Both acute and chronic diseases can affect nutritional status and growth. Acute disease exerts reversible effects on rate of weight gain whereas chronic disease may result in changes in weight and height gain with potential long-lasting effects including poor response to disease treatment and reduced final adult height. Nutritional support is needed in many different clinical conditions ranging from children with anorexia associated with acute infectious disease to malnourished children with chronic disease. Administration of appropriate nutritional support is conditioned by the understanding of the multiple changes that take place in dietary intake, metabolic rate and changes in physical activity. Proper nutritional support should both prevent weight loss in the short term and promote appropriate growth in the long term. Chronic disease may also affect pubertal progress which in turn may have led to a number of effects including poor growth. This chapter presents a selection of last year’s publications that focused on the nutritional support and growth in several of the most common chronic diseases of children.
Innate dysfunction promotes linear growth failure in pediatric Crohn’s disease and growth hormone resistance in murine ileitis

D’Mello S 1 , Trauernicht A 1 , Ryan A 1 , Bonkowski E 1 , Willson T 1,3 , Trapnell BC 2 , Frank SJ 4 , Kugasathan S 5 , Denson LA 1,3

1 Gastroenterology, Hepatology, and Nutrition, Cincinnati Children’s Hospital Medical Center and the University of Cincinnati College of Medicine, University of Cincinnati, Cincinnati, OH, USA; 2 Pulmonary Biology, Cincinnati Children’s Hospital Medical Center and the University of Cincinnati College of Medicine, University of Cincinnati, Cincinnati, OH, USA; 3 Department of Cancer and Cell Biology, University of Cincinnati, Cincinnati, OH, USA; 4 Department of Medicine, University of Alabama at Birmingham School of Medicine, and Medical Service, Birmingham VA Medical Center, Birmingham, AL, USA; 5 Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

Inflamm Bowel Dis 2012; 18: 236–245

**Background:** A previous study by the same authors suggested that patients with elevated granulocyte macrophage colony-stimulating factor autoantibodies (GM-CSF Ab) are more likely to experience complicated ileal disease requiring surgery. The aim of this report was to investigate any association between GM-CSF Ab and CARD15 risk allele (C15+GMAb+) with growth failure in CD, and growth hormone (GH) resistance in a model of murine ileitis.

**Methods:** 229 children with Crohn’s disease (CD) recruited at two sites had CARD15 genotype, serum GM-CSF Ab, GH-binding protein (GHBP), height (HtSDS) and weight (WtSDS) z-scores evaluated at diagnosis. There were 45 patients with both a CARD15 risk allele and elevated GM-CSF Ab (C15+GMAb+) and 184 patients with one or neither, and served as controls. Age at diagnosis, age at blood sample collection, gender, and frequency of moderate-to-severe disease activity at diagnosis were similar between the groups. Ileitis was induced in CARD15-deficient mice by GM-CSF neutralization and NSAID exposure. Hepatic GH receptor (GHR) abundance and GH-dependent Stat5 activation were determined by Western blot and IGF-1 mRNA expression by realtime PCR.

**Results:** Patients with both elevated GM-CSF Ab/CARD15 have reduced mean HtSDS (–0.48) at diagnosis compared to –0.07 in the disease control cohort (p < 0.05). The proportion of growth retardation (HtSDS ≤ –1) and growth failure (HtSDS ≤ –1.8) were higher in the C15+GMAb+ group (38 and 16%, respectively) when compared to controls (18 and 6%). No difference was found in WtSDS between groups. Circulating GHBP, as a surrogate indicator for tissue GHR abundance, was significantly decreased in the C15+GMAb+ group. In univariate analysis, the C15+GMAb+ state was strongly associated with small bowel location. The C15+GMAb+ state was not associated with WtSDS. In stepwise multivariate analysis, the inclusion of small bowel location reduced the effect of C15+GMAb+ state upon HtSDS, while the inclusion of WtSDS reduced the effect of small bowel location upon HtSDS. Hepatic GHR abundance and GH induction of Stat5 tyrosine phosphorylation and IGF-1 mRNA expression in male CARD15-deficient mice with ileitis was reduced.

**Conclusion:** The study showed that defects in innate immunity that are due to the presence of GM-CSF Ab in the CARD15-deficient host are associated with growth impairment in CD and hepatic GH resistance in murine ileitis. Growth failure in patients with CD and GH resistance in the animal model occurred in the absence of differences in inflammation or weight, suggesting a specific effect of the C15+GMAb+ state.
Several reports have investigated the possible mechanisms implicated in growth impairment in children with CD. However, many gaps still exist in our knowledge of this important complication. Studies have consistently shown that proximal small bowel disease location is associated with reduced linear growth [1, 2]. Male gender has also been associated with a predisposition to reduce linear growth [1, 2]. In this study, growth impairment in patients and GH resistance in the animal model occurred in the absence of differences in inflammatory cytokines (TNF-α and IL-6) or weight between two groups. Defective barrier function in small intestine has been suggested to directly induce GH resistance and growth failure. The authors highlight that in IBD, patient-dependent factors may also modulate growth independent of inflammation. This link between the gastrointestinal system and growth may also exist in conditions other than IBD.

**Serum antibodies and anthropometric data at diagnosis in pediatric Crohn’s disease**

Trauernicht AK, Steiner SJ

Division of Pediatric Gastroenterology/Hepatology/Nutrition, James Whitcomb Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, IN, USA

*Dig Dis Sci* 2012; 57: 1020–1025

**Background:** Patients diagnosed with IBD have variable immune responses to microbial antigens including the formation of antibodies to *Escherichia coli* outer-membrane protein C (OmpC) and *Saccharomyces cerevisiae* (ASCA), and autoantigens to perinuclear antineutrophil antibody (pANCA)/neutrophil-specific nuclear autoantibodies (NSNA). These serum immune responses may correlate with the location of the disease and may be used to predict disease progression. An increased number of serum immune responses and an increased level of response are positively correlated with the severity of the disease. In this research the authors evaluated serum immune responses and anthropometric measurement at the time of initial diagnosis for pediatric CD patients.

**Methods:** This retrospective report looked at height and weight z-score in 102 children (mean age 11.9 years) with CD before diagnosis and compared the anthropometric data among groups according to presence of specific antibodies at time of diagnosis.

**Results:** The authors showed that the mean weight and height z-score were lower in subjects with positive ASCA titers than in patients without any antibodies present.

**Conclusion:** The newly diagnosed CD patients with positive ASCA antibodies had lower mean height and weight z-scores. The authors claimed that some groups of children with CD can be at greater risk of growth impairment before diagnosis.

**Comments** This is the first report which examines the correlation between growth data at the time of diagnosis and serum immune responses in children with IBD. Although it is possible that this information may allow improvement in tailoring of therapy to optimize growth outcome in an individualized manner, there is a need to perform some longitudinal studies to confirm this impression. These data also highlight the need to a better understanding of the interaction between circulating markers of inflammation and the endocrine and paracrine control of growth.
Pharmacokinetic Study

Mathematical modeling to restore circulating IGF-1 concentrations in children with Crohn’s disease-induced growth failure: a pharmacokinetic study

Rao A1, Standing JF2, Naik S1, Savage MO3, Sanderson IR1

1Centre for Digestive Diseases, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, London, UK; 2Infectious Diseases and Microbiology Unit, Institute of Child Health, University College London, London, UK; 3Centre for Endocrinology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, London, UK

BMJ 2013; 3: 1–11

Background: Around a third of the children with CD experience impairment in linear growth, caused in part by undernutrition and in part by the direct effects of inflammation on growth. Children with active CD have high cytokine levels and low IGF-1. In vitro studies have shown a strong link between inflammatory cytokines, IGF-1 and poor growth and reported of a state of functional GH insensitivity secondary to decreased response of IGF-1 to GH. Control of inflammation/significant reduction in cytokine levels and subsequent increase in IGF-1 hence are the first steps in improving growth. However, in some of children, inflammation remains intractable despite use of advanced therapy and there is no agreed growth-promoting treatment for them. Recently, recombinant human IGF-1 (rhIGF-1) has been used as a growth-promoting therapy for children with GH insensitivity syndrome. This group of researchers hypothesized that IGF-1 concentration in children with active CD and poor linear growth could be restored by administration of rhIGF-1. The difficulty is that restoring the IGF-1 level within a normal range is not straightforward and high and sustained IGF-1 levels over time have been associated with an increased incidence of colon cancer in adults with acromegaly. This could, in theory, represent an additional hazard for children with CD, already exposed to chronic inflammation, also a risk factor for intestinal cancer. The authors postulate that developing a mathematical model for IGF-1 treatment may better define the dosing regimen which restores IGF-1 concentration to a normal range without the further risk of cancer.

Methods: This was a pharmacokinetics intervention study in 8 children over 10 years with active CD (C-reactive protein >10 mg/l or erythrocyte sedimentation rate >25 mm/h) and height velocity SDS < -2 SDS. Subcutaneous rhIGF-1 (120 μg/kg) per dose was given over two admissions: the first as a single dose and the second over 5 days as twice-daily doses. The primary endpoint was a significant increase in serum IGF-1.

Results: Twice-daily subcutaneous rhIGF-1 led to a significant increase of circulating IGF-1 over a sustained period with low variability between peaks. In covariate analysis, disease activity significantly reduces endogenous production of IGF-1.

Conclusion: IGF-1 dosing using a mathematical model including age, weight and disease activity, normalized the IGF-1 level in over 95% of children with CD and achieved levels below +2.5 SDS of normal population mean, a level not associated with cancer risk.
Comments

The study is the first interventional study on IGF-1 treatment in children with CD. The authors used a mathematical model to determine the dose of rhIGF-1 that maintained serum IGF-1 level within the physiological range. The dosing schedule which reflects the age dependency of circulating IGF-1 in normal children and the state of GH resistance in children with CD was $21 + 1 \mu g/kg/PCDAI$ point for the 10- to 12-year-olds and $41 + 1.4 \mu g/kg/PCDAI$ point for the 12- to 14-year-olds. Growth-promoting therapies such as rhGH, rhIGF-1 or the two in combination are currently being explored as possible methods of promoting growth in children with disease-related growth retardation and this study may assist in the design of future clinical trials. The study also showed that the extent of protein-losing enteropathy measured by fecal α₁-antitrypsin level did not alter IGF-1 or IGFBP-3 levels. Administration of rhIGF-1 to children with a decreased level of IGFBP-3 may lead to increased free IGF-1 but this was not evaluated in this study. However, the authors stated that the level of IGFBP-3 was not severely depressed as it remained with 2 SDs of normal even in the most severely affected cases.

Nutrition and Growth

Clinical progress in the two years following a course of exclusive enteral nutrition in 109 paediatric patients with Crohn’s disease

Cameron FL¹, Gerasimidis K², Papangelou A², Missiou D², Garrick V¹, Cardigan T¹, Buchanan E¹, Barclay AR¹, McGrogan P¹, Russell RK¹

¹Department of Paediatric Gastroenterology, Hepatology and Nutrition, Royal Hospital for Sick Children, Glasgow, UK; ²Life Course Nutrition and Health, Centre for Population and Health Sciences, Institute of Health and Wellbeing, College of Medicine, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK

Aliment Pharmacol Ther 2013; 37: 622–629

Background: Exclusive enteral nutrition (EEN) is increasingly considered an effective initial method of controlling inflammation in children with active CD. This paper investigates the short- and long-term outcome of EEN on both the clinical course of disease and growth indices.

Methods: In this study, case notes of 109 (68 males) newly diagnosed CD patients with a median age 11.2 years who completed an 8-week course of EEN were retrospectively reviewed. Data on demographics, growth, disease characteristics and inflammatory markers (albumin, CRP, ESR and platelets) were collected at EEN initiation and at 1, 2, 6, 12 and 24 months after initiation of therapy.

Results: In total, 65 patients were in remission, 32 improved, and 12 had no improvement after 8 weeks of EEN. By 4 weeks, weight SDS, BMI SDS and all inflammatory markers improved. Relapses occurred in 63/109 (58%) during follow-up and 44/63 (70%) responded to a second course of EEN. Although use of EEN increased height velocity up to 6 months in responders, it was not associated with improvement in HtSDS over 24 months. Use of azathioprine within 6 months of diagnosis also did not show any benefit in terms of improvement height outcomes at 24 months.

Conclusion: An 8-week course of EEN resulted in an improvement in weight parameters up to 2 years but not in height z-score.
Comments

This relatively large retrospective study confirms previous observations that despite disease remission (as assessed by global patient assessment in combination with clinical parameters), improvement in weight and short-term improvement in height velocity, the use of EEN may not be associated with a sustained improvement in HtSDS over the longer term. Thus, there is a need to continue investigating novel forms of growth promotion in these children. The authors also point out that improvement in weight and inflammatory markers was already present by 4 weeks, thus questioning the need for 8 weeks of EEN.

