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Original article

Impact of oral nutritional supplements (ONS) on growth outcomes and IGF-1 level in underweight older children and young adolescents (5-14 years) with short stature and no systemic disease: High versus normal calories density formula

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Abstract. *Objectives:* This controlled trial investigated the effects of energy-dense pediatric oral nutritional supplements ONS versus standard ONS in pediatric patients requiring oral nutritional support for low body mass index (BMI) or weight gain per day (WGD) below the average for age and sex. *Patients and Methods***:** 34 children and adolescents (mean age 10.2 years) with faltering growth requiring ONS were randomized to cONS (n =22) or sONS (n = 12) for a year. We recorded their weight (WT), height (HT) and calculated height growth velocity (GV), Ht-SDS, BMI, WGD, every 3 months for a year. *Results:* The WGD, height growth velocity (GV: cm/year), and Ht-SDS increased significantly, in both groups, during the year of ONS. The use of the cONS resulted in significantly greater mean total WGD and BMI-SDS after 6 months and 1 year, compared to the sONS group. The increase in IGF1-SDS was significantly higher in the cONS groups versus the sONS group. Moreover, the WGD was correlated significantly with the height GV during the year of ONS intake. *Conclusions:* ONS improved the growth of underweight old children and adolescents who had no systemic illness. There was a significantly higher WGD and BMI-SDS in the group on cONS compared to those on sONS. In both groups, long-term use of ONS significantly improved Ht-SDS. (www.actabiomedica.it)

Key words: Underweight, older children and adolescents, oral nutritional supplementation (ONS), anthropometric assessment, Insulin-like growth factor 1 (IGF1).

Introduction

Prolonged loss of appetite associated with poor weight gain or loss of weight usually indicates a serious chronic illness, either organic or psychogenic. However, many healthy and active children and adolescents have a low appetite and faltering growth (slow weight gain and/or slow height growth velocity (GV) without any apparent illness. Weight faltering is defined as a weight falling through centile spaces, low weight for height or low WGD, while growth faltering is defined as crossing down through length/height centile(s) as well as weight, a low height centile or height less than expected from parental heights (1,2).

According to World Health Organization (WHO), childhood undernutrition includes wasting

[weight-for-height z-score (WHZ) < –2SD], stunting [height-for-age z-score (HAZ) < –2SD], underweight [weight-for-age z-score (WAZ) < –2SD], using World Health Organization (WHO) 2006 growth reference standards (3), and micronutrient deficiencies or insufficiencies.

Chronic undernutrition occurs due to long-term insufficient intake of nutrients and a complex interplay of intergenerational and environmental factors, resulting in stunting. Nutrition-specific factors include inadequate food and nutrient intake, poor feeding, caregiving, and parenting practices, and burden of infectious diseases (3).

Stunting is the most prevalent form of undernutrition: 151 million children under 5 years old were stunted in 2017 and more than 90% of stunted children live in Africa and Asia (4). Being stunted is associated with reduced cognitive development and adult productivity, adverse maternal reproductive outcomes, and risks of non-communicable diseases in adulthood (5,6).

Adolescence is the second fastest period of growth after infancy, and thus a period of high nutritional requirements to meet the physiological demand for development. Approximately 20% of total height gain occurs in adolescence and up to 50% of adult bone mass is achieved during this period. To achieve this growth, nutritional requirements, both for energy as well as micronutrients, increase relative to childhood (7,8).

Globally, there are 1.8 billion children and adolescents ages 5–19 years: nearly 90 percent live in low- and middle-income countries (LMICs) (9). Little information about the prevalence and consequences of malnutrition is available for children and adolescents ages 5 - 19 years, although they constitute 27 percent of the population in LMICs (8,9).

