Annals of Nutritional Disorders & Therapy

Open Access

Austin Publishing Group

Research Article

Growth-Promoting Effects of Omega-3-Fatty Acid Supplementation in Children with Short Stature

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Received: June 03, 2020; **Accepted:** June 24, 2020; **Published:** July 01, 2020

Abstract

We proof the effect of an omega-3-fatty acid supplementation (245 days on average) on height and 24-hours Heart Rate Variability (HRV) in 34 children with short stature of whom 17 children received an ongoing growth hormone treatment.

Results: During Omega-3-fatty acid supplementation±growth hormone treatment the height percentile increased from the 6.2±9.7% to 7.0±9.4% (p=0.306) but the height standard deviation score significantly increase from -2.2±1.1 to -2.0±1.0 (p=0.009). Growth velocities are not significantly different after omega-3-fatty supplementation between growth hormone treated and untreated children (8.2±4.8 cm/year versus 8.1±3.4 cm/year; p=0.103). Mean 24-hours heart rate decreased from 103.9±16.1 bpm to 96.6±13.2 bpm (p<0.0001). Mean HRV significantly increased as indicated by a significant higher SDNN (111.9±30.8 ms versus 97.6±30.2 ms, p=0,001), RMSSD (29.4±12.2 ms versus 25.2±11.5 ms, p=0,003) and very low frequency power (1524±957 ms^2 versus 1122±708 ms^2, p=0,001).

Conclusion: Omega-3-fatty acid supplementation in children with short stature improves height and heart rate variability independently from an ongoing growth hormone treatment.

Introduction

Per definition 3% of a population "suffers" from short stature. There are many discussions about the psychosocial burden of short stature and the need for further diagnostics and consecutive therapies with in part high economic burden. However, there are some diseases that have to be treated like coeliac disease and an often unrecognized impact of short stature on cardiovascular prognosis that is far away to be well defined. However, the Development Origin of Health and Disease (DOHaD) hypothesis occupied a lot researcher worldwide who try to explain the statistical relationship of fetal growth, short stature and cardiovascular risk. In this context there is a link to omega-3-fatty supplementation recently reviewed by MR Skilton [1]. There is a further link to a phenomenon called stunting in nearly 180 million children due to under nutrition most of all in the developing world who suffer from short stature and cognitive impairment [2].

Within the last 10 years we develop a pathophysiological model that try to explain short stature induced by early life stress due to heart failure, intrauterine growth retardation and genetic syndromes [3]. We use 24 hours analysis of Heart Rate Variability (HRV) to detect early stress and monitor the effect of therapeutic interventions on HRV in children:

1) We found a pathologic HRV response to clonidine in children with short stature [4],

2) We found reduced HRV in children with short stature except those with constitutional growth delay [3],

3) We found normal HRV in children with short stature after cessation of growth hormone therapy [5],

4) We found an improvement of HRV in children with short stature after 3 month omega-3-fatty acid supplementation [6].

We now proof the effect of omega-3-fatty acid supplementation on height in 34children with short stature.

Methods

Patients

The current study included 34 children with short stature with an age of 6.6±4.4 years on average who were referred to the outpatient clinic in the Pediatrics Department of the Caritas Hospital in Bad Mergentheim, Germany between the years 2013 and 2019 for further diagnostics and therapy of short stature. All patients and their parents were informed about recombinant growth hormone treatment according to the current guidelines. Cardiovascular risk stratification using 24-hour HRV analysis, measured by 24-hour Holter ECG is part of our clinical routine in children with short stature. In those children with significantly reduced 24-hour HRV we also offered the opportunity to supplement omega-3 fatty acids and participate in the study. If the supplementation was not covered by health insurance, patients usually purchased different products based upon 1-2 g fish oil per day from a retail store. The following dose recommendations were given: Children up to an age of 8 years should receive at least 400mg Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) as a suspension per day. Children who were able to swallow capsules should receive at least 800mg EPA and DHA per day. The following patients agreed to participate in the study (Figure 1):

1) Thirteen children with intrauterine growth retardation, 6 children had a genetic syndrome (Turner-, Silver Russell -, Downs- and VACTERL syndrome); 7 received growth hormone therapy.

Citation: Buchhorn R. Growth-Promoting Effects of Omega-3-Fatty Acid Supplementation in Children with Short Stature. Ann Nutr Disord & Ther. 2020; 7(1): 1064.

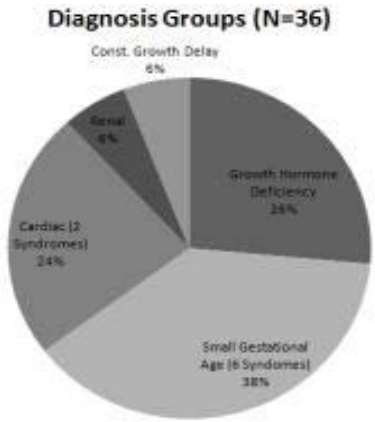

Figure 1: Diagnosis Groups of the 36 children with short stature.