Biologics and Growth

Partial normalization of pubertal timing in female mice with DSS colitis treated with anti-TNF-α antibody

DeBoer MD, Steinman J, Li Y
Division of Pediatric Endocrinology, University of Virginia, Charlottesville, VA, USA
J Gastroenterol 2012; 47: 647–654

Background: Delayed puberty is a common concern for children with IBD, and especially CD, and is associated with inadequate growth, defective bone mineralization and poor self-esteem. Currently, biologic agents are the mainstay in children with more severe forms of IBD resistant to conventional treatment. Biologic agents are engineered proteins which selectively neutralize or block the effects of different cytokines. One of the commonly used agents is infliximab, a monoclonal antibody to tumor necrosis factor-α (TNF-α). Some studies have reported that the use of infliximab is associated with improved growth in children with CD whose disease improves. However, whether infliximab treatment affects the timing of puberty is not yet clear. This experimental study was designed to determine whether TNF-α antibodies normalize pubertal progress and whether infliximab causes any change in the function of the hypothalamic-pituitary-gonad (HPG) axis in female mice with induced colitis.

Methods: Dextran sodium sulfate (DSS) colitis was induced in 23-day-old female mice and the treatment groups were divided into three groups: control + TNF-α antibodies, DSS-induced colitis + control antibodies, and DSS-induced colitis + TNF-α antibodies. All groups were monitored for the timing of vaginal opening until day 33 of life, when they were euthanized for serum and colon collection.

Results: Timing of vaginal opening in DSS + TNF-α and control + TNF-α antibodies was similar and occurred earlier compared with DSS + control antibody group. Also, DSS + TNF-α antibody had a higher LH level after GnRH stimulation and lower systemic interleukin-6 compared to the DSS + control antibody group. No differences were observed in weight gain, growth, or colon histological inflammatory scores between the three groups over the course of the experiment.

Conclusion: The authors demonstrated that treatment with monoclonal antibodies to TNF-α was associated with partial normalization in the timing of pubertal onset in female mice with DSS colitis.
The authors of this study have previously shown that female mice with DSS colitis had a later timing of vaginal opening than food-restricted mice of the same body weight. In the current study they confirmed this finding and showed that this difference persisted in spite of similar weight gain and circulating leptin. The only difference was in the extent of inflammation as assessed by circulating cytokines and gut inflammation. The raised levels of LH in DSS colitis model treated with TNF-α antibodies are intriguing and the authors did not have a good explanation for this. This effect was not observed in the control group suggesting that colitis may sensitize the hypothalamic pituitary axis to GnRH stimulation. The hypothalamic-pituitary-gonadal axis is under negative feedback control by circulating sex steroids and it is possible that the increased responsiveness to GnRH may reflect direct suppression of sex steroid synthesis at the level of the peripheral steroid-secreting organs by the cytokines. The investigators suggest that in humans the use of biologics may be associated with pubertal progress or increased gonadal activity, but this requires further investigation.

Long-term outcome of tumor necrosis factor-α antagonist’s treatment in pediatric Crohn’s disease

Assa A1,4, Hartman C1,4, Weiss B2,4, Broide E3,4, Rosenbach Y1,4, Zevit N1,4, Bujanover Y2,4, Shamir R1,4

1Institute of Gastroenterology, Nutrition and Liver Disease, Schneider Children’s Medical Center, Petach-Tikva, Israel; 2Pediatric Gastroenterology Unit, Edmond and Lily Safra Children’s Hospital, Sheba Medical Center, Tel Hashomer, Israel; 3Pediatric Gastroenterology Unit, Assaf Harofeh Medical Center, Zerifin, Israel; 4Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

J Crohn Colitis 2013; 7: 369–376

Background: The efficacy of infliximab for both induction and maintenance of moderate to severe pediatric CD is widely accredited. However, its effect on optimization of linear growth seems to be variable. Some studies demonstrated a short-term increase in height velocity during infliximab treatment while others showed no significant change during a similar follow-up time. One of the secondary outcomes of this study was to examine the long-term outcome of anti-TNF-α on the growth of children with IBD.

Methods: In this multicenter study, 102 IBD children who received anti-TNF-α therapy at a mean age of 13.4 ± 3.9 years for a median duration of 15 (2–90) months were retrospectively studied. The authors recorded long-term response rates, predictors for loss of response as well as the effect of treatment on anthropometric parameters.

Results: A short-term beneficial response on disease was observed in 91/102 (89%) of the cohort following induction and a prolonged response for more than 6 months occurred in 84/102 (84%). The mean BMI z-score improved significantly in responders (−0.8 to −0.4, p = 0.04) compared to non-responders. A tendency towards enhanced growth velocity was also found in responders compared to non-responders. Only male responders showed a significant increase in height velocity during treatment.

Conclusion: In agreement with the current literature, the study showed that biologic agents were effective and safe in the long term. Furthermore, the clinical response was associated with improved weight and BMI.
The ability of biologic agents to improve growth and growth failure in children with CD continues to be an area of controversial debate. The growth data from this study needed to be interpreted with caution because of a lack of pubertal growth information. In addition, a large proportion of the cohort patients were on glucocorticoids which may also have affected growth.

The effects of anti-TNF-α treatment with adalimumab on growth in children with Crohn’s disease


1 Bone & Endocrine Research Group, Royal Hospital for Sick Children, Yorkhill, Glasgow, UK; 2 Department of Paediatric Gastroenterology & Nutrition, Royal Hospital for Sick Children, Yorkhill, Glasgow, UK; 3 University of Edinburgh, Child Life and Health, Edinburgh, UK; 4 Great Ormond Street Hospital Paediatric Gastroenterology Department, London, UK; 5 Royal Aberdeen Children’s Hospital, Department of Medical Paediatrics, Aberdeen, UK; 6 Bart’s and the London Children’s Hospital, London, UK; 7 Our Lady’s Children’s Hospital Crumlin, Children’s Research Centre, Dublin, Ireland; 8 Royal Manchester Children’s Hospital, Manchester, UK

J Crohn Colitis 2012; 6: 337–344

Background: Adalimumab is a humanized anti-TNF therapy that has been shown to be effective for induction and maintenance of remission for adults with Crohn’s disease (CD). Clinical studies of adalimumab in children are relatively limited; no studies have yet examined the effect of adalimumab on growth. In this multicentre retrospective study the authors assessed the influence of adalimumab therapy on growth and disease activity in children with CD.

Methods: Growth and disease activity of 36 children with CD who started adalimumab at a median age of 14.7 years (11.3–16.8) were collected at 6 months before (T–6), at baseline (T0) and 6 months after (T+6) starting adalimumab.

Results: Remission occurred in 28/36 children (78%). 15 children (42%) demonstrated improvement in their growth, median change in height z-score (ΔHtSDS) increased from –0.3 at T0 to +0.3 at T+6. The improvement in ΔHtSDS was more likely in children who achieved remission (ΔHtSDS) increased from –0.2 at T0 to +0.2 at T+6. In those in pubertal Tanner stage II–III, median ΔHtSDS improved from –0.4 at T0 to +0.2 at T+6. In those with immunosuppression background, ΔHtSDS increased from –0.2 at T0 to +0.1 at T+6. When adalimumab was indicated because of infliximab allergy, median ΔHtSDS increased from –0.3 at T0 to +0.3 at T+6. The change in height SDS also improved in children who were on prednisolone when starting adalimumab.

Conclusion: This study showed that the clinical response to adalimumab therapy was associated with an improvement in linear growth in children with CD.

Comments: The results of this study suggest that the use of adalimumab can be helpful in terms of linear growth improvement in children with CD. By looking at the results, growth improvement in this cohort may be credited to both controlling of inflammation and progression of puberty, as the increase in ΔHtSDS was more likely in those who achieved remission as well as in pre-puberty and in-puberty children. However, it is uncertain yet from this study and other studies whether this short-term improvement in linear growth is maintained over a longer period and whether there is an improvement in final height, which is the ultimate objective in any patients with growth impairment. It is anticipated that future efforts will be directed to also explore the effect of biologics on final height in adults with childhood-onset CD.
Growth in children receiving contemporary disease-specific therapy for Crohn’s disease

Malik S1,2, Mason A1, Bakhshi A3, Young D4, Bishop J2, Garrick V2, McGrogan P5, Russell RK2, Ahmed FS1

1Department of Child Health, University of Glasgow, Bone and Endocrine Research Group, Royal Hospital for Sick Children, Yorkhill, Glasgow, UK; 2Department of Paediatric Gastroenterology and Nutrition, University of Glasgow, Royal Hospital for Sick Children, Yorkhill, Glasgow, UK; 3School of Mathematics and Statistics, University of Glasgow, Glasgow, UK; 4Department of Statistics and Modelling Science, University of Strathclyde, Glasgow, UK

Arch Dis Child 2012; 97: 698–703

Background: Data from recent studies have shown that despite improvements in therapy, nutrition and a decrease in the use of glucocorticoid (GC) therapy, there is a persisting concern that poor growth still exists. The mechanism of growth failure in children with IBD is multifactorial and includes poor nutrition, chronic inflammation, and the prolonged use of steroids. These factors interfere with growth through disturbance of the GH-IGF axis at the peripheral or central level. Growth improvement through manipulation of the GH-IGF axis may offer a therapeutic option which needs further exploration. Nonetheless, the assessment of prevalence of growth impairment in children receiving advanced therapy may be needed before launching studies of alternative forms of growth-promoting endocrine therapy.

Methods: The study is a retrospective analysis of growth and therapy data of 116 children with CD (mean age at diagnosis 10.8 years), at time of diagnosis (T0), at 1 (T1), 2 (T2) and 3 years (T3) after diagnosis and at maximum follow-up (MF).

Results: There was a significant reduction in mean height z-score (HtSDS) between T0 and T1. No significant difference was observed in HtSDS after that. Moreover, no change was observed in mean ΔHtSDS at T1, T2, T3 and MF. However, there was a significant increase in mean HVSDS (10th, 90th) from –1.4 (–7.4 to 7.4) to –0.6 (–7.5 to 6.1) between T1 and T2, from –0.6 to –0.1 between T2 and T3 and from –0.1 to 0.6 between T3 and MF. There was a negative association between HtSDS and the use of prednisolone, azathioprine, methotrexate and weight SDS. A negative association was also found between ΔHtSDS and use of prednisolone and a positive association between HVSDS with age and WtSDS.

Conclusion: The authors concluded that short stature and slow growth continue to be encountered in a subgroup of children with CD despite advances in therapy. They suggest that change in HtSDS may be a more robust parameter in children with chronic disease when there is a high prevalence of children of peripubertal age.

Comments

Although the majority of children with CD are not particularly short and there is an improvement in growth during the first year after diagnosis, this study provides clear evidence that despite advances in therapy, short stature and slow growth continue to be encountered in a subgroup of children with CD. The mean HtSDS of our population as well as the percentage of children with HtSDS <–2 were similar to those reported in other recent studies. Our observation that HtSDS did not improve in spite of significant improvement in HVSDS is similar to the findings in previous reports and may suggest that the reduction in growth deceleration, as reflected by improving HV, is not sufficient to improve overall height but simply prevents any further deterioration in height. Many studies of growth in children with a complex condition such as IBD explore the association between growth and disease factors, including drug therapy. The study highlights that investigation of such associations need a long follow-up as the choice and duration of therapy for IBD depends on the acute presentation and subsequent progress.
Overall Commentary: Over the last year a number of studies have evaluated growth impairment as well as the outcomes of therapeutic intervention aimed to improve growth in children with IBD. Given the persistent deficit in height in children with IBD, there is a need for further improvements in therapy that focus on growth. Clinicians and investigators need to pay more attention to puberty aspects, especially in this group of conditions which often present during the peripubertal period, since a substantial amount of growth occurs during puberty. It has been suggested that pubertal development and progress is not significantly affected in children with IBD treated with the current therapeutic modalities. It would, therefore, be useful to investigate whether growth during puberty is optimal or not. The studies that have been performed over the last year also highlight the large variation amongst investigators as to how they describe growth and pubertal progress. There is a need for greater consistency and harmony in reporting results. Finally, these studies cannot be performed without close collaboration between a multidisciplinary group of experts from fields that include anthropometry, endocrinology, nutrition medicine and gastroenterology.

Acknowledgements: M.A.A is funded by the Higher Education Ministry of Libyan Government. S.F.A is supported by the Chief Scientist Office of Scotland and ISPEN.

Cystic Fibrosis

Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis

Yen EH¹, Quinton H², Borowitz D³

¹Department of Pediatrics, Harvard Medical School, Division of Gastroenterology and Nutrition, Children’s Hospital Boston, Boston, MA, USA; ²Dartmouth Medical School, Lebanon, NH, USA; ³Department of Pediatrics, State University of New York at Buffalo School of Medicine and Biomedical Sciences, Women and Children’s Hospital of Buffalo, Buffalo, NY, USA

J Pediatr 2013; 162: 530–535.e1

Aims: The aim of the current study was to evaluate the impact of nutritional status early in life on the timing and velocity of height growth, lung function, complications of CF, and survival through age 18 years.