The World Health Organization (WHO) currently recommends the provision of nutrient-dense supplementary food to children with moderate undernutrition to meet the child's extra needs for weight and height gain and functional recovery (WHO 2012). There are currently no evidence-informed recommendations on the composition of supplementary foods used to treat undernourished children. Oral supplementary foods are defined as specially formulated foods in ready-to-eat, milled or powdered form which is modified in energy density, protein, fat, and/or micronutrient composition to help meet the nutritional requirements of undernourished children. These foods are intended to supplement the home diet, and not to meet the total daily nutritional intake requirements of these children (10).

Ready-made oral nutritional supplements (ONS) designed for children and available on prescription typically provide 1–1.5 kcal/ml in 200 ml bottles. However, children and adolescents with increased energy requirements, poor feed tolerance, and/or appetite loss, may struggle to achieve their nutritional requirements with currently available options. One possible strategy to improve nutrient intake in children with faltering growth is to reduce ONS volume by increasing the energy and nutrient density. Therefore, these formulas may be used in underweight children and adolescents with volume sensitivity or those with poor appetite (11). When undertaken with food this kind of ONS has been shown to increase energy intake and appetite without affecting fullness in infants and young children. Moreover, a positive correlation has been found between ONS compliance and ONS energy-density (12,13).

ONS is used successfully in the management of underweight infants and young children with undernutrition. However, the major global focus of health has been on children under the age of 5 years and pregnant women, while older children (aged 6–9 years) and adolescents (aged 10–19 years) have not received the due attention until lately. Consequently, ONS use in older children and adolescents with underweight and/or poor weight gain has not been fully reported.

The aim of the present study was to evaluate the effect of liquid ONS with two different caloric density on linear growth and weight gain in short underweight children and adolescents with no systemic illness.

Patients and methods

45 underweight older children and young adolescents (aged 10 ± 4 years) with short stature (HtSDS <-2 or > 1 SD below their mid-parental Ht-SDS) with BMI-SDS < -1 >-2, and /or weight gain /day (WGD) below average for age and sex were enrolled in our study. All were born at term with normal physical examination, with no systemic illness or complaints. They had normal thyroid, renal and hepatic functions, normal erythrocyte sedimentation rate (ESR), and normal hemogram.

Exclusion criteria were hepatic/renal dysfunction, celiac disease, and malabsorption, chronic diarrhea or vomiting, anemia, and any endocrine or systemic illness.The subjects were divided randomly into two groups according to the type of NS and advised to take 500 Kcal/d, in addition to their habitual diet for one year. Group 1 (N=12) received (1cal/1 ml) formula (sONS) and Group 2 (N=22) received 1.5 Kcal/1ml formula (cONS) to be taken orally every day for 12 months (Table 1). The ONS volume was determined by the dietitians according to local protocols and based on clinical judgment.

Two experienced pediatric dietitians calculated the energy and protein intake and evaluated the compliance of parents and children every clinic visit based on the 24h recall method, dietary history, and WGD. Nutrient intake from ONS alone was calculated from ONS compliance, which was recorded by the parents daily, and only children with a mean ONS compliance ≥ 75% calculated were included in the study. 12 out of 15 children on sONS and 22 out of the 30 children on the cONS were compliant with the ONS.

Improvement in appetite and gastrointestinal tolerance and severity of gastrointestinal symptoms at baseline and during subsequent visits were recorded at 3, 6 and 12-months visits. No severe gastrointestinal symptoms occurred that required discontinuation of the ONS.

Anthropometric Assessment

The weight (WT), height (Ht), body mass index (BMI), were measured every visit and their WGD, Ht-SDS, and growth velocity /year (GV) were calculated every 3 months for a year. Bodyweight was measured with light clothes and without shoes and jackets using an electronic weighing scale and recorded to the nearest 0.1 kg. Standing height was measured with a stadiometer and recorded to the nearest 0.1 cm. Classification of the nutritional status of the children were based on sex- and age-specific Z- scores using WHO Growth Standards (14).