2) Nine children with growth hormone deficiency, 8 received growth hormone therapy.

3) Eight children with heart disease none received growth hormone therapy.

4) Two children with renal disease who receive growth hormone therapy.

5) Two children with constitutional growth delay with additional autonomic dysfunction, none received growth hormone therapy.

The HRV was measured at baseline and a second time after an average of 245 days of omega-3 fatty acid supplementation by Holter ECG.

The height and weight were measured for each patient by nurses who are not informed about fatty acid supplementation. The Body Mass Index (BMI), height- and BMI percentiles as well as the Standard Deviation Score (SDS) were calculated.

Control group

For controls, data from normal healthy children (N=85) were retrieved from a previous project investigating normal HRV in children [7]. Therefore, the data from these patients, who attended our outpatient clinic for exclusion of cardiac arrhythmia, was analyzed retrospectively. The retrospective analysis was approved by the ethical board of our states medical chamber (Landesärztekammer Baden Württemberg) and recently published.

24 hour ECG and analysis of heart rate variability

Fundament of every HRV data analysis is a group of successive normal RR intervals in sinus rhythm (so called NN intervals in comparison to RR intervals in cardiac arrhythmia) in 24 hours.

Measurement and interpretation of HRV parameters in the current sample were standardized according to the Task Force Guidelines [8]. Cardiac autonomic functioning was measured by 24-hour Holter 12-bit digital ECG (Reynolds Pathfinder II, Spacelabs, Germany; 1024 scans/sec). Daytime and night-time periods were defined according to patient protocols. All Holter recordings were reviewed by the same experienced cardiologists (RB and CW) and were edited to validate the systems QRS labelling. Measures of HRV were calculated employing only normal-to-normal intervals. QRS-complexes classified as noise were excluded from the data. A minimum of 23 hours of analyzable data and minimally 95% of analyzable NN intervals were required for data to be included. For time domain measures, mean RR interval, resulting heart rate and the following HRV parameters were calculated.

For didactic reasons in this study we focus on the statistical analysis of the following 4 parameters, which are briefly outlined below:

1) Heart rate: The easiest but very important HRV parameter is the average sinus rhythm heart rate, since all other parameters are significantly affected by the heart rate.

2) SDNN: Standard deviation of all normal RR intervals in a time frame. This global HRV parameter represents the overall variability of the autonomic nervous system.

3) rMSSD: Square root of the arithmetic mean of the squared deviation of successive normal RR intervals in a time frame. This parameter is mainly influenced by the parasympathetic nervous system.

4) pNN50: Number of pairs of adjacent NN intervals differing by more than 50ms divided by the total number of all NN intervals multiplied by 100. This parameter is mainly influenced by the parasympathetic nervous system.

For frequency domain measures, beat-to-beat fluctuations were transformed to the frequency domain using Fast Fourier Transformation. Spectral power was determined over three frequency regions of interest: Very low frequency (VLF, <0.04Hz), low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.4 Hz) with derived HF/LF ratio. Low frequency power reflects mostly sympathetic activity, high frequency power vagal tone.

Statistical analysis

All results were reported as mean±Standard Deviation (SD). Parametric statistics were used for all comparisons as most variables were normally distributed. Patients were compared before and after omega-3 fatty acid supplementation using a paired samples t-test for equality of means. Patients were divided in two groups each with 17 children according the ongoing growth hormone therapy and were

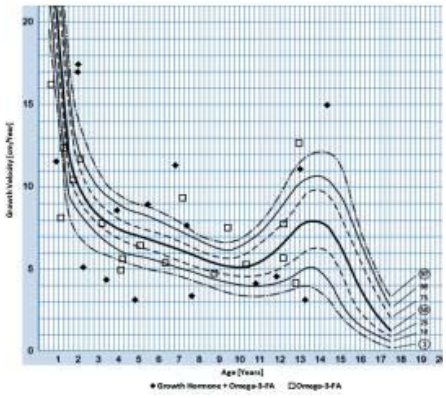

Figure 2: Growth velocities of the 36 children with short stature after Omega-3-fatty acid supplementation in comparison to healthy boy's percentiles.

compared using an independent samples t-test for equality of means.

Results

Patient characteristics and 24-hour mean values from the Holter ECG monitor, age, height, and Body Mass Index (BMI) are summarized in Table 1&2. All patients had short stature and height below third percentile using the reference charts of Kromeyer-Hauschild et al. However, seventeen children received recombinant growth hormone therapy and showed significant "catch–up" growth up to the 45th percentile before omega-3 fatty acid supplementation. As shown in table 3, age, height and body mass indices were not significantly different between growth hormone treated and untreated children before omega-3 fatty acid supplementation.