Methods: The study included the data extracted from the CFF Patient Registry for patients born between 1989 and 1992. The patients were stratified by peak weight-for-age percentile (WAP) at age 4–5 years into 4 groups: <10th percentile, 10th to <25th percentile, 25th to <50th percentile, and ≥50th percentile. Outcomes were assessed through 2009 at the age of 18 years and comparisons between height-for-age percentile (HAP), predicted forced expiratory volume in 1 s (FEV1)% and survival were made across strata. Other outcomes included BMI, pulmonary exacerbations, cystic fibrosis-related diabetes mellitus (CFRD), Pseudomonas aeruginosa infection, and survival.

Results: The cohort consisted of 3,142 patients. On average, patients with CF who achieved a WAP >50% at age 4 years reached a much higher HAP early on in life and maintained their height advantage into adulthood over the group of patients with CF and a WAP <50% at age 4 years. This gain in HAP by WAP at age 4 years was incremental and was sustained throughout childhood, in-
indicating a strong association between WAP at age 4 years and height throughout life. Each higher WAP group had incrementally better FEV1% predicted throughout the period of observation, but the greatest difference in FEV1% predicted occurred between the WAP <10% and 10–25%. The rate of decline in FEV1% predicted was similar across all WAP groups until age 18–19 years. There were 294 deaths during the observational period; cumulative survival over the whole follow-up period in the entire population was 91%. Survival was highest on average in patients with better nutritional status at age 4 years. Higher WAP and HAP at age 4 years predicted a higher rate of survival into adulthood (p < 0.0001). CF-related diabetes, acute exacerbations, and hospital days by age 18 years were also strongly associated with WAP at age 4 years.

**Conclusions:** Patients in the highest weight and height percentiles at age 4 years achieved better heights by 18 years, had fewer pulmonary exacerbations, spent fewer days in the hospital, and had improved survival.

---

**Growth during puberty in cystic fibrosis: a retrospective evaluation of a French cohort**

Bournez M¹, Bellis B², Huet F¹

¹Department of Paediatrics, University Hospital, Dijon, France; ²National Institute of Demographic Studies, Paris, France

*Arch Dis Child* 2012; 97: 714–720

**Aims:** The primary outcome of the study was to assess the longitudinal growth pattern in a large cohort of French patients with CF and to determine the extent to which growth during puberty affects final height. In addition, the study aimed to explore the potential relationships between growth, nutritional status and respiratory function in children with CF.

**Methods:** The study included the data from the French CF registry collected between 1999 and 2004. Eight groups of patients aged 8–15 in 1999 were selected. Individual characteristics (age, height, weight) and lung function, evaluated by FEV1 were recorded. The means of individual heights in each age group were used to construct the height curves by sex.

**Results:** The study evaluated a sample of 729 children with CF among the 1,108 children born between 1984 and 1991 and followed by the registry from 1999 to 2004. For the 331 girls the height curve was very close to the median curve until the age of 12, when the curve descended to the –1 SD reference curve. The mean z-score of mean height was –0.32 at age 8 and –0.53 at 11 years. The z-score then decreased to a minimum of –0.88 at age 15, and remains under –0.50 after this age. The final height of 160.4 cm was reached at age 19, much later than the age of final height in the reference population which is attained at age 16. The age of pubertal onset was similar to the reference, but the peak height velocity (PHV), although occurring at the same age as in reference girls, was lower, and the pubertal spurt accounted for 16.7% (compared to 18.6% in healthy girls) of the final adult height. The mean height curve for boys (n = 389) showed normal growth until age 14, and then downgraded to the –1 SD of the reference curve. The final height in boys was reached at age 19, similar to the age of final height in healthy boys. The mean final height in boys with CF was less than that in the overall population (z-score –0.73). The age of pubertal onset was similar to that in reference boys (13 years), but the PHV was lower and the pubertal spurt accounted for 15.5% (18.4% in healthy boys) of the final height of CF boys. No correlations were found between BMI and PHV (r = 0.03, p = 0.71 in girls; r = 0.05, p = 0.44 in boys). No relationships were found either between lung function expressed by FEV1 and growth in boys (r = 0.09, p = 0.16), but there was a weak but significant positive relationship between growth and FEV1 (r = 0.17, p = 0.02) in girls.
Conclusions: The longitudinal follow-up of this French cohort of patients showed that the onset of puberty in children with CF was comparable to healthy children, but PHV was decreased and contributed less to the final adult height. The final height was significantly lower than that in the reference population, even though it remained within the normal range. Growth and lung function were not correlated in boys, however there was a weak but significant correlation between lung function and growth in girls, which might be explained by the greater rest energy expenditure in girls than in boys after the pubertal spurt.

Pubertal height velocity and associations with prepubertal and adult heights in cystic fibrosis

Zhang Z, Lindstrom MJ, Lai HJ

1 Departments of Nutritional Sciences, 2 Biostatistics and Medical Informatics, and 3 Pediatrics, University of Wisconsin-Madison, Madison, WI, USA

J Pediatr 2013; 163: 376–382.e1

Aims: Using the US CFF Registry data of patients’ anthropometry and follow-up the authors evaluated the relationship between prepubertal and pubertal growth velocity (timing and magnitude) and final adult height in children with CF.

Methods: Using height measurements, the authors constructed puberty height velocity (PHV) curves for CF patients. Using longitudinal standards of PHV for healthy North American children developed by Tanner and Davies, PHV was classified into normal (PHV neither delayed nor attenuated), delayed (PHV delayed but not attenuated), attenuated (PHV attenuated but not delayed), and delayed and attenuated. CF phenotypes, prepubertal nutritional status and genetic height potential were introduced as variables.

Results: Of the 4,198 individuals with CF born in 1984–1987, 309 died, 951 were lost to follow-up before age 18 years, and 1,076 had <3 height measurements per year during age 10–18 years, leaving 1,862 patients to include in the study. PHV in children with CF occurred later (0.5 years later in boys and 0.6 years later in girls) and showed reduced magnitude (1.1 cm less in boys and 1.3 cm in girls). Results from fitting individual curves revealed that PHV was normal in 60.3%, delayed in 9.4%, attenuated in 20.8%, and delayed and attenuated in 5.3%. In the remaining 4.2%, PHV could not be ascertained. More boys had normal PHV than girls, p = 0.002. PHV magnitude and total gain from height take-off at puberty was different and depended on whether the puberty was delayed and/or attenuated. Considering parental height, 80% of boys with CF and 77% of girls with CF had adult heights below their average parental height percentiles. Multivariate analyses revealed PHV age, PHV magnitude, and prepubertal height at age 7 years were stronger predictors of adult height (all with p < 0.001). Specifically, later PHV was associated with smaller magnitude of PHV but greater adult height. Larger PHV magnitude was associated with greater adult height after adjusting for PHV age.

Conclusions: Using a novel, semi-parametric growth curve model, this study showed that 23% of boys with CF and 30% of girls with CF had impaired PHV magnitude that was below the 5th percentile of healthy children. Besides that, children with CF born in the mid-1980s experienced delayed pubertal PHV compared with healthy children and had lower final height, as the majority (80% of boys and 70% of girls) did not reach their genetic potential. Prepubertal height at age 7 years was found to be a strong determinant of adult height in both sexes. Since the greatest likelihood of achieving optimal growth at age 6 years is through maximizing weight gain during the first years of life, this study further emphasize the importance of maintaining adequate growth through pre-adolescence.
Longitudinal trends in nutritional status and the relation between lung function and BMI in cystic fibrosis: a population-based cohort study

Stephenson AL\textsuperscript{1,4}, Mannik LA\textsuperscript{1}, Walsh S\textsuperscript{1}, Brotherwood M\textsuperscript{1}, Robert R\textsuperscript{1}, Darling PB\textsuperscript{2,4}, Nisenbaum R\textsuperscript{2,4}, Moerman J\textsuperscript{3}, Stanojevic S\textsuperscript{3,4}

\textsuperscript{1}The Adult Cystic Fibrosis Program, St. Michael’s Hospital, Toronto, ON, Canada; \textsuperscript{2}The Keenan Research Centre in the Li Ka Shing Knowledge Institute of St. Michael’s Hospital, Toronto, ON, Canada; \textsuperscript{3}The Research Institute, The Hospital for Sick Children, Toronto, ON, Canada; \textsuperscript{4}Departments of Medicine and Nutritional Sciences and Institute of Health Policy, Management, and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

\textit{Am J Clin Nutr} 2013; 97: 872–877

\textbf{Aims:} The aim of the present study was to investigate the nutritional status evolution during a long-term follow-up of a CF cohort followed at the Adult CF Clinic in Toronto.

\textbf{Methods:} The study examined nutritional status assessed as WHO BMI and the relationship between BMI and lung function in 909 individuals with CF. FEV1 expressed as a percentage of the normal predicted values for height and sex (FEV1\% predicted), height and weight were measured at every clinic visit. The subjects were classified in 4 cohorts based of birth year (<1960, 1960–1969, 1970–1979, >1979) and the BMI was parted according to the year the clinical measurements were taken (<1990, 1991–1999, >2000). Due to the skewed distribution of BMI and age, these variables were log transformed.

\textbf{Results:} The study cohort study included 909 individuals followed from 1985 to 2011. The average BMI increased from 20.7 ± 2.7 before 1990 to 22.3 ± 3.4 in the most recent decade (2000–2011). The proportion of underweight individuals has also decreased from 20.6% before 1990 to 11.1% in the most recent decade. The proportion of adequate-weight subjects slightly decreased (72.4% in 1980s, 72.6% in the 1990s, to 70.5% in the 2000s), whereas the proportion of overweight/obese subjects increased from 7.0% in the 1980s to 15.8% in the 1990s and to 18.4% in the most recent cohort (p trend <0.001). Multivariable models showed that, overall, BMI increased by 0.4%/year from 1985 to 2011. The rate of BMI increase in PS subjects was much greater than in PI subjects (3.8% compared with 0.4%/year, respectively; p < 0.001). The BMI of 651 individuals evaluated between 2000 and 2011 showed that 17% of CF subjects were underweight, 60% had adequate weight, 18% were overweight, and 3.8% were obese. After adjustment for age, height, sex, CFRD, pancreatic status, and birth cohort, lung function showed improvement as BMI increased. The magnitude of FEV1 improvement was different across BMI categories: in the underweight group, a 10% increase in BMI resulted in a 4% relative increase in FEV1, in the subjects within adequate range BMI there was a 5% relative increase in FEV1, and in those overweight there was a 2% increase in FEV1. On average, FEV1 decreased at a rate of 1%/year, and there were no significant differences in the rate of FEV1 decline in the three BMI categories. Other significant independent predictors of FEV1, identified in the multivariable model, included age (older age was associated with lower FEV1\% predicted; p < 0.001), pancreatic status (PS subjects had higher FEV1\% predicted), and the presence of CFRD (CFRD subjects had lower FEV1\% predicted).

\textbf{Conclusion:} This longitudinal, population-based cohort showed a significant shift over a 25-year period in the distribution of BMI in adults with CF. Within a contemporary cohort of individuals with CF, fewer individuals were malnourished and more individuals were overweight compared with 20 years earlier. The study showed that improvements in nutritional status were associated with improvements in lung function which was better in the average BMI subgroup of the CF population.
Stunting is an independent predictor of mortality in patients with cystic fibrosis

Vieni G\textsuperscript{1,2}, Faraci S\textsuperscript{2}, Collura M\textsuperscript{3}, Lombardo M\textsuperscript{2}, Traverso G\textsuperscript{3}, Cristadoro S\textsuperscript{2}, Termini L\textsuperscript{3}, Lucanto MC\textsuperscript{2}, Furnari ML\textsuperscript{3}, Trimarchi G\textsuperscript{4}, Triglia MR\textsuperscript{2}, Costa S\textsuperscript{1,2}, Pellegrino S\textsuperscript{1,2}, Magazzù G\textsuperscript{2}

\textsuperscript{1}Clinical and Biomolecular Hepato-Gastroenterology of Pediatric and Adult Age, University Hospital ‘G. Martino’, Messina Italy; \textsuperscript{2}Pediatric Gastroenterology and Cystic Fibrosis Unit, University Hospital ‘G. Martino’, Messina Italy; \textsuperscript{3}Cystic Fibrosis Regional Centre, 2nd Pediatric Unit, Children’s Hospital ‘Di Cristina’, Palermo, Italy; \textsuperscript{4}Department of Statistics, University of Messina, Messina, Italy

\textit{Clin Nutr} 2013; \textit{32}: 382–385

\textbf{Aims:} The relationship between nutritional status and survival in patients with CF has been much studied. This study aim was to evaluate the relationship between stunting (as a measure of chronic malnutrition) and mortality in a nested case-control CF population cohort.