Serum insulin growth factor 1 (IGF-1) was measured, at baseline and after 1 year, by automated LIAISON XL assay, manufactured by DiaSorin, with intraassay CV= 5.1% at 70 ng/mL, 3.5% at 183 ng/mL and 3% at 589 ng/mL, and inter assay CV = 9.6% at 80 ng/mL, 7.1% at 187 ng/mL and 5.6% at 317 ng/mL using a commercial kit.

Ethical Approval

Information about the objective of the study, procedures, potential risks, and benefits were given to the parents before their children were enrolled in the study.

Statistical analysis

Student t-test was used to compare variables between the two groups, before and after ONS, when the data were normally distributed, and Wilcoxon rank-sum test was used when the data were not normally distributed. The linear regression equation was used to study possible relations between variables. P was accepted as significant at < 0.05.

Results

The provision of both sONS and cONS, in addition to appropriate nutrition, for a year significantly improved total nutrient intakes and improved appetite.

After 6 months on ONS, the WGD and BMI-SDS increased more significantly in the cONS group

Table 1. Nutritional composition of the ONS (cONS versus sONS)

Nutritional composition	cONS per 200 ml bottle	sONS per 200 ml bottle
Energy, Kcal	300	200
Energy density, Kcal/ml	1.5	1
Protein, g	6.8	4.8
Carbohydrate, g	37.6	23.6
Fat, g	13.6	9
Osmolality. mOsmo/kg	350-595	230

versus the sONS group. The height GV and Ht-SDS increased significantly during the year of ONS (Table 2) in both groups. After 1 year on ONS the GV-SDS and the gain in the Ht-SDS increased significantly in both groups with no statistical difference between them.

The WGD was correlated significantly with the height GV in all children on ONS (Figure 1 and table 3).

The IGF1-SDS and BMI-SDS increased more in the cONS group versus the sONS group. The IGF1-SDS was correlated significantly with the height GV, GVSDS and BMISDS. (Figures 2 and 3, table 4). After a year of ONS the Ht-SDS was significantly correlated with the BMI-SDS (Figure 4).

We considered children who consumed > 75% of their prescribed cONS as compliant. The compliance with cONS did not differ significantly between the cONS group versus the sONS (22/30 (73%) vs. 12/15 (80%) respectively (p = 0.49).

Discussion

Faltering growth is the failure of children to achieve adequate growth at a normal rate for their age, because of inadequate nutritional intake/absorption of nutrients in relation to their requirements. This can occur at any stage in children from birth to adolescence.

In a clinical setting, many otherwise healthy children and adolescent who present with short stature or decreased linear growth are underweight and/or have slow weight gain.

In these children, parents usually describe lack of appetite and/or picky eating behavior. The contribution of undernutrition and poor intake (quality and quality) to their slow linear growth can be assessed by supplying adequate nutrition (proteins and calories) enough to support a catch-up process. However, if faltering growth continues and dietary intake alone proves

Table 2. Anthropometric data of children on oral nutritional supplementation [high caloric density (cONS) vs standard caloric density (sONS)]

Variables	sONS at baseline (12 pts.)	cONS at baseline (22 pts.)	P value	sONS at 6 months (12 pts.)	cONS at 6 months (22 pts.)	P	sONS at 12 months (12 pts.)	cONS at 12 months (22 pts.)	P value
Age at baseline	8.94 ± 4.84	10.1 ± 3.82	NS	-	-	-	-	-	-
HT-SDS	-2.25 ± 0.82	-2.3 ± 0.67	NS	-1.99 ± 0.77	-2.05 ± 0.59	NS	-1.735* ± 0.76	-1.84* ± 0.69	NS
MPH-SDS	-0.43 ± 0.72	-1.09 ± 0.74	**0.02**	-	-	-	-	-	-
BMI-SDS	-1.08 ± 0.54	-1.32 ± 0.41	NS	-1.24 ± 0.58	-0.98 * ± 0.47	NS	-1.19 ± 0.59	-1.15 ± 0.40	NS
GV-SDS	-1.09 ± 1.28	- 0.4 ± 1.82	**0.02**	0.36* ± 1.29	0.08 * ± 0.90	NS	1.168* ± 0.83	1.31* ± 1.00	NS
Δ HT-SDS	-	-	-	0.27 ± 0.55	0.08 ± 0.28	NS	0.52* ± 0.43	0.48* ± 0.32	NS
Δ BMI-SDS	-	-	-	-0.16 ± 0.29	0.34 * ± 0.50	**0.006**	-0.11 ± 0.34	0.17* ± 0.47	**0.057**
WGD	5.20 ± 2.10	4.50 ±1.80	NS	8.65 ± 3.98	14.13 * ± 7.78	**0.045**	9.85 ± 4.71	11.6* ± 6.58	NS
IGF1-SDS	-0.6 ± 0.3	-0.48 ±0.5	NS	-	-	-	-	-	-
Δ IGF1- SDS	-	-	-	-	-	-	0.35* ± 0.16	1.5* ± 0.6	**0.02**