Using a paired t-test, all children are growing with significantly higher heights and weights while the body mass index remained unchanged (Table 1). During Omega-3-fatty acid supplementation ± growth hormone therapy the height percentile increased from the 6.2±9.7% to 7.0±9.4% (P=0.306) but the height standard deviation score significantly increase from -2.2±1.1 to -2.0±1.0 (P=0.009).

As shown in Figure 2, growth velocities are not significantly different after omega-3-fatty supplementation between growth hormone treated and untreated children (8.2±4.8 cm/year versus 8.1±3.4 cm/year; p=0.103; Table 3).

As previously published [3,9], baseline HRV in our study group is significantly reduced, and mean heart rates are significantly enhanced, relative to healthy controls (Table 2, Figure 3&4). After supplementation of omega-3-fatty acids, the mean HRV significantly increased as indicated by a significant higher SDNN (111.9±30.8 ms versus 97.6±30.2 ms), RMSSD (29.4±12.2 ms versus 25.2±11.5 ms) and very low frequency power (1524±957 ms^2 versus 1122±708 ms^2). Mean heart rate decreased from 103.9±16.1 bpm to 96.6±13.2 bpm (p<0.0001). Mean heart rate reduction was comparable at both day (8.0bpm on average) and night (7.3bpm on average), but due to a lower standard deviation, only the nighttime values reached statistical significance (p=0.002). Global HRV remained significantly reduced despite the HRV improvement as shown in figure 3+4. Mean heart rates are in the normal range before and after omega-3-fatty supplementation.

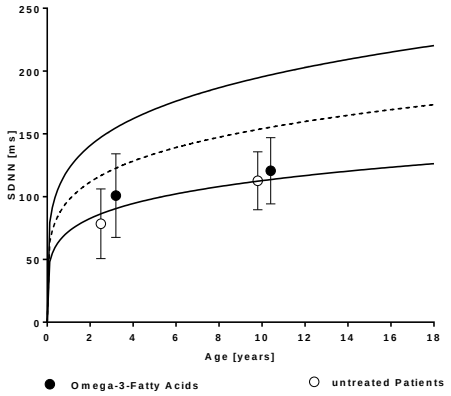

Figure 3: Effect of omega-3-fatty acid supplementation on global heart rate variability SDNN in children with short stature compared to healthy children (mean±1standard deviation).

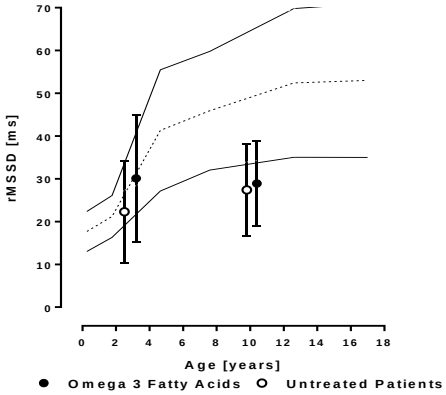

Figure 4: Effect of omega-3-fatty acid supplementation on the vagus parameter rMSSD in children with short stature compared to healthy children (mean±1standard deviation).

Discussion

We found a significant growth-promoting effect of Omega-3-Fatty Acid supplementation in children with short stature, indicated by a significant increase of the height standard deviation score from -2.2±1.1 to -2.0±1.0 (P=0.009) within a mean supplementation duration of 245 days. This beneficial effect seems to be independent of the ongoing growth hormone therapy in 17 of 34 children. Both groups show normal growth velocities on average (8.2±4.8 cm/year versus 8.1±3.4 cm/year; p=0.103; Table 3 and Figure 2). As recently published [6], this beneficial growth promoting effect of Omega-3-Fatty Acid supplementation in children with short stature is accompanied by a highly significant improvement of the impaired autonomic regulation indicated by reduced 24 hours heart rate variability.

Our data are in good accordance with a recently published study about Omega-3-Fatty Acid supplementation in children with sickle cell disease in Saudi Arabia [10]. The authors measure comparable growth velocities of 6.2cm/year in 16 children with an age of 5-10 years and 14 cm/year in 8 children with an age between 11-16 years. In this study better growth is related to a significantly higher calorie intake.

We didn't measure calorie intake but 24-hour heart rate variabilities, if our primary intention for Omega-3-Fatty Acid supplementation was to improve the enhanced cardiovascular risk indicated by significant reduced heart rate variability. However, despite the significant improvement of heart rate variability the global heart rate variability SDNN remained reduced in nearly 50% of children at the mean age of 10 years (Figure 3). At this age even more children showed a reduced vagus activity indicated by the parameter RMSSD as shown figure 4.Both parameters are important surrogate parameter of an enhanced cardiovascular risk [11].