\textbf{Methods:} This retrospective case-control study included a cohort of 393 CF patients older than 6 years of age, 193 pediatric (less than 18 years) and 200 adult patients followed at the CF Regional Center in Palermo and at the Satellite Center in Messina through December 2007. The study cases included 95 patients who died, 47 children and 48 adults. The controls were 298 alive patients, 146 younger and 152 older than 18 years. Short stature (stunting) was defined by a height <5th percentile. Body wasting was defined by a body mass index (BMI) <10th percentile in pediatric patients, and <18.5 in adult patients.

\textbf{Results:} The prevalence of stunting was 24.4%, similar in males and females (24.5 and 24.3%, respectively). The prevalence of wasting was 35.3%; not significantly higher in females than in males (38.3 and 32.3%, respectively). In the multivariate analysis, stunting, body wasting, and FEV1 significantly predict the risk of mortality. Stunting (OR 2.22; 95\% CI 1.10–4.46), wasting (OR 5.27; 95\% CI 2.66–10.41), and FEV1 <40\% of predicted (OR 10.60; 95\% CI 5.43–20.67) increased the risk of death in this cohort.

\textbf{Conclusions:} In this study, stunting, wasting and FEV1 were independently predictors of mortality risk.

Use of body mass index percentile to identify fat-free mass depletion in children with cystic fibrosis

Engelen MP\textsuperscript{1}, Schroder R\textsuperscript{1}, Van der Hoorn K\textsuperscript{1}, Deutz NE\textsuperscript{1}, Com G\textsuperscript{2}

\textsuperscript{1}Center for Translational Research in Aging and Longevity, Donald W. Reynolds Institute on Aging, University of Arkansas for Medical Sciences, Little Rock, AR, USA; \textsuperscript{2}Pediatric Pulmonology, University of Arkansas for Medical Sciences and Arkansas Children’s Hospital, Little Rock, AR, USA

\textit{Clin Nutr} 2012; \textit{31}: 927–933

\textbf{Aims:} The study aimed to evaluate: (1) the prevalence of underweight [diagnosed by body mass index (BMI) percentile] and free fat mass (FFM) depletion, (2) the association of FFM depletion with changes in body composition and increased morbidity (reduced lung function, loss of bone mineral density), and (3) use of BMI percentiles as predictors of FFM depletion and morbidity.

\textbf{Methods:} 77 children, aged 8–21 years, with CF were evaluated in this retrospective study. Height and weight were obtained and BMI percentiles calculated. Fat-free mass (FFM), fat mass (FM),
bone mineral content (BMC) and density (BMD) were obtained by dual-energy x-ray absorptiometry (DXA).

**Results:** 24 children (31%) were malnourished, as defined by the FFMI and/or BMI% criteria; 16% had low BMI% and low FFMI; 14% had normal BMI and low FFMI (hidden depletion), and 1% had low BMI% and normal FFMI. Overall, 30% of patients were characterized by FFM depletion. The sensitivity of BMI% for detecting FFM depletion was 52% and the specificity was 98%. BMC (percentage of normative data) was reduced in the group with low BMI% and FFMI (p < 0.001) and in the hidden FFMI depletion group (p < 0.05) as compared to the normal BMI% and FFMI group. BMD of the whole-body and spine z-score were lower (p < 0.01) in those with low BMI% and FFM as compared to normal BMI% and FFMI. Below the 20th BMI% the percentage of patients with a BMD z-score <–1 SD increased steeply whereas no differences were found in the percentage of patients with a reduced BMD in the 20–49th BMI% group. FEV1 and forced vital capacity (FVC) were reduced in both the hidden FFM depletion group (p < 0.05) and the low BMI% and FFM group (p < 0.01). FEV1 was significantly correlated with FFMI (% norm, r = 0.39, p < 0.001) and FM (% norm, r = 0.30, p < 0.01) but not with FM/FFM (r = 0.21). With the decline in BMI%, there was also a gradual reduction in mean FEV1. Below the 20th BMI%, mean FEV1 dropped below 80% predicted, a threshold for abnormal lung function in children with CF. Investigation of the BMI% cut-off point that would predict FFM depletion and poor clinical outcome showed a gradual reduction in FFMI% with the decline in BMI%. Below the 20th BMI%, there was a drop in FFMI% below 90% of normative values which corresponds to FFMI <5th percentile. 57% of the patients in the 10–20th BMI% group had FFM depletion, compared to 18% in the 20–30th BMI% group. Nearly all patients (92%) with BMI% <10 were FFM depleted.

**Conclusions:** FFM depletion in children with CF is prevalent and is poorly detected when using the 10% BMI cut-off, indicating that a large share of patients with hidden FFM depletion would have been missed when malnutrition was defined only by these criteria. Low FFM values were associated with reduced lung function and bone mineral loss indicating the clinical importance of measuring body composition in children with CF.

---

**Genetic modifiers of nutritional status in cystic fibrosis**

Bradley GM¹, Blackman SM¹, Watson CP², Doshi VK², Cutting GR¹,²

¹Department of Pediatrics, Johns Hopkins University, Baltimore, MD, USA; ²McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD, USA

*Am J Clin Nutr* 2012; 96: 1299–1308

**Aims:** The study investigated the influence of modifier genes on nutritional status of children with CF.

**Methods:** Longitudinal height and weight data were collected from 2000 to 2010 from the CF Twin-Sibling Study. Family members all shared the same CFTR genotype. BMI and z-scores for weight and height were calculated. A phenotype was derived by calculating the average-per-quarter BMI z-scores from 5 to 10 years of age (BMI- z5to10). Sex, birth cohort, age at CF diagnosis, diagnosis by newborns’ screening, F508del homozygosity, pancreatic insufficiency (PI), history of meconium ileus (MI), presence of a gastrostomy, FEV1_6to10, and insurance type were evaluated for their contributions to variability in BMI- z5to10.

**Results:** Longitudinal height and weight data were collected for 1,124 subjects (130 monozygous twins and 952 siblings) with CF from 800 families. The median height z-score for all included
subjects was −0.58 (range −4.61 to 2.46), which corresponded to the 28th CDC percentile; the median weight z-score was −0.42 (range −6.23 to 2.38), which corresponded to the 34th CDC percentile. The median BMI z-score was −0.07 (range −3.89 to 2.30), which corresponded to the 47th CDC percentile. There were no significant differences in the average BMI z-score between monozygous twins and siblings and dizygous twins and siblings. All covariates in the model remained independent predictors of BMI−z5to10 in the multivariate models. Adjusted BMI z-score phenotypes were generated for female sex, birth cohort, PI, and history of MI (BMI−zadj) and in a second analysis for BMI−zadj plus for FEVq6to10 (BMI−zadjFEV), which considered the influence of lung function on BMI for subsequent heritability and linkage analyses. There was a high degree of concordance for BMI in individuals who shared 100% of genes, for monozygous twins (0.80–0.85 for 58–65 pairs). The dizygous twin-only groups had lower correlation coefficients (0.58–0.66 for 21 dizygous twin pairs; 0.41–0.57 for 13 same-sex, dizygous twin pairs), which indicated a lower concordance in this group of twins who shared, on average, 50% of genes. Correlation coefficients for the dizygous twin and sibling group were 0.5 (0.25–0.31 for 122–148 pairs). Linkage results for individuals with PI (BMI−zadj−PI; 358 sibling pairs) revealed 2 prominent genome-wide significant peaks on chromosomes 1p36.1 (LOD: 5.3) and 5q14 (LOD: 5.1). Restriction of the analysis to the 219 sibling pairs who were homozygous for the F508del mutation (BMI−zadj−F508del) preserved the peak on chromosome 1p36.1 (LOD: 4.6) but decreased the evidence for linkage on chromosome 5q14 (LOD: 3.4). Adjustment of BMI for lung function (BMI−zadjFEV−PI; 350 sibling pairs) decreased the LOD score for the locus on chromosome 1p36.1 (LOD: 3.4) but increased the evidence for linkage at an adjacent region from chromosome 1p31–22 (LOD: 2.4); linkage on chromosome 5q14 (LOD: 5.2) was unaffected. Quantitative trait locus (QTL) heritability at 1p36.1 and 5q14 after correction for potential bias represented ≥16% and ≥15% of the BMI variance.

Conclusions: This is the first study on the nutritional status of young twins and siblings with CF which shows that genes other than CFTR influence the variation in BMI. Specifically, the results from this study suggested that modifier genes located at the 1p36.1 locus influence both nutritional status and lung function, whereas chromosome 5q14 encompasses a gene that modifies nutritional status that is independent of lung disease severity.

Oral calorie supplements for cystic fibrosis

Smyth RL1, Walters S2

1Institute of Child Health, UCL, London, UK; 2c/o CFGD Group, Institute of Child Health, University of Liverpool, Liverpool, UK

Cochrane Database Syst Rev 2012; 10: CD000406

Aims: This Cochrane systematic review aimed to evaluate the benefits of dietary advice or oral nutritional supplementations for at least 1 month in patients with CF on different outcomes, i.e. weight gain and growth, body composition (primary outcomes), lung function, gastrointestinal adverse effects or activity levels (secondary outcomes).

Methods: The authors searched the Cochrane CF Trials Register for randomized or quasi-randomized controlled trials which compared the use of oral calorie supplements to increase caloric intake with no specific intervention.

Results: The literature search identified 21 trials. Only three trials (131 patients) fulfilled the inclusion criteria [3–5] and were included in the final meta-analysis. There was no significant difference between the groups at any time point with regard to change in weight, weight percentile, height,
height percentile, weight for height or body mass index (BMI) (primary outcomes). There were no differences between intervention (oral supplementation) and non-intervention groups with regard to secondary outcomes including total (oral or supplemented) intake of calories, protein, fat, feeding behavior or measures of quality of life. Forced expiratory volume in 1 s (FEV1) (% predicted) was significantly decreased at 3 months in the control group but not at 6 and 12 months. The change in forced vital capacity (FVC) (reported only by Poustie et al. [5]), was not significantly different between groups at 3, 6 or 12 months. The single study [5] that evaluated the presence of adverse effects of oral supplements reported no differences on diarrhea, appetite, abdominal bloating, episodes of distal intestinal obstruction syndrome and any other adverse effects between intervention and non-intervention groups.

Conclusions: This systematic review showed that short-term use of oral supplements did not improve the nutritional status in children with CF and mild to moderate malnutrition. Since no difference in nutritional status or lung function was reported with the use of oral nutrition supplements, one may conclude that dietary advice alone is also a satisfactory approach to the management of people with CF and moderate malnutrition. This systematic review raises questions about the utility of the practice of prescribing oral nutrition supplements for the nutritional care and rehabilitation of children with CF.

Nutritional outcomes following gastrostomy in children with cystic fibrosis

Bradley GM1, Carson KA2, Leonard AR1, Mogayzel PJ Jr3, Oliva-Hemker M1

1Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University School of Medicine, Baltimore, MD, USA; 2Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; 3Eudowood Division of Pediatric Respiratory Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Pediatr Pulmonol 2012; 47: 743–748

Aims: The primary aim of the study was to evaluate the ability of nutrient supplementation using a gastrostomy tube (GT) to improve nutritional status in children with CF and low BMI. Furthermore, the study evaluated the effects of GT placement and supplemental nutrition on lung function, number of hospitalizations for pulmonary exacerbation and complications during and after GT placement.

Methods: This retrospective study evaluated 40 patients (20 children with GT and 20 controls) 2–20 years old with data at least 1 year after GT placement. Each one of the ‘cases’ (children with GT) was pair-matched with a child with CF who did not have a GT (‘controls’). The cases and controls were matched for age ± 2.5 years, sex, pancreatic status, BMI percentile ± 10% and, when available, FEV1 ± 20%. Data on GT placement technique, complications during and after GT placement and nutritional supplementation through GT were collected in the ‘cases’ group. For the controls, use of oral nutritional supplementation, appetite stimulant and/or a gastroenterology (GI) referral for GT placement at any time during the 1-year follow-up period were recorded. Nutritional and lung function data (including height, weight, BMI, and percent predicted FEV1) were obtained at the enrollment visit, 6-month (±3 months) and 1-year (±3 months) follow-up. The number of hospitalizations required for pulmonary exacerbation during the 1-year follow-up period was also recorded.

