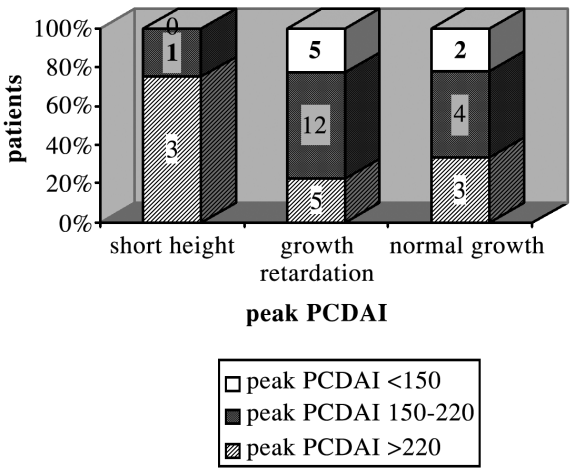

Figure 1. Comparison of peak PCDAI in patients with growth failure and patients with normal growth.

(mean: 3.9 years; median: 3 years). The influence of the daily dosage of corticosteroids is summarized in Table 3. Results were not significant ($p<0.05$).

There was no significant difference regarding growth outcome comparing daily to alternate-day corticosteroid therapy (Table 4).

Serum IGF-1 in blood was only examined in 10 patients retrospectively: 4 had finished growth (Tanner pubertal stage V) at the time of the IGF-1 determination, whereas pubertal stages of the other 6 patients were I-IV. All these patients showed IGF-1 values ranging from 5th to 95th percentile with normal age-related values.

Thirteen patients needed a surgical procedure (Table 5). Postoperative growth rate increased in 6 cases. In a 13-year-old boy with short stature, growth velocity rose from <3rd percentile to the 50th

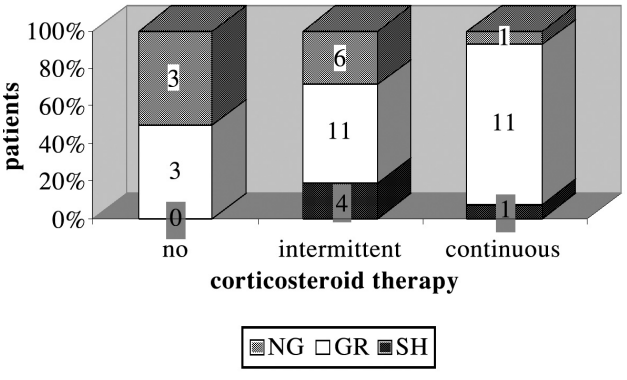

Figure 2. Relation between growth failure and corticosteroid therapy.

Table 3. Relation between growth failure and daily dosage of corticosteroids in 34 patients

	Mean mg/kg/d (mg/m²/d)	Median mg/kg/d (mg/m²/d)	Range mg/kg/d (mg/m²/d)
Normal growth	0.14 (3.7)	0.12 (2.4)	0.04-0.27 (0.8-8.4)
Short stature	0.25 (6.7)	0.24 (7.4)	0.13-0.36 (2.3-10.8)
Growth retardation	0.21 (5.7)	0.21 (5.7)	0.06-0.37 (1.2-9.8)

percentile. In 5 patients with growth retardation (13 to 17 years old, median: 15 years), growth rate increased. In the one-year postoperative observation period, growth rate showed an increase of 7 to 25 percentile (median: 15 percentile) in these 5 patients. The results were not significant.

To investigate the influence of disease activity on growth, detailed data of patients with short stature either at the time of diagnosis and/or at the time of the study were ascertained. Evaluation of patients with short stature within the observation period led to the following findings:

At the time of diagnosis of CD, 5 patients had short stature. At this time, none of them had received corticosteroids. Disease activity varied from low to moderate levels (PCDAI values of these patients ranged from 110 to 220, mean: 169).

During the observation period, the growth rate in 2 of 5 patients improved and height became normal. The PCDAI at the beginning of the observation period (mean: 130) and at the time of the study (mean: 141) showed a low activity index. Both patients were treated with corticosteroids (prednisolone and prednisone, mean daily dosage 0.19 mg/kg/d).

There was no growth improvement in 3 patients with short stature at the time of the diagnosis and height remained short during the disease period. At the beginning of the observation period, PCDAI was moderate (mean: 208). At the time of the investigation and examination of uGH, PCDAI was moderate (mean: 169) as well. These patients were undergoing daily corticosteroid treatment (prednisolone and prednisone; mean daily dosage 0.23 mg/kg/d).

In 2 patients, growth was impaired during the observation period, so that height decreased from normal to short stature. PCDAI at the beginning of the observation period was low (mean: 133) and revealed moderate activity (mean: 190). Both patients received corticosteroids (prednisolone and prednisone, mean daily dosage: 0.27 mg/kg/d).