Legend= *HT-**SDS:** standing height SDS; **MPH-SDS:** mid parental height SDS; **BMI-SDS:** body mass index SDS; **GV-SDS:** growth velocity/year SDS; **WGD:** weight gain per day; **IGF1-SDS**: Insulin growth factor- 1 SDS; ***:** p<0.05 after vs before oral nutritional supplementation (ONS).*

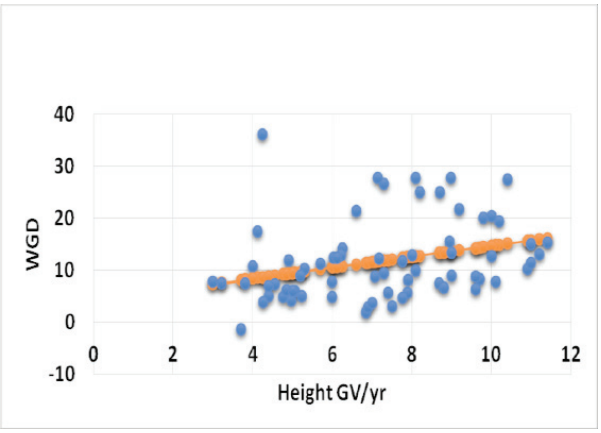

Figure 1. Correlation between heigh growth velocity/year (GV/yr) and weight gain per day (WGD) after nutritional supplements (ONS) (r= 0.31; P:0.01).

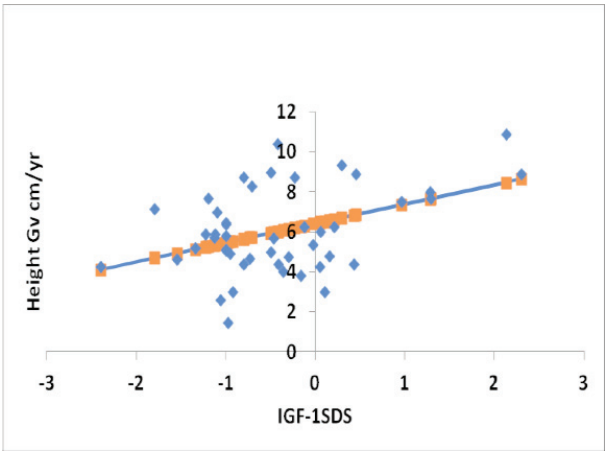

Figure 2. Correlation between IGF 1-SDS and height growth velocity (GV:cm/yr) (r= 0.427; P:0.003).