Results: GT placement was without complications in 15/20 and whole protein formula was given to 18/20 children. GT delivered about 50% of the 110–200% dietary reference intake recommendation. The whole GT supplementation was delivered continuously overnight. A dose of pancre-
atic enzymes was given at the beginning and the end of the feeds. At the 6-month follow-up visit, 7 (35%) of the cases and 1 (5%) of the controls reached BMI ≥50th percentile (p < 0.04). The patients supplemented by GT were almost 10 times as likely to reach BMI ≥50th percentile at 6 months compared to the control group (OR = 9.70; 95% CI 1.05–484.7). At 1-year follow-up, 8 (40%) of the cases and 3 (15%) of the controls had reached BMI ≥50th percentile (p < 0.16) (OR = 3.65; 95% CI 0.69–25.86). The mean ± SD BMI was significantly better compared to controls (p < 0.001) at 6 months, but not at 12 months. The mean weight z-score improved significantly from the baseline compared to controls at 6 months (p < 0.001) and 12 months (p < 0.01) but the change in mean height z-score was comparable between cases and controls. At 6 months, the mean ± SD BMI and mean weight z-score in the GT group improved from the baseline compared to controls (p < 0.001), while there was no difference in mean height z-score between the two groups. At 1 year, the cases still had a higher mean BMI z-score than the controls, but the difference from baseline no longer achieved statistical significance. The change in mean weight z-score was still statistically significant (p < 0.01), but the change in mean height z-score was again comparable. The groups were similar in the change in mean predicted FEV1 from baseline to 6 and 12 months and there were no statistically significant differences between the cases and controls in the number of hospitalizations required for pulmonary exacerbation. By 1 year, 1 child was no longer receiving supplemental nutrition via the GT. At 1 year, 12/20 controls were advised to take oral supplements and 6 were prescribed an appetite stimulant. One patient was referred for GT placement.

**Conclusions:** In this retrospective study, nutritional support using supplemental feedings via a GT was shown to improve weight gain in patients with CF. According to the current study, children with CF who had a BMI <50th percentile for age and received a GT were almost 10 times as likely to reach BMI ≥50th percentile at 6 months compared to matched patients who did not receive a GT and were 3.65 times as likely to reach BMI ≥50th percentile by 12 months. The conclusions are weakened by the fact that these changes did not reach statistical significance.

---

**Recombinant growth hormone therapy for cystic fibrosis in children and young adults**

Thaker V1, Haagensen AL2, Carter B3, Fedorowicz Z4, Houston BW5

1Haverstraw Pediatrics, Haverstraw, NY, USA; 2Children’s Hospital Boston, Boston, MA, USA; 3Cancer Research UK Clinical Trials Unit, School of Cancer Sciences, Birmingham University, Birmingham, UK; 4The Cochrane Collaboration (UKCC), Awali, Bahrain; 5School of Health & Social Care, Teesside University, Middlesbrough, UK

*Cochrane Database Syst Rev* 2013; 6: CD008901

**Aims:** The study aimed to review the evidence on the effectiveness and safety of recombinant human growth hormone (rhGH) therapy in improving lung function, quality of life and clinical status of children and young adults with CF.

**Methods:** This is a systematic review of all the randomized controlled trials (RCT) trials that reported the results of rhGH treatment in children and adolescents with CF.

**Results:** The authors identified 22 potentially eligible studies for further evaluation. Only four studies (161 participants) were included in the final review. Two of the studies were RCT of parallel design [6, 7]. One was a cross-over study with two periods of treatment [8] and one study was quasi-randomized [9]. Three studies used rhGH in a standard dose of approximately 0.3 mg/kg/week.
compared with no treatment; one study had three treatment arms: placebo, standard dose (0.3 mg/kg/week) and high dose (0.5 mg/kg/week). Pulmonary function reported as FEV1 or FVC [6] showed no evidence of an effect from rhGH treatment. Height and weight were not significantly changed by rhGH treatment [9], but height velocity showed a significant difference in favor of rhGH, MD 2.10 (95% CI 0.54–3.66). Fasting blood glucose at 6 months [6] showed a significant increase in the rhGH treatment group, MD 12.40 (95% CI 3.76–21.04), however the difference in postprandial glucose levels was not significant, MD 12.10 mg/dl (95% CI –7.18 to 31.38) (0.54–3.66). Muscle strength and the number of pulmonary exacerbations were also no different in the rhGH treatment.

**Conclusions:** rhGH treatment in children with CF achieved modest improvements in anthropometric measures (height, weight, height and weight velocity and lean tissue mass). At this stage, the question of whether this improvement translates into better pulmonary outcomes, reduction in morbidity and improved quality of life has not been answered from the available evidence, due to scarcity of data.

**Comments**

Cystic fibrosis (CF) is a common autosomal recessive genetic disorder, diagnosed in approximately 1 in 2,500 births, more often in populations of Caucasian descent. The gene, the CF transmembrane regulator (CFTR) located on chromosome 7, encodes a protein that functions as a cAMP-regulated chloride channel and controls the flow of sodium and chloride ions across the cell membrane. Most patients with CF (85%) carry mutations which are associated with pancreatic insufficiency. The clinical features of CF can be highly variable, including non-specific respiratory symptoms or gastrointestinal symptoms and malnutrition. In the past, growth failure and weight loss were seen as inevitable in the face of progressive lung disease.

In 1988, Corey et al. [10] reported growth, pulmonary function and survival in 499 CF patients from Boston (USA) and 534 from Toronto (Canada) followed from 1972 to 1981. Although patients' characteristics were comparable in the two populations, height and weight percentiles were higher in patients from Toronto than in Boston and also their survival (30 vs. 21 years). The only difference was that Canadian patients had a better nutritional status resulting from a non-restricted dietary fat diet and the use of coated pancreatic enzymes. Since that report, many studies have shown that nutritional status during childhood is the most important single factor determining pulmonary status (and hence likely survival) in CF individuals.

In order to achieve the most favorable outcomes, the care of children with CF should address both nutritional status and lung function. Normal growth, therefore, has been decreed by Cystic Fibrosis Foundation (CFF) as the key goal of nutritional support in children with CF [11]. Nutritional status by all parameters (wasting, stunting, body composition) has been shown to affect lung function and survival in patients with CF in many studies before and this year too (cf. Yen et al., Bournez et al., Zhang et al., Stephenson et al., Vieni et al.). As children get older, the nutrient requirements increase, but progression of lung disease compromises nutritional status by increasing daily energy demands, interfering with appetite, and resulting in a decreased overall energy intake. Many studies have shown that growth deviation takes place during the puberty years as patients with CF have delayed puberty and diminished growth pubertal spurt (cf. Zhang et al., Bournez et al.). This maturational delay affects negatively final adult height, as 70–80% of children with CF did not reach their genetic potential. Growth delay and deficit do not affect only the final adult height but also survival, as shown in the study by Vieni et al.
Evaluation of nutritional intake and growth must be made at every visit. Every effort should be made to maintain ideal body weight (IBW%) in children <2 years (>95%) and BMI in children >2 years (ideally >50th percentile). BMI is an easy, quick, safe, and low-cost method that is considered the gold standard to approach nutritional status in children with CF >2 years. Data from the CFF Registry has consistently demonstrated a positive association between BMI and lung function. Several studies have also explored the relationship between BMI and lean muscle mass and measures of disease severity in CF. Engelen et al. have shown that FFM depletion is prevalent and not always detected using BMI%, furthermore, FFM was correlated with FEV1 (a measure of lung function).

Using the data from CF Twin-Sibling Study and Cystic Fibrosis Foundation Patient Registry, the original study of Bradley et al. had evaluated the relative contribution of genetic modifiers to the nutritional status of young children with CF. Linkage analyses pointed that genes on chromosomes 1 and 5 significantly influence the BMI variation in children with CF. The search for CF-modifying genes represents the opportunity to further insight into the pathophysiology of malnutrition in children with CF and discovery of potential new targets for nutritional intervention.

There is evidence that nutritional support can delay the decline in lung function, translating into improved health, quality of life, and length of survival in these patients. Studies in the early 1980s, which reported positive effects of dietary counseling and/or supplements, were however conducted in patients who had been placed on a low-fat diet before the study. The recent Cochrane systematic review (cf. Smyth and Walters), however, reported no improvement in nutritional parameters or pulmonary function in children with CF on oral nutritional supplements. Enteral tube feeding, using gastrostomy, usually delivered as overnight feeds with appropriate enzyme therapy, may provide approximately 30–50% of estimated daily energy requirements. Supplemental gastrostomy feedings were shown to be associated with improvements in weight and height percentiles for age, increases in percent of body fat and fat-free mass and sustained growth. The retrospective study of Bradley et al. however reported no effect on pulmonary function status or disease severity (hospitalizations). Currently, most studies on supplemental gastrostomy feedings are, however, retrospective and since randomization is not feasible/ethical, only cohort longitudinal studies at best will be expected.

Use of rhGH for the treatment of growth deficit as well as an anabolic agent has been addressed by several studies. A systematic review published in 2010 which evaluated 10 controlled clinical trials and 8 observational studies showed that in the controlled trials, markers of pulmonary function, anthropometrics, and bone mineralization appeared to be increased compared with controls [12]. With regard to long-term health issues, such as pulmonary exacerbations, hospitalizations, or mortality, the only significant finding was that GH therapy seemed to reduce the rate of hospitalizations. The recent Cochrane systematic review (cf. Thaker et al.) which included 4 RCTs found only modest improvements in anthropometric measures (height, weight, height and weight velocity and lean tissue mass) but no evidence of better pulmonary function, reduced morbidity or improved quality of life.

According to CFF nutrition consensus, children and adolescents with CF are expected to experience typical growth when appropriate nutrition and pancreatic enzyme replacement therapy are provided. In 2008, nutritional recommendations for infants and children with CF provided evidence-based and consensus recommendations for many aspects of nutrition in CF patients [3]. Unfortunately, good quality evidence to support precise nutrition recommendations for patients with CF is missing, although
efforts have been made to use available evidence to set care standards. Moreover, the benefit of providing invasive nutrition besides improving the patient’s nutritional status and growth is questionable in terms of survival and lung function. In general, awareness of clinician staff about the overall nutritional status of their patient population and timely nutritional support when clinical indices fall below standards should be standard of care [13].

Cerebral Palsy

Energy requirements in preschool-age children with cerebral palsy
Walker JL1,2, Bell KL1–4, Boyd RN2–4, Davies PSW1

1Children’s Nutrition Research Centre, School of Medicine, The University of Queensland, Brisbane, QLD, Australia; 2The Queensland Cerebral Palsy and Rehabilitation Research Centre, School of Medicine, The University of Queensland, Brisbane, QLD, Australia; 3The Queensland Children’s Medical Research Institute, The University of Queensland, Brisbane, QLD, Australia; 4The Queensland Paediatric Rehabilitation Service, Royal Children’s Hospital, Brisbane, QLD, Queensland, Australia

Am J Clin Nutr 2012; 96: 1309–1315

Aims: The study aimed to evaluate the energy requirements (ER) in a group of children with cerebral palsy (CP) using the doubly labeled water (DLW) method. The authors compared measured ER among children with CP and different functional abilities or motor dysfunction with typically developing children (TDC) and published estimation equations.

Methods: The study enrolled and evaluated 32 children with CP and 16 typically developed children (TDC) aged 2.9–4.4 years. Children with disorders or children on medications known to affect growth or metabolism were excluded from the study. Each child was given a dose of oxygen-18 and deuterium water (1.25 g/kg 10% H218O and 0.05 g/kg 99.8% 2H2O). A single urine sample was collected at baseline, daily urine samples were examined thereafter for 10 days. The production rate of carbon dioxide was calculated as the difference between the elimination rates of deuterium and oxygen-18 in conjunction with their dilution space. Oxygen consumption was determined by assuming a respiratory quotient of 0.85, and TEE was calculated using Weir equation [14]. Anthropometric measurements included weight, height/length/knee height. Functional ability (Gross Motor Function Classification System – GMFCS) and motor dysfunction type and distribution were evaluated using internationally accepted and validated criteria and classifications.

Results: The children with CP were shorter, lighter, and had lower free-fat mass indexes (FFMIs) than did the TDC (p < 0.01). Mean height z-scores and FFMI for children with CP decreased as ambulatory status declined (p < 0.05). Children with CP had significantly lower energy requirements (ERs) than did TDC [p < 0.001; mean difference (MD) = 1212kJ/d]. Ambulant CP children had, on average, an ER that was 16% lower than that of TDC. Marginally ambulant and non-ambulant children had an ER that was 31% lower than that of TDC and 18% lower than that of ambulant CP children. No statistical difference in ERs was found between ambulant children and TDC. The difference in GMFCS were responsible for 67% of the variability in ER (r2 = 0.67). The FFM of the children contributed most to ERs variability. Correlation analyses of variables known to con-
Nutrition and Growth in Chronic Diseases

Tribute to ERs showed that ERs were strongly positively correlated with FFM, weight, and height. When the influence of functional ability in the children with CP was considered, ERs decreased with increasing severity of disability (marginally ambulant and non-ambulant children had lower ER than did ambulant children). The estimated ERs from Rieken et al. [15] models were significantly less than the measured ER values, with a consistent bias of −1089kJ, representing an underestimation in ERs in the current population of 22%.

Conclusions: The results of this study confirm that ER recommendations, equations and energy intakes of typically developed children are not valid for use in children with CP, especially in more affected children. Motor disability (ambulation vs. non-ambulation) and FFM explained about 67% of the variability in ERs in this group of children with CP.