Bone age of 35 patients was obtained during the observation period. Bone age was equivalent to chronological age in 11 patients of the observed patient group, while bone age was retarded in 24 patients. Bone age retardation ranged from 1.5 to 6.5 years. In the group showing bone age retardation, 5 patients had short stature, 16 had growth retardation and 3 had normal growth.

Twenty-one patients with bone age retardation were undergoing corticosteroid treatment. Two patients with growth retardation and 1 patient with normal growth showed bone age retardation without undergoing corticosteroid treatment (Table 6).

The fact that short stature was found in patients at the time of the diagnosis of CD before undergoing corticosteroid treatment and the known suppressive side effects of chronic inflammation on growth led to the presumption that disease activity is a major factor responsible for growth failure in children and adolescents with CD. To confirm this theory, we compared the data of patients without corticosteroid treatment during the observation period to highlight the impact of disease activity on growth.

Although the observed number of patients was low, normal growth was related to low disease activity when comparing patients without corticosteroid treatment whereas impaired growth was related to higher disease activity. Disease activity is an influencing factor of impaired growth in children and adolescents with CD that should not be underestimated.

Table 4. Relation between growth failure and alternate-day corticosteroid treatment

	Daily corticosteroid therapy	Alternate-day corticosteroid therapy
Normal growth n=7	2	5
Short stature n=5	2	3
Growth retardation n=22	10	12

Table 5. Growth rate in 13 patients before and after resection of inflammatory bowel segments

	Normal growth	Short height	Growth retardation
Before surgery	2	2	9
After surgery	8	1	4

Table 6. Mean bone age retardation

	Short stature		Growth retardation		Normal growth	
	CS treatment	No CS	CS treatment	No CS	CS treatment	No CS
Number of patients	5	-	14	2	2	1
Mean bone age retardation (years)	4.3	-	2.4	1.75	2	2

CS: Corticosteroid.

DISCUSSION

Evaluating the correlation between uGH secretion and growth failure in children and adolescents with CD, growth failure in these patients is not based on GH deficiency. There is also no correlation between growth failure and IGF-1 levels.

Determination of uGH by immunoradiometric assay is a valid, noninvasive and simple screening method to detect GH deficiency (20-23). For variability in GH excretion, it is necessary to determine uGH on several days (24). In patients with renal insufficiency, uGH is not a reliable parameter for hypothalamic-pituitary dysfunction, so renal function has to be supervised (25). Using the ratio of uGH to creatinine, the pubertal peak of GH production is blunted. uGH secretion depends on pubertal status (19, 26-28).

In our study, several patients had already finished puberty at the time of uGH examination. Therefore, the interpretation of our data is limited. In some patients only IGF-1 levels were examined.

Hormonal disorders like GH deficiency or hypothalamic-pituitary dysfunction are controversially discussed as a reason for growth failure in patients with chronic inflammatory bowel disease (10-15). In individual cases of patients with chronic inflammatory bowel disease, an altered GH secretion was found (14, 29). Investigations of a large number of patients suggested secondary hypopituitarism in chronic inflammatory bowel disease (12). The investigation of uGH in children with chronic inflammatory bowel disease by Braegger (10) showed results comparable with ours.

Use of corticosteroid therapy to reduce disease activity (30) is only one factor for growth failure in patients with CD. The impact of daily corticosteroid dosage on growth must be interpreted in correlation with disease activity, respectively PCDAI. In patients with growth failure, daily corticosteroid dosage was higher than in patients with normal growth.

Slonim et al. (17) demonstrated that improved growth can be obtained at the beginning of corticosteroid treatment by controlling the underlying disease. Bone age acceleration might be another possible factor explaining this phenomenon. Six of our patients (18%) showed the same occurrence.

Regarding patients with alternate versus daily corticosteroid treatment, there were more patients with normal growth in the alternate-day group. Beneficial effects of alternate day versus daily corticosteroid therapy concerning growth have been largely discussed (31-35). Disease activity is a major factor influencing growth failure in children and adolescents with CD.

Although the circumscribed number of analyzed parameters especially in patients without corticosteroid therapy must be considered, disease activity in patients with short stature seems to be higher than in patients with growth retardation versus low disease activity in patients with normal growth. In CD patients under steroid treatment, normal growth and low activity were correlated with low daily corticosteroid dosage, while growth failure and moderate activity were combined with higher daily corticosteroid dosage.

Griffiths et al. (36) revealed in 100 children with CD that linear growth velocity is mainly based on the severity of gastrointestinal symptoms that influence the PCDAI according to Harms (18).