Table 3. Correlations between weight gain per day (WGD) and linear growth parameters after starting oral nutritional supplementation (ONS)

	WGD	GV	GV-SDS	Ht-SDS
WGD	1.00			
GV	0.31*	1.00		
GV-SDS	0.19	0.83*	1.00	
Ht-SDS	0.19	0.32*	0.29	1.00

Legend= WGD: *weight gain per day;* ***GV:*** *growth velocity/year;* ***GV-SDS:*** *growth velocity/year SDS;* ***HT-SDS:*** *standing height SDS;* ****:*** *P <0.05.*

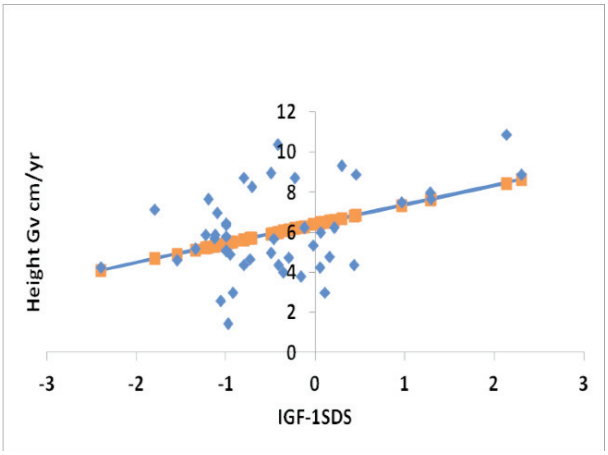

Figure 3. Correlation between IGF 1-SDS and body mass index SDS (BMI-SDS) (r= 0.356; P:0.015).

insufficient, a complete oral nutritional supplements (ONS) specifically designed for children should be considered to help children to satisfy their nutritional intake and to improve their weight gain (12, 15,16).

The present study evaluated the effects of intake of energy dense, low-volume, pediatric cONS versus standard pediatric sONS on linear growth and WGD of older children and young adolescents with faltering growth. Ready-made liquid ONS, especially the

Table 4. Correlations between IGF1- SDS and linear growth parameters

	Ht-SDS	BMI	BMI-SDS	GV cm/y	GV-SDS	IGF-1SDS
Ht-SDS	1					
BMI	-0.01829	1				
BMI-SDS	0.103232	0.107725	1			
GV (cm/y)	0.090506	0.113137	0.142	1		
GV-SDS	0.334585*	0.142922	0.051	0.57*	1	
IGF1-SDS	0.243258	0.070208	0.356*	0.42*	0.23*	1

Legend= HT-SDS: *standing height SDS;* ***BMI:*** *body mass index;* ***BMI-SDS:*** *body mass index;* ***GV:*** *growth velocity/year;* ***GV-SDS:*** *growth velocity/year SDS;* ***IGF1-SDS:*** *Insulin growth factor 1 SDS;* ****:*** *P <0.05.*

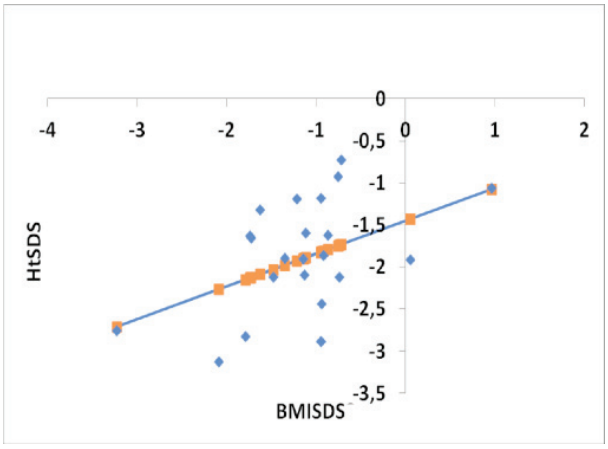

Figure 4. Correlation between body mass index SDS (BMI-SDS) and standing height SDS (HtSDS) after oral nutritional supplements (ONS) for 1 year (r= 0.45; P:0.031).

cONS, is suggested to increase compliance in children and adolescents and increase their total energy and protein intakes. No long-term comparative studies have been published to address this issue in this age group (17).

During the year of the study the GVSDS and the WGD increased significantly in both groups taking cONS and sONS. A significantly higher increase in the IGF1-SDS was associated with higher gain in WGD and BMI-SDS in the cONS versus the sONS group. In both groups the Ht-SDS improved during the year of ONS intake with no statistical difference between them.