Validation of a modified three-day weighed food record for measuring energy intake in preschool-aged children with cerebral palsy

Walker JL1,3,4, Bell KL2–6, Boyd RN2,4,5, Davies PS1,3

1 Children’s Nutrition Research Centre, UQ Department of Paediatrics and Child Health, Royal Children’s Hospital, Herston, QLD, Australia; 2 Queensland Cerebral Palsy and Rehabilitation Research Centre, Department of Paediatrics and Child Health, The University of Queensland, Royal Brisbane Hospital, Herston, QLD, Australia; 3 Children’s Nutrition Research Centre, School of Medicine, The University of Queensland, Brisbane, QLD, Australia; 4 Queensland Cerebral Palsy and Rehabilitation Research Centre, School of Medicine, The University of Queensland, Brisbane, QLD, Australia; 5 Queensland Children’s Medical Research Institute, The University of Queensland, Brisbane, QLD, Australia; 6 Department of Paediatric Rehabilitation, Royal Children’s Hospital, Brisbane, QLD, Queensland, Australia


Aims: The aim of the current study was to validate the use of a modified 3-day weighed food record for measuring energy intake (EI) in a population of young children with CP.

Methods: The study included children aged between 35 and 54 months with a diagnosis of CP living in the community in the State of Queensland, Australia, and compared them to typically developing children (TDC) in the same age range residing in the same area. The children underwent the following evaluations: anthropometry measurements, functional ability using the Gross Motor Function Classification System (GMFCS) [16], energy assessment by a 3-day weighed food record, total energy expenditure (TEE) using the doubly labeled water (DLW) technique and oral motor and swallowing skills rating using the Feeding and Swallowing Competency Subset of the Dysphagia Disorders Survey for Paediatrics [17]. Validation of the 3-day weighed food record was done by comparing reported EI to measures of TEE for each individual child over the 10-day data collection period and the difference between reported EI and measured TEE (when expressed as a percentage of TEE) was less than 19%, an EI/TEE ratio of 1.00 indicating perfect reporting.

Results: The study population included 31 children (61% male) with CP aged from 2.9 to 4.4 years and 15 TDC (63% male) aged from 3.0 to 4.5 years. 13 children (42%) had moderate to severe feeding problems and 11/13 of these children were classified as GMFCS III, IV or V. Six children (19%) were tube-fed, all classified as GMFCS level V. In general, children with CP were shorter and lighter than the TDC. EI was statistically significantly less than TEE values for the children with CP as a total population and for the TDC [4,628 ± 1,325 vs. 5,142 ± 1,265 kJ/day (p < 0.01) in CP children and 5,310 ± 846 vs. 6,397 ± 779 kJ/day (p < 0.01) in TDC]. Evaluation of the EI as a percentage of
TEE for each group showed that children with moderate to severe CP had the most accurate reporting with a result of 4.3%. On average, 75% of the children with CP had EI results that were within 20% of their TEE values. The study showed no substantial overreporting as reported in previous literature. Considering functional ability, in children with moderate to severe CP the ratio of EI/TEE was 0.96 indicating greater accuracy compared to the TDC (0.83). Considering the influence of feeding method on the accuracy of reporting showed that orally-fed children displayed more accurate reporting when compared to those who were tube-fed, evidenced by a very low EI/TEE ratio of 1.01 indicating nearly perfect reporting.

**Conclusions:** Evaluation of 3-day weighed food record for assessment of energy intake in children with CP is a valid tool in pre-school children with CP among all the levels of functional ability and feeding difficulties or methods. The findings from this study are in contrast to previous literature reported by Stallings et al. [18] that reported gross overestimation of EI in school-aged children with CP.

---

**The use of bioelectrical impedance analysis to estimate total body water in young children with cerebral palsy**

Bell KL1–4, Boyd RN1,2, Walker JL1,3, Stevenson RD5, Davies PS3

1 Queensland Cerebral Palsy and Rehabilitation Research Centre, School of Medicine, The University of Queensland, Brisbane, QLD, Australia; 2 Department of Paediatric Rehabilitation, Royal Children’s Hospital, Brisbane, QLD, Australia; 3 Children’s Nutrition Research Centre, School of Medicine, The University of Queensland, Brisbane, QLD, Australia; 4 Queensland Children’s Medical Research Institute, The University of Queensland, Herston, QLD, Australia; 5 Division of Developmental Pediatrics, University of Virginia (UVA) School of Medicine and UVA Children’s Hospital, Charlottesville, VA, USA

*Clin Nutr* 2013; 32: 579–584

**Aims:** The study aimed to evaluate: (1) the reliability of body impedance (BIA) measurements in young children with cerebral palsy (CP) across different grades of motor severity, (2) appropriate electrodes’ placement for BIA in children with CP and unilateral involvement, (3) the best equation for the calculation of total body water (TBW) from the BIA in pre-school children with CP.

**Methods:** The study included 55 preschool children aged 2.40 ± 0.59 with CP and different ranges of Gross Motor Function Classification System (GMFCS) levels. Impedance (ohm) and TBW were measured and TBW was estimated from impedance using three previously published equations [19–21]. These equations were selected as they were all developed in groups containing children of preschool age and are all based on BIA.

**Results:** (1) Duplicate BIA measurements were performed in 50 children (91%) on the left-hand side of the body and 49 children on the right side. Duplicate measurements showed minimal differences: 0.5% variation on the left side of the body and 0.1% variation on the right side. However, there was a significant variation within some individuals and a third measurement was required in 44% measurements for the left-hand side and 35% occasions for the right-hand side of the body, since the duplicate measures were >5 ohm apart. (2) The mean differences of BIA results obtained from measurements conducted on either side of the body in young children with and without unilateral impairment were 1.2 and 0.8% respectively. (3) In children with bilateral impairment the estimated ± SD the mean of estimated and measures TBW ± SD were greatest for the Pencharz equations (10.4 ± 1.5 and 9.0 ± 1.4, respectively) and lowest for the Fjeld equation (7.6 ± 1.1 and
7.6 ± 1.2, respectively). In children with unilateral impairment, estimated TBW was lowest on the impaired compared to the unimpaired sides of the body for all three equations. Mean differences between the impaired and unimpaired sides were: for the Kushner equation: 0.3 liter (3%) (t = 2.55, p < 0.02); for the Pencharz equation: 0.5 liter (4%) (t = 4.53, p < 0.00), and for the Fjeld equation: 0.2 liter (2%) (t = 4.52, p < 0.00).

Conclusions: The ability of BIA to assess TBW accurately depended on the equation chosen. The Fjeld equation proved highly accurate at the population level for both children with bilateral and unilateral impairment, although individual results varied by up to 18%.

Micronutrient, antioxidant, and oxidative stress status in children with severe cerebral palsy

Schoendorfer NC¹, Vitetta L², Sharp N¹, DiGeronimo M³, Wilson G³, Coombes JS³, Boyd R⁴, Davies PS¹

¹Children’s Nutrition Research Centre, The University of Queensland, Brisbane, QLD, Australia; ²Centre for Integrative and Molecular Medicine, The University of Queensland, Brisbane, QLD, Australia; ³Exercise and Oxidative Stress Research Group, School of Human Movements, The University of Queensland, Brisbane, QLD, Australia; ⁴Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland, Brisbane, QLD, Australia


Aims: The study evaluated the micronutrient and antioxidant status in children with CP.

Methods: Red cell folate (RCF), magnesium, superoxide dismutase (SOD), glutathione reductase, and peroxidase, as well as serum methylmalonic acid and vitamin C were measured. Plasma hemoglobin, C-reactive protein, α-tocopherol, cholesterol, zinc, protein carbonyls, and total antioxidant capacity were also quantified in 24 children with CP and 24 typically developing healthy children, aged 4–12 years.

Results: There were no significant differences between the groups for concentrations of red cell glutathione peroxidase, red cell magnesium, hemoglobin z-score, serum α-tocopherol z-score/cholesterol z-score ratio, protein carbonyl, or total antioxidant capacity. Red cell glutathione reductase (U/g Hb) was lower in orally-fed children compared with the other children (12.22 ± 2.41 in CP tube-fed vs. 10.15 ± 1.69 in CP orally-fed vs. 11.51 ± 1.67 in controls, p < 0.05). SOD activity (U/mg Hb) was also found significantly reduced in the enterally-fed children compared with the other groups (24.3 ± 1.4 in CP tube-fed vs. 25.7 ± 1.8 in CP orally-fed vs. 27.0 ± 2.8 in controls, p < 0.05). Plasma zinc z-score was found to be lower in the orally-fed group (–1.05 ± 0.73 in CP tube-fed vs. –1.10 ± 0.83 in CP orally-fed vs. –0.54 ± 0.54 in controls, p < 0.05). Red cell folate (nmol/l) was significantly higher in the enterally fed group (1,422 ± 70 in CP tube-fed vs. 843 ± 80 in CP orally-fed vs. 820 ± 43 in controls, p < 0.001), whereas MMA (nmol/l) was lower in this group, suggesting adequate B₁₂ status (88 ± 21 in CP tube-fed vs. 142 ± 101 in CP orally-fed vs. 157 ± 84 in controls, p < 0.05).

Conclusions: This study demonstrates a range of nutrition imbalances between tube-fed and orally-fed children with CP and TDC. Orally-fed children particularly showed several micronutrient deficiencies and enterally-fed children displayed certain excesses. Assessment of nutrient quality and not only quantity is obviously important in children with CP, either fed by tube or orally.
Fractures in children with cerebral palsy: a total population study

Uddenfeldt Wort U1, Nordmark E2, Wagner P3, Düppe H4, Westbom L5

1Department of Clinical Sciences, Social Medicine and Global Health, Lund University, Malmo, Sweden; 2Department of Health Sciences, Health Sciences Centre, Lund University, Lund, Sweden; 3National Centre for Quality Registers Skane University Hospital, Lund, Sweden; 4Department of Orthopaedics Skane University Hospital, Malmo, Sweden; 5Division of Paediatrics, Department of Clinical Sciences, Lund University, Lund, Sweden

Dev Med Child Neurol 2013; 55: 821–826

Aims: The study aimed to evaluate the prevalence, the type and the risk factors for fractures in children with CP compared to typically developed children (TDC).

Methods: The study is based on the data from the Skane CPUP programme, an epidemiological population study from Skane, Sweden, that collected data on body function, activity, and treatment in a CP follow-up registry. The present paper reported retrospective information on fracture events in children and young adults with CP born 1990–2005.

Results: The study population included 536 children (214 females): 11% were thin (BMI <–2 SD), 8% were obese (BMI >2 SD) and 12% were stunted. There were 103 fractures in 79 children, 13 children had more than one fracture. 19 (18%) occurred without any known trauma, 2 (2%) were in children in GMFCS levels I–III and 17 (16%) in children in GMFCS levels IV–V; 56 (54%) occurred after slight and 28 (27%) after moderate trauma. The majority of fractures occurred in children in GMFCS level I, and the fractures without trauma were most common in children with spastic CP and those in GMFCS levels IV–V. Of the 15 fractures of the femur, 14 occurred in children in GMFCS levels IV–V, and in 11 of those cases there was no known trauma involved. Children classified in GMFCS levels IV–V on antiepileptic drugs had a twofold increased (p = 0.004) fracture risk. The risk for fractures without trauma was also increased in stunted growth (height for age <–3SD) and for those who did not use standing devices, adjusted incidence ratio (AIRR) 4.16 (p = 0.011) and 3.66 (p = 0.010), respectively. The risk of fractures in gastrostomy-fed children was reduced for fractures with trauma, but increased for fractures without trauma (AIRR 0.10, p = 0.003 and 4.36, p = 0.012), respectively. The risk for fractures for children in GMFCS levels I–III was not significantly associated with any of the studied risk factors.

Conclusions: Children with CP with severe functional disabilities are at increased risk of fractures, especially if they are on antiepileptic drugs, stunted, do not use standing devices and are malnourished.

Timing of gastrostomy insertion in children with a neurodisability: a cross-sectional study of early versus late intervention

Sharma R1, Williams AN1, Zaw W2

1Department of Paediatrics, Virtual Academic Unit, Child Development Centre, Northampton, UK; 2Department of Paediatrics, Northampton General Hospital, Northampton, UK

BMJ Open 2012; 2: e001793

Aims: The study aimed to evaluate whether early nutritional support using gastrostomy feeding in children with neurologic disabilities resulted in better weight gain and health outcome.
Methods: This was a retrospective, cross-sectional study which reviewed the pre- and post-gastrostomy weight and health outcome (hospitalization days) in 24 children who had gastrostomy placed before the age of 18 months and 17 children who had the gastrostomy placed after the age of 18 months.