If indicated, surgical intervention and resection of inflamed bowel sections may have beneficial effects on growth in CD patients when performed before epiphysial closure. After surgery, 55% of our patients with growth failure revealed improved growth with increased growth rate and a decrease in PCDAI. Discussion regarding surgical intervention to improve growth in CD patients has been controversial (37), with conflicting results after surgical intervention (37-39).

This study was performed to investigate growth and growth velocity in children and adolescents with CD and to correlate it with GH secretion. In the observed patient group, growth failure was not related to uGH secretion but to the disease activity index.

Corticosteroid therapy was not the only factor responsible for growth failure in children and adoles-

cents with CD. If corticosteroid therapy becomes necessary, it is advisable to choose the lowest and shortest therapeutical dosage. Treatment with mesalazine and sulfasalazine, azathioprine, infliximab and others might have beneficial effects in reducing corticosteroid dosage and disease activity (30, 40, 41). Alternate-day treatment is used prior to daily corticosteroid therapy after resolving episodes of acute exacerbation.

When indicated, surgical intervention can be effective in both reducing the activity of inflammation and improving growth in children and adolescents with CD.

There are only a few studies focusing on GH treatment in patients with CD with beneficial effects on growth (16, 42). A preliminary study of GH therapy for adult CD patients showed reduced disease activity and a significant increase in IGF-1 levels (17). A pilot study of recombinant GH treatment in seven children with CD and short stature revealed no significant growth stimulation in these patients. IGF-1 levels correlated with height velocity. The detailed impact of GH on disease activity indicated by a PCDAI score was not investigated in this study (43). Further detailed studies of GH treatment for CD should be considered. Nevertheless, GH therapy for growth-impaired but not deficient children and adolescents with CD should only be conducted in well-monitored trials.

REFERENCES

1. Kemp SF, Elders MJ, Fiser RH Jr, Butenandt O. Disorders of growth. In: Eichenwald HF, Ströder J, eds. Current therapy in pediatrics. 2nd ed. Toronto: BC Decker Inc., 1989; 199-201.
2. Ballinger A. Fundamental mechanisms of growth failure in inflammatory bowel disease. Horm Res 2002; 58: 7-10.
3. Barton JR, Ferguson A. Failure to record variables of growth and development in children with inflammatory bowel disease. Brit Med J 1989; 298: 865-6.
4. Bresson JL, Schmitz J. Malnutrition in Crohn's disease: substrate deficiency or misuse. Horm Res 1992; 38: 76-8.
5. Cezard JP, Touati G, Alberti C, et al. Growth in paediatric Crohn's disease. Horm Res 2002; 58: 11-5.
6. Charron M. Inflammatory bowel disease in pediatric patients. Q J Nucl Med 1997; 41: 309-20.
7. Ferguson A, Glen M, Ghosh S. Crohn's disease: nutrition and nutritional therapy. Baillieres Clin Gastroenterol 1998; 12: 93-114.
8. Griffiths AM. Crohn's disease in adolescents. Baillieres Clin Gastroenterol 1998; 12: 115-32.
9. Kirschner BS. Permanent growth failure in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1993; 16: 368.
10. Braegger CP, Torresani T, Murch SH, et al. Urinary growth hormone in growth-impaired children with chronic inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1993; 16: 49-52.
11. Chong SK, Grossman A, Walker-Smith JA, Rees LH. Endocrine dysfunction in children with Crohn's disease. J Pediatr Gastroenterol Nutr 1984; 3: 529-34.
12. Farthing MJ, Campbell CA, Walker-Smith J, et al. Nocturnal growth hormone and gonadotropin secretion in growth retarded children with Crohn's disease. Gut 1981; 22: 933-8.
13. Kirschner BS, Sutton MM. Somatomedin-C levels in growth-impaired children and adolescents with chronic inflammatory bowel disease. Gastroenterology 1986; 91: 830-6.
14. Ogura T, Kageyama J, Itano Y, et al. Crohn's disease associated with growth hormone secretory dysfunction. Intern Med 1995; 34: 112-7.
15. Tenore A, Berman WF, Parks JS, Bongiovanni AM. Basal and stimulated serum growth hormone concentrations in inflammatory bowel disease. J Clin Endocrinol Metab 1977; 44: 622-8.
16. Henker J. Therapy with recombinant growth hormone in children with Crohn's disease and growth failure. J Pediatr 1996; 12: 1066-7.
17. Slonim AE, Bulone L, Damore MB, et al. A preliminary study of growth hormone therapy for Crohn's disease. N Engl J Med 2000; 342: 1633-7.
18. Harms HK, Blomer R, Bertele-Harms RM, et al. A paediatric Crohn's disease activity index (PCDAI). Is it useful? Acta Paediatr Suppl 1994; 395: 22-6.
19. Main K, Jarden M, Angelo L, et al. The impact of gender and puberty on reference values for urinary growth hormone excretion: a study of three morning urine samples in 517 healthy children and adults. J Clin Endocrinol Metab 1994; 79: 865-71.
20. Fortes ES, Chacra AR, Kunii HS, et al. Nocturnal urinary growth hormone excretion as a criterion for growth hormone deficiency. Braz J Med Biol Res 1995; 28: 433-8.
21. Georges P, Liefooghe J, Ponchaux D, et al. Urinary growth hormone excretion: results of a multicenter study in France. Horm Res 1997; 47: 30-7.
22. Okuno A, Yano K, Itoh Y, et al. Urine growth hormone determinations compared with other methods in the assessment of growth hormone secretion. Acta Paediatr Scand 1987; 337: 74-81.
23. Walker JM, Wood PJ, Williamson S, et al. Urinary growth hormone excretion as a screening test for growth hormone deficiency. Acta Paediatr Jpn 1988; 30: 35-8.
24. Thalange NK, Gill MS, Gill L, et al. Infradian rhythms in urinary growth hormone excretion. Clin Endocrinol Metab 1996; 81: 100-6.
25. Turner G, Skinner A, Woodhead JS. Urinary growth hormone measurements in children with renal insufficiency. Ann Clin Biochem 1993; 30: 540-4.
26. Bona G, Petri A, Rapa A, et al. The impact of gender, puberty and body mass on reference values for urinary growth hormone (GH) excretion in normally growing nonobese and obese children. Clin Endocrinol 1999; 50: 775-81.
27. Castro C, Trivin C, Souberbieille JC, et al. Growth hormone deficiency: permanence and diagnosis in young adults. Horm Res 2002; 58: 165-71.
28. Toublanc JE. Modifications of growth hormone secretion during female puberty. Ann N Y Acad Sci 1997; 816: 60-75.