In support of our data, Fatima et al. (18) compared the effect of four weeks supplementation with therapeutic foods RUTF (a high-protein peanut-based paste) versus ONS (500 kcal/day) on nutritional outcomes of 68 underweight (weight Z-score: -2 to -1) Pakistani children (5-10 yrs). All nutritional outcomes and height improved with both supplements. Substantially, weight gain (kg) and changes from baseline for weight, height, triceps, and sub-scapular thickness Z-scores did not differ comparing the two supplements. The mean WGD was 23.4g/day in the ONS group versus 21 g/d in ready-to-use therapeutic food (RUTF)

group. However, post- supplementation, there was a tendency for weight and height Z-score to return to baseline. These data and Huynh et al. studies (19,20) suggest that prolonging the duration of ONS is important to maintain the required weight gain and linear growth. Therefore, it seems that although ONS can increase the WGD early, a longer period of intake may be necessary to ensure significant increase in the height gain as reported also by other Authors (19-21).

Moreover, the use of energy-dense ONS (2.4 kcal/ml) with higher caloric density than that used in our study (1.5 Kcal/ml) was also successful to improve nutrient intakes, growth, and appetite in children requiring ONS compared with standard energy density ONS (17). Collectively, our study, supported by others, showed that long-term use of energy-dense, cONS were effective for children with faltering of growth and was tolerated well and associated with higher weight gain compared to sONS.

In our study in older children and young adolescents, there was a lag of height gain after proper weight gain. There are some interesting observations in the literature on the temporal patterns of gains in height and in weight. Brown et al. (22) in Bangladesh made a longitudinal study of the growth of children (6- 60 months of age) over a period of 14 months. Weight gains were minimal in August, towards the end of the monsoon, and then, as food became available, reached a peak in February. Height gains were minimal in January and reached a peak in April-May. Thus, height gains followed weight gains by 3-4 months. Seasonal effects on growth have been observed also by Nabarro et al. in Nepal (23).

Before introducing ONS, our older children and young adolescents had a relatively low IGF1-SDS (-0.6 and -0.5, respectively) that increased significantly after ONS. This increase in the IGF1-SDS was correlated significantly with the BMI-SDS and Ht-SDS after a year of ONS (increased caloric and protein intake) and was more significant in the cONS group versus the sONS group. Nutrition is a major factor in regulating IGF-1 secretion, if caloric intake is reduced by approximately 50% a significant reduction in IGF-1 secretion quickly occurs, but even smaller reductions result in changes in IGF-1 levels. Both protein and energy balance participate in the regulation of hepatic synthesis with energy regulating IGF-1 gene transcription and protein functioning primarily to regulate mRNA stability and translation (24,25).

In mice, the potential function of central IGF-1 in energy metabolism was investigated after intracavernous injection of IGF-1 and an anti-IGF-1 antibody. IGF-1 increased food intake while the anti-IGF-1 antibodies decreased appetite. These data showed that increasing IGF-1 in the brain circulation had a stimulant effect on appetite centrally and improved insulin sensitivity peripherally. Therefore, increasing IGF-1 through nutritional supplement may explain the improved appetite observed in our children who received ONS. (26.)

IGF-1 data derived largely from animal models also demonstrated that altered levels of endogenous circulating and/or local IGF-1 accompany changes in growth of intestinal epithelium. Systemically administered or transgene derived IGF-1 potently increase the mass of small bowel epithelium in normal adult animals and preclinical models of TPN. Studies in transgenic mice indicate that IGF-1 consistently and potently increases epithelial mass, crypt proliferation, and small bowel length than growth hormone (GH), and that IGF-1 but not GH has anti-apoptotic effects on crypt epithelial cells (27,28).

Moreover, experiments showed that cirrhotic (an IGF-1 deficiency condition) rats had diminished amino acid and glucose intestinal absorption and that IGF-1 replacement therapy was able to restore both alterations to normal, suggesting a role of IGF-1 in the position of transporters. In normal piglets, IGF-1 stimulates intestinal villus growth, increases jejunal lactase phlorizin hydrolase activity (LPH activity) and LPH mRNA abundance, and stimulated intestinal cell hyperplasia (29-31).