Results: The mean weight pre-gastrostomy z-score in the <18 month group was −2.78 SD and −1.17 SD in the >18 month group. The mean weight post-gastrostomy z-score in the <18 month group was −1.45 SD and −0.72 SD in the >18 month group. The weight pre-gastrostomy z-score was significantly lower in the younger age group (p = 0.014), however there was no significant difference in z-score between the groups post-gastrostomy (p = 0.178). The mean difference in the z-score pre- and post-gastrostomy was significantly greater in the younger age group than in the older group (p = 0.021). There was no significant difference in the hospital admission rates pre- and post-gastrostomy in the early or the late group.

Conclusions: The results of the study shows that gastrostomy use for nutritional support improved weight gain at any age, but younger children achieved greater weight gain.

Gastrostomy tube feeding of children with cerebral palsy: variation across six European countries

Dahlseng MO1, Andersen GL2, Da Graca Andradam3, Arnaud C4, Balu R5, De la Cruz J6, Folha T7, Himmelmann K8 Horridge K9, Júlíusson PB10, Pählman M8, Rackauskaite G11, Sigurdardottir S12, Uldall P13, Vik T1, Surveillance of Cerebral Palsy in Europe Network

1Department of Laboratory Medicine, Children’s and Women’s Health, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; 2The Cerebral Palsy Registry of Norway, Vestfold Hospital Trust, Tønsberg, Norway; 3The Cerebral Palsy Registry of Portugal, Federacao das Associacoes Portuguesas de Paralisia Cerebral, Lisbon, Portugal; 4Inserm, UMR 1027, Toulouse, France; 5Paediatric Department, Sunderland Royal Hospital, Sunderland, UK; 6Clinical Research Unit, Imas12-Ciberesp, Hospital 12 Octubre, Madrid, Spain; 7Calouste Gulbenkian Cerebral Palsy Rehabilitation Centre, Lisbon, Portugal; 8Department of Pediatrics, Institute of Clinical Sciences, Queen Silvia Children’s Hospital, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden; 9City Hospitals Sunderland NHS Foundation Trust, and North of England Collaborative Cerebral Palsy Survey, Sunderland, UK; 10Department of Paediatrics, Haukeland University Hospital, Bergen, Norway; 11Department of Paediatrics, Aarhus University Hospital, Aarhus, Denmark; 12State Diagnostic, Counselling Centre, Kopavogur, Iceland; 13Child Department, Rigshospitalet, Copenhagen University, Copenhagen, Denmark

Dev Med Child Neurol 2012; 54: 938–944

Aims: The aims of the study were to evaluate the approach to feeding difficulties and the indications for gastrostomy tube feeding (GTF) in children with CP in different European centers.

Methods: The study was part of the Surveillance of Cerebral Palsy in Europe Network (SCPE-NET), a 3-year programme based on the Surveillance of Cerebral Palsy in Europe, a collaboration of 21 registers in 13 European countries aimed at promoting best practice in the care of children with CP. Children with all CP subtypes and all GMFCS levels, born from 1999 to 2001, were included in the study. The primary outcome was the presence of a GTF. Secondary outcomes were age at placement of gastrostomy, growth and feeding difficulties.

Results: A total of 1,295 children (754 males, 541 females; mean age 5.11 years, range 6 months to 11.8 years) were included in this study. There were significant differences between areas in the proportions of various CP subtypes and GMFCS levels. In all, 133/1,295 (11%) children had a
gastrostomy tube placed (22% in Sweden to 3% in Iceland). Gastrostomy feeding was given to 67% of children with GMFCS level IV and V in western Sweden, but only to 12% of children in Portugal. Median age at placement of gastrostomy was 22 months (range 1–120). The median age range between different countries was 16 months in western Sweden (5–108 months) to 70 months in northern England (12–120 months). The mean z-scores for weight was −0.86 (SD 1.71) and −0.87 for height (SD 1.50). In children in GMFCS level IV and V, there were significant differences in z-scores for weight and height between the areas. Portuguese children had lower weight z-scores compared with Norwegian, Swedish and Danish children (p < 0.001), while their height z-scores were lower only compared with Swedish and Danish children (p = 0.002). For children in GMFCS levels I and II, no significant differences in weight (p = 0.114) or height (p = 0.472) z-scores were observed between the different populations. The differences in z-scores between the countries were more marked when using the WHO growth references and also resulted in statistically significant differences for height z-scores between countries among children in GMFCS levels I and II.

Conclusions: The study showed considerable variations in the prevalence of growth restriction, feeding difficulties and the use of GTF in children with CP across different areas in six European countries. The differences were even more marked in children with GMFCS levels IV and V, the group most likely to have associated feeding difficulties. Among these children, those living in areas where GTF was less used were more growth-restricted than children in countries where GTF was more prevalent. This study outlines the lack of clear guidelines and differences in the decision-making with regard to nutritional support of children with CP in different centers.

Comments

Children with neurologic disabilities present complex management challenges, both for their families and for the professionals involved in their care. Growth retardation and feeding disorders are common in these children and represent a particular challenge to clinicians providing nutritional support. The first difficulty to face is to accurately assess the child’s height and weight, which may not be possible using standard methods; therefore, proxies such as arm span or knee height may be required. The second challenge is to correctly assess their energy and nutrient needs to avoid over- or underprovision of nutrients. The single previous study that evaluated the EI in children with CP reported 44–54% overestimation compared to TEE data [18]. These differences could be explained by different populations or accuracy of food intake assessment and reporting. The significance of these discrepancies is that nutrition support should be based on objective and individualized evaluation in each child with CP, as generalizing data from different studies or populations may be subject to large deviations from the actual requirements. Historical cohorts demonstrate significant levels of malnutrition, however the clinician has to be aware that some children may not follow a standard growth trajectory and follow a growth trajectory set by their own genetic potential/disease. Several studies have shown that body composition and resting energy expenditure (REE) is variable in children with cerebral palsy (CP) and are affected by multiple factors (functional capacity, degree of mobility, severity of disease, level of altered metabolism disease, medication, type of feeding, etc.). Height and weight are not necessarily reliable predictors of REE with most studies demonstrating significantly lower REE than expected or compared with control groups. Total energy expenditure (TEE) is generally (although not always) reduced in children with neurologic disability; those with the most severe motor impairment having the lowest TEE. As illustrated by the study of Walker et al., direct measurement of REE in children with CP is therefore the only reliable way to accurately evaluate energy needs. Measurement of body composition is an indispensable component of nutritional assessment and
is paramount to the success of any nutritional program. There are few studies incorporating body composition analysis in assessment of the nutritional status of children with CP. The study of Bell et al. reported the calculated values of body water spaces (from BIA) and compared them with the measured values (from dilution isotopes) and good concordance (differences against mean) was reported, suggesting that BIA is a reliable method for estimating total body water and extracellular water in children with CP.

Evaluation of bone mineral density is another important aspect of nutrition evaluation of children with neurologic disabilities. The study of Uddenfeldt Wort et al. reports on the risk factors associated with fractures in a population of children with CP and different degrees of functional disabilities. The availability of new techniques, such peripheral quantitative CT, will improve our ability to diagnose poor bone quality and timely identify the children at risk of fractures.

The other studies presented in this chapter demonstrate furthermore the contradictions among the health caregivers with regard to nutritional support (type and timing) of children with CP. Lack of an objective measure of nutritional needs and clear guidelines of when and how and what to give for nutritional support are evident obstacles for appropriate care.

Future studies should address the particularities of energy metabolism and its regulation in this population. When adequately nourished, children and adolescents with cerebral palsy appear more tranquil and require decreased feeding time, which gives caregivers time to develop the child’s functional independence and character. Understanding energy requirements of this population will provide caregivers and health professionals with guidelines for providing and promoting optimal nutritional status.

**Autistic Spectrum Disorders**

**Early Growth Patterns in Children with Autism**

Surén P\(^1,2\), Stoltenberg C\(^2\), Bresnahan M\(^3,4\), Hirtz D\(^5\), Lie KK\(^2\), Lipkin WI\(^3\), Magnus P\(^2\), Reichborn-Kjennerud T\(^2,6\), Schjølberg S\(^2\), Susser E\(^3,4\), Oyen AS\(^2,7\), Li L\(^1\), Hornig M\(^3\)

\(^1\)Centre for Paediatric Epidemiology and Biostatistics, UCL Institute of Child Health, London, UK; \(^2\)The Norwegian Institute of Public Health, Oslo, Norway; \(^3\)The Mailman School of Public Health, Columbia University, New York, NY, USA; \(^4\)New York State Psychiatric Institute, New York, NY, USA; \(^5\)National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA; \(^6\)Institute of Psychiatry, University of Oslo, Oslo, Norway; \(^7\)Nic Waals Institute, Lovisenberg Hospital, Oslo, Norway

*Epidemiology* 2013; 24: 660–670

**Aims:** The study reports the data from the population-based longitudinal Norwegian Mother and Child Cohort Study (MoBa) on growth pattern of head circumference (HC), length, and weight in children with autism spectrum disorders (ASD).

**Methods:** The MoBa cohort is a Norwegian nationwide registry and includes 109,000 children born from 1999 to 2009. Cases of ASD in the cohort were identified by a substudy of autism, the Autism
Birth Cohort Study. Growth trajectories were modeled using mixed-effects models to take into account the within-subject correlation of head and body sizes.

**Results:** A total of 376 children in the study sample (106,082 children) had been diagnosed with ASD (310 boys and 66 girls). The mean birth HC in boys was not different in children with or without ADS. The mean HC in boys was similar after birth in cases and non-cases (HC mean difference <0.1 cm), but the variability of HC was greater in cases and there was an increase in the proportion with macrocephaly in ASD boys by age 12 months, to 8.7% (4.7–14.4%). The difference between cases and non-cases in girls reached 0.5 cm at 12 months of age. Adjustment for covariates attenuated the difference to 0.2 cm at 12 months. Boys with ASD had similar lengths to non-cases at birth, but grew faster after birth and were taller by 0.5 cm at 6 months and 1.1 cm at 12 months, but the mean difference reverted to 0.6 cm by age 3 years. In girls with ASD the mean birth length was 0.64 cm lower than the mean for girls without ASD but the differences in means were smaller at other ages. The birth weight of boys with ASD was similar to birth weight in non-cases, but after birth, ASD boys had a more rapid increase in mean weight and were on average about 300 g heavier than other boys from age 12 months. In girls with ASD, mean birth weight was lower than the mean for other girls and continued to be 150–350 g lower up to age 3 years, but the difference in means largely disappeared after adjustment for covariates. Boys with ASD had similar mean BMIs to other boys at all ages. Girls with ASD had somewhat lower mean BMIs throughout, as a result of their lower mean weight, although the 95% CIs were always overlapping with those of non-cases.

**Conclusions:** Growth trajectories for HC, length and weight in children with ASD were different from those of other children and the differences are sex-specific. Boys showed higher prevalence of macrocephaly and increased mean length and weight up to 12 months. For girls with ASD, the reductions in length, weight, and HC were attenuated by adjustment for covariates.

**Nutrition, physical activity, and bone mineral density in youth with autistic spectrum disorders**

Soden SE¹, Garrison CB¹, Egan AM¹, Beckwith AM²

¹Section of Developmental and Behavioral Sciences, Department of Pediatrics, Children’s Mercy Hospitals and Clinics, Kansas City, MO, USA; ²Department of Neurodevelopmental Pediatrics, Children’s Specialized Hospital, Mountainside, Mountainside, NJ, USA

_J Dev Behav Pediatr_ 2012; 33: 618–624

**Aims:** The aim of the study was to (1) assess the nutritional intake of children with ASDs, (2) evaluate bone mineral density (BMD) in a sample of 10- to 18-year-olds with ASDs, and (3) correlate medical history and body mass index (BMI), diet, activity, and parental perceptions of lifestyle with BMD.

**Methods:** The study included 26 children aged 10–18 years with ASDs. Anthropometries, Tanner stage, medication and medical diagnoses were collected by parent interview and from the clinic record. Parents were asked to rate their child’s dietary habits, their average physical activity level and to estimate the sunlight exposure in a typical week. Dual-energy x-ray absorptiometry (DXA) was used to measure BMD of the lumbar spine (L1–L4). Laboratory tests included serum 25-OHD, alkaline phosphatase, parathyroid hormone, erythrocyte indices, electrolytes, liver and renal function tests, thyroid-stimulating hormone, and free T₄.

**Results:** There were 21 males (80.8%) and 5 females (19.2%) aged from 10.3 to 18.2 years (mean 13.4). Mean body mass index (BMI) percentile was 47.9 (SD 36.37, range 1st to 99th), 27% of participants were overweight, while 23% were underweight. Food diaries indicated that participants’
Nutrient intakes were deficient for several nutrients including vitamins A, B₃, D, E, K, zinc, calcium, folate, fiber and potassium. The mean BMD z-score was –0.1 (SD 1.51, range –3.3 to –2.7). Four participants (15%) had a z-score ≤ –2.0. BMD was significantly positively correlated with BMI percentile (r = 0.47, p < 0.05), percent of recommended calcium intake (r = 0.46, p < 0.05), and percent of recommended caloric intake (r = 0.58, p < 0.01) calculated from diet diaries.