29. Kotake M, Nakai A, Mokuno T, et al. Short stature due to growth hormone deficiency associated with Cushing's disease and ulcerative colitis. Horm Metab Res 1996; 28: 565-9.
30. Rosenthal SR, Snyder JD, Hendricks KM, Walker WA. Growth failure and inflammatory bowel disease: approach to treatment of a complicated adolescent problem. J Pediatr 1983; 72: 481-9.
31. Broyer M, Guest G, Gagnadoux MF. Growth rate in children receiving alternate-day corticosteroid treatment after kidney transplantation. J Pediatr 1992; 120: 721-5.
32. Curtis JJ, Galla JH, Woodford SY, et al. Comparison of daily and alternate-day prednisone during chronic maintenance therapy: a controlled crossover study. Am J Kidney Dis 1981; 1: 1166-71.
33. Hokken-Koelega AC, de Muinck Keizer-Schrama SM, Drop SL. Effects of alternate-day or daily prednisone treatment on GH and cortisol levels in growth retarded children after renal transplantation. J Pediatr Endocrinol 1994; 7: 119-25.
34. Hyams J, Carey D. Corticosteroids and growth. J Pediatr 1988; 113: 249-54.
35. Polito C, Oporto MR, Totino SF, et al. Normal growth of nephrotic children during long-term alternate-day prednisone therapy. Acta Paediatr Scand 1986; 75: 245-50.
36. Griffiths AM, Nguyen P, Smith C, et al. Growth and clinical course of children with Crohn's disease. Gut 1993; 34: 939-43.
37. McLain BI, Davidson PM, Stokes KB, Beasley SW. Growth after gut resection for Crohn's disease. Arch Dis Child 1990; 65: 760-2.
38. Kirschner BS, Klich JR, Kalman SS, et al. Reversal of growth retardation in Crohn's disease with therapy emphasizing oral nutritional restitution. Gastroenterology 1981; 80: 10-5.
39. Kirschner B. Nutritional consequences of inflammatory bowel disease on growth. J Amer Coll Nutr 1988; 7: 301-8.
40. Borrelli O, Bascietto C, Viola F, et al. Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. Dig Liver Dis 2004; 36: 342-7.
41. Newby EA, Sawczenko A, Thomas AG, Wilson D. Interventions for growth failure in childhood Crohn's disease. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD003873. DOI: 10.1002/14651858.CD003873.pub2
42. Chen K, Nezu R, Inoue M, et al. Beneficial effects of growth hormone combined with parenteral nutrition in the management of inflammatory bowel disease: an experimental study. Surgery 1997; 121: 212-8.
43. Calenda KA, Schornagel IL, Sadeghi-Nejad A, Grand RJ. Effect of recombinant growth hormone treatment on children with Cohn's disease and short stature: a pilot study. Inflamm Bowel Dis 2005; 11: 435-41.