These data suggested that correction of the low IGF-1 level in children with faltering growth, through nutritional supplementation, can increase their weight gain through stimulation of appetite (increased nutrient intake) as well increasing absorption of nutrients. In addition, IGF-1 increases peripheral glucose uptake and a decreases production of hepatic glucose causing increased insulin sensitivity (anabolic effect). These effects, in addition to the anabolic effects of IGF-1 in protein synthesis and fat metabolism may explain the higher weight gain in these children (32,33) (Figure 5).

In summary, the use of ONS to increase caloric and protein intake significantly increased WGD

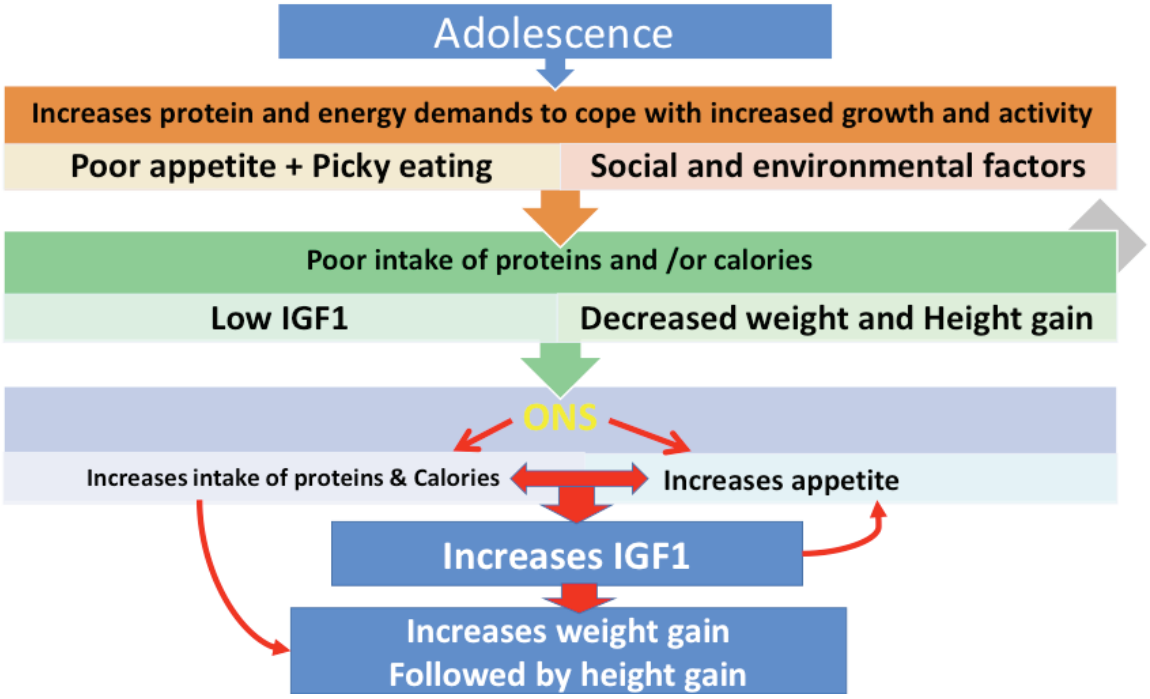

Figure 5. Effects of oral nutritional supplementation (ONS) on IGF-1 and growth

and BMI-SDS which was associated with increased IGF1-SDS and followed by significant gain in Ht-SDS. Using cONS was coupled with higher increase in IGF1-SDS and more significant gain in weight and BMI-SDS compared to the sONS. The significant weight gain in our children with faltering growth is likely due to both increased lean body mass (anabolic action of IGF-1 on protein synthesis) and linear growth (longitudinal bone growth and bone mineral accretion).

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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