**Conclusions:** Children and adolescents with ASDs are at risk of low BMD due to their low calcium and vitamin D intake. Screening for low BMD should therefore be performed in children with ASDs based on an understanding of which patients are at greatest risk.

---

**Nutrient intake from food in children with autism**

Hyman SL¹, Stewart PA¹², Schmidt B³, Cain U³, Lemcke N¹, Foley JT¹, Peck R², Clemons T⁴, Reynolds A², Johnson C⁶⁷, Handen B⁷, James SJ⁸, Courtney PM⁹, Molloy C¹, Ng PK¹

¹Department of Pediatrics, University of Rochester Medical Center, Rochester, NY, USA; ²Clinical and Translational Science Institute, University of Rochester School of Medicine, Rochester, NY, USA; ³Boston University School of Medicine, Boston, MA, USA; ⁴EMMES Corporation, Baltimore, MD, USA; ⁵Department of Pediatrics, University of Colorado School of Medicine, Denver, CO, USA; ⁶Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; ⁷Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; ⁸Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR, USA; ⁹Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

*Pediatrics* 2012; 130(suppl 2): S145–S153

**Aims:** The study evaluated the food intake of children with autism spectrum disorders (ASD) and compared it to food intake the general pediatric population by using the National Health and Nutrition Examination Survey (NHANES) data.

**Methods:** The study population was recruited among children treated at five Autism Treatment Network (ATN) sites. Height and weight were measured and BMI and BMI percentile were calculated. Parents completed a 3-day food record containing all foods, beverages and supplements ingested by the child over 3 consecutive days.

**Results:** The study enrolled 367 children with ASD (2–11 years); nutrition data were based on 252 food records. Dietary restriction of gluten, casein, or processed sugars was reported by 18% of participants. Use of food supplement (vitamins, minerals, herbal, or botanical compounds) was reported by 66% of study participants, compared with 35% in the NHANES and 61% in a national sample of children with chronic disease. Compared to children in NHANES, children with ASDs aged 2–5 years were more likely to be overweight (p < 0.05) or obese (p < 0.001) and children aged 6–11 years were proportionately more underweight (p < 0.05). Children on restricted diets were more likely to be underweight than those not on restricted diets (p = 0.02). Macronutrient intakes were within the acceptable macronutrient distribution range by age, however children with ASDs (ages 4–8 years) consumed less energy, lower percentage of protein and greater percentage of carbohydrates than the NHANES (2007–2008) matched sample. Children with ASDs had lower intakes of vitamin D (2–11 years), lower levels of phosphorus intake (9–11 years) and reported lower intakes of vitamin A, vitamin C, and zinc compared with the NHANES controls. Many children with ASDs have intakes above the upper limit, from food alone, for micronutrients such as copper, retinol (vitamin A), folic acid, zinc, and manganese.

**Conclusions:** The data from this study shows that overweight and underweight, as well as micronutrient deficiencies or excesses are prevalent among children with ASDs. These results indicate
the importance of nutritional surveillance in primary care for all children, especially children with ASDs. The best way to achieve that is periodic dietary assessment corroborated with anthropometric and laboratory data, and consideration of referral to a registered dietitian.

**Iron status in children with autism spectrum disorder**

Reynolds A¹, Krebs NF¹, Stewart PA², Austin H¹, Johnson SL¹, Withrow N¹, Molloy C³, James SJ⁴, Johnson C⁵, Clemons T⁶, Schmidt B⁵, Hyman SL²

¹Department of Pediatrics, University of Colorado, Denver, CO, USA; ²Department of Pediatrics, University of Rochester, Rochester, NY, USA; ³Department of Pediatrics, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA; ⁴Department of Pediatrics, University of Arkansas, Little Rock, AR, USA; ⁵Department of Pediatrics, University of Pittsburgh, Pittsburgh, PA, USA; ⁶EMMES Corporation, Rockville, MD, USA

*Pediatrics* 2012; 130(suppl 2): S154–S159

**Aims:** The study aims were to determine the prevalence of iron deficiency in children with ASD and evaluate the iron intake, and the relationship of iron intake to iron status.

**Methods:** The study population was recruited among children treated at five Autism Treatment Network (ATN) sites. Parents completed a 3-day food record containing all foods, beverages, and supplements ingested by the child over 3 consecutive days. Laboratory tests included complete blood count, serum ferritin (SF), transferring saturation (TS), iron, and total iron-binding capacity (TIBC).

**Results:** Iron status was evaluated in 222/368 (60%, mean age 5.3 years, range 2–11) children with ASDs enrolled in the Diet and Nutrition Study. Low iron stores were found in 8% of children (SF <12 ng/ml). One child had IDA. ID rates were lower in all age groups of children with ASDs, compared with NHANES data. The percentage of children with iron intakes less than EAR was 2% and increased with age. Children with ASD did not differ from the NHANES population in iron intake. The major sources of iron in the diet of these children were from enriched or fortified foods, such as breakfast cereals.

**Conclusions:** Children with ASD have low iron intakes and are at risk for low SF. Taking into consideration the important consequences of iron deficiency on developmental and behavioral function in infants and children, dietary history and screening for iron stores should be considered in children with ASD and inadequate iron intake.

**Comments**

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impaired social and communication interactions as well as limited, repetitive interests and behavior. The longitudinal population-based Norwegian registry reported that children with ASD also have different growth trajectories when compared to other children.

Conventional treatment is based on the combination of behavioral and pharmacotherapy. Dietary manipulations are frequently adopted by families of children with ASD seeking to improve their children behavior. Dietary manipulations in conjunction with children’s peculiar feeding habits may easily result in multiple nutritional deficiencies, undernutrition or overweight and poor bone status, as illustrated by the studies published this last year. An important part of autism children’s care is evaluation and support of patient’s nutritional status to prevent further neurological and behavior deterioration as a result of nutritional deficiencies. Many studies have shown
the need to supplement the missing nutrients from the diets of autistic patients with fatty acids omega-3, probiotics, vitamins and minerals. Adopted diets should take into consideration nutritional requirements and food preferences of the patient. It is important to emphasize that continual monitoring of the diet and nutritional status of children with ASD is required. Parents and caregivers should be aware of the benefits and dangers of nutritional manipulations and the need for proper monitoring of diet and growth of children with ASD.

Anorexia Nervosa

Growth hormone level at admission and its evolution during refeeding are predictive of short-term outcome in restrictive anorexia nervosa

Nogueira JP1, Valéro R1,2, Maraninchi M1, Lorec AM3, Samuelian-Massat C2, Bégu-Le Corroller A2, Nicolay A1,3, Gaudart J4, Portugal H1,3, Vialettes B1,2

1UMR 1062 INSERM/1260 INRA, Aix-Marseille University, Marseille, France; 2Department of Nutrition, Metabolic Diseases and Endocrinology, APHM, La Timone Hospital, Aix-Marseille University, Marseille, France; 3Department of Biochemistry, APHM, La Timone Hospital, Aix-Marseille University, Marseille, France; 4Biostatistics Research Unit (LERTIM), Faculty of Medicine, APHM, Aix-Marseille University, Marseille, France


Aims: Investigation of prognostic value of GH, IGF-1 levels, adipocytokine profiles, insulin sensitivity, body composition and energy expenditure on the outcome in restrictive anorexia nervosa (AN).

Methods: Eleven patients diagnosed with AN (age 21 ± 0.39 years) and 10 healthy age-matched young women aged were studied at admission (T0, BMI 16), at discharge, (T2, BMI 17.5) and at 6 months after discharge (T3).

Results: At baseline (T0), plasma GH and serum ghrelin levels were higher in AN patients compared with controls (p < 0.05 for both). Plasma levels of IGF-1, estradiol, free tri-iodothyronine (fT3), leptin and adiponectin were significantly lower in patients with AN compared with control subjects (p < 0.05 for all). Plasma levels of glucose, insulin and HOMA-IR were also significantly lower in patients with AN than in control subjects (p < 0.05 for all). At the first stage of refeeding (T1) body fat mass (BFM) and body lean mass, resting energy expenditure (REE), active energy expenditure and total energy expenditure (TEE) increased significantly (p < 0.05 for all). A significant decrease in GH, ghrelin and testosterone levels and an increase in IGF-1 fT3 and estradiol concentrations were observed (p < 0.05 for all). A significant increase was only seen with adiponectin (p < 0.05). There was a significant increase in glucose, insulin and HOMA-IR levels (p < 0.05 for all). At T1, there was a significant negative association between GH and plasma glucose levels and between GH levels and active energy expenditure (r = 0.7, p < 0.04 and r = 0.8, p < 0.02, respectively). At T2 stage of refeeding (T1) REE increased significantly (p < 0.05). There was a significant increase in IGF-1 and leptin levels (p < 0.05 for both). Glucose and HOMA-IR levels increased significantly (p < 0.05 for both). Plasma GH levels were negatively and significantly associated with leptin levels (r = 0.8, p < 0.03). At 6 months after discharge with a BMI >17.5 (Δ = T2–T0), stepwise multivariate analysis showed that GH was the strongest determinant of BMI at T3, accounting for 74% of its variability (r = 0.74, p < 0.05).
Conclusions: GH level at admission was an important contributor in the variability of the final BMI. GH at admission and evolution during refeeding may predict short-term clinical outcome after weight recuperation. Specifically, low GH levels at admission in hospital and lower amplitude of plasma GH variation between admission and discharge from hospital were strongly associated with relapse 6 months after discharge.

Linear growth and final height characteristics in adolescent females with anorexia nervosa

Modan-Moses D1,2, Yaroslavsky A2, Kochavi B2, Toledano A2, Segev S2, Balawi F2, Mitrany E2, Stein D2,3

1Pediatric Endocrinology and Diabetes Unit, The Edmond and Lily Safra Children’s Hospital, The Chaim Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel; 2Pediatric Psychosomatic Department, The Edmond and Lily Safra Children’s Hospital, The Chaim Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel; 3The Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel


Aim: The aim of this study was to assess linear growth and final height in female adolescent inpatients with anorexia nervosa (AN).

Methods: This retrospective study reviewed all the medical charts of female patients hospitalized for the treatment of AN between 1/1/1987 and 31/12/1999. Pre-morbid and admission height and weight measurements were obtained from patients’ files. Final height (defined as height at age 18 or older, and at least 3 years after menarche) was measured in 69 patients 2–10 years following discharge from their index hospitalization.

Results: The mean age of the 211 patients on admission was 16.6 ± 4.2 years; the mean BMI was 15.7 ± 1.02, and the mean age at menarche was 12.7 ± 2.4 years. The mean height SDS on admission was −0.285 ± 1.02, and increased during hospitalization to −0.271 ± 1.02. Final height was available for 69 patients (32.7%). On admission, the mean height SDS of these 69 patients was −0.231 ± 1.103. During hospitalization, height SDS increased to −0.197 ± 1.122. Mean final height SDS was −0.258 ± 1.04 (161.6 ± 6.8 cm), which, similar to the admission and discharge height SDS, was significantly lower than expected in a normal population (p = 0.04). Height SDS on admission was a strong predictor of final height SDS (p < 0.001). A significant (p = 0.019) interaction was found between final height and pubertal status at admission. Patients admitted less than 1 year after menarche showed less catch-up growth and their final height was more severely compromised in comparison to patients admitted more than 1 year after menarche.

Conclusions: Growth retardation is present female adolescents with AN and affects final height, especially of younger adolescents. It seems that in order to achieve height catch-up to the pre-morbid percentile pre-morbid growth data should be obtained, and target weight should be based on the expected, rather than the measured height percentile at the time of diagnosis.

Comments

Anorexia nervosa (AN) is a psychiatric disorder that occurs mainly in female adolescents and young women. The obsessive fear of weight gain, critically limited food intake and neuroendocrine aberrations characteristic of AN have both short- and long-term consequences for the reproductive, cardiovascular, gastrointestinal and skeletal systems. The short-term, life-threatening complications include electrolyte abnormalities and cardiac complications such as sinus bradycardia, a prolonged QT interval on electrocardiography, arrhythmias, myocardial mass modification and hypotension.
Decrease in bone mineral density and the increased risk of spontaneous fractures are some of the most important medical consequences of AN. To this we should add growth retardation and lower final adult height, as shown by the study by of Modan-Moses et al. The treatment of AN should therefore aim not only at fast recovery but also to prevent and treat the long-term effects of this disorder. Monitoring GH levels at admission and during refeeding in patients suffering from AN was shown to have some prognostic value. The role of this factor in the disease is however, probably indirect, reflecting specific changes associated with the adapted response to starvation. Further investigations of the long-term disease risk of relapse and the approach to their prevention and treatment are needed.

References