Our patient selection for Omega-3-Fatty Acid supplementation in children based upon a reduced 24-hour HRV in Holter ECG monitoring and the study group is a negative selection of all children treated in our outpatient clinic in the Pediatrics Department of cause short stature who had probably the highest cardiovascular risk.

There are many attempts to predict the cardiovascular risk in

Table 1: Anthroprometric measurement before and after Omega-3-fatty supplementation.

		Baseline		Omega-3-FA Supplementation		
	N	Mean	SD	Mean	SD	P-value
Age [Years]	34	6,6	4,4	7,3***	4,4	0
Height [cm]	34	108,7	27,8	113,8***	26,7	0
Height Perc. [%]	34	6,2	9,7	7,0	9,4	0,306
Height SDS	34	-2,2	1,1	-2,0**	1,0	0,009
Weight [kg]	34	20,2	11,8	22,2***	13,2	0
Weight Perc. [%]	34	13,1	21,3	13,2	20,7	0,921
Body Mass Index [kg/m²]	34	15,5	2,5	15,7	2,9	0,369
BMI Perc. [%]	34	29,9	30,6	30,6	31,5	0,741
BMI SDS	34	-0,9	1,3	-0,9	1,5	0,983
Systolic BP [mmHg]	11	106,6	12,3	107,8	8,3	0,728
Diastolic BP [mmHg]	11	59,4	12,7	61,3	9,3	0,537

BMI: Body Mass Index; Perc.: Percentile; BP: Blood Pressure; SDS: Standard Deviation Score.
Paired t-test before and after Omega-3-fatty supplementation: *P-value<0.05; **P-value<0.01; ***P-value<0.001.

Table 2: 24-hours heart rate variability before and after Omega-3-fatty supplementation.

		Baseline		Omega-3-FA Supplementation		
	N	Mean	SD	Mean	SD	P-value
Heart Rate [bpm]	34	103,9	16,1	96,6***	13,2	0
SDNN [ms]	34	97,6	30,2	111,9***	30,8	0,001
RMSSD [ms]	34	25,2	11,5	29,4**	12,2	0,003
pNN50 24h [%]	31	10,0	9,7	12,3	11,5	0,126
TP 24h [ms²]	33	2327	1666	3173	2598	0,07
VLF 24h [ms²]	33	1122	708	1524***	957	0,001
LF 24h [ms²]	33	689	582	829	553	0,158
HF 24h [ms²]	33	429	566	648	1211	0,345
HF/LF 24 h	31	0,621	0,352	0,726	0,577	0,189

SDNN: Standard Deviation of all NN intervals; RMSSD: The Square Root of the Mean of the Sum of the Squares of Differences between adjacent NN intervals; pNN50: Number of pairs of adjacent NN Intervals differing by more than 50ms divided by the total number of all NN intervals; TP: Total Power; VLF: Very low Frequency Power; LF: Low Frequency Power; HF: High Frequency Power; HF/LF: Ratio HF to LF.
Paired t-test before and after Omega-3-fatty supplementation: *P-value<0.05; **P-value<0.01; ***P-value<0.001.

early childhood, when arterial blood pressure is in the normal range. MR Skilton et al published data upon the beneficial effect of omega-3-fatty acid supplementation on cardiovascular risk in children born with low birth weight. In the prospective studies using the surrogate parameter blood pressure [12] and arterial wall thickening [13] this group found beneficial effects.

For cardiovascular risk stratification, we prefer the mean 24-hour heart rate that is related to all cause and cardiovascular mortality in a big cohort of Swedish adolescents (1968-2005; n=1008485; mean age=18.3 years) [14]. We found a very stable reduction of the mean 24-hour heart rates by 7-8 bpm in all our published cohorts after Omega-3-Fatty Acid supplementation as recently published in the International Journal of Cardiology [15]. This beneficial effect on

Table 3: Anthroprometric measurement before and after Omega-3-fatty supplementation with respect to an ongoing growth hormone treatment.

	Growth Hormone + Omega-3-Fatty Acids		Omega-3-Fatty Acids		
	Mean	SD	Mean	SD	P-value
Patients	N=17		N=17		
Age [Years]	7,1	4,5	6,0	4,3	0,778
Growth Velocity [cm/Year]	8,2	4,8	8,1	3,4	0,103
Time [Days]	290,2	232,9	200,1	168,4	0,367
Height [cm]	114,2	29,2	103,1	26,0	0,553
Height Perc. [%]	8,9	12,8	3,5	3,7	0,001
Height SDS	-2,1	1,3	-2,3	1,0	0,331
Weight [kg]	23,4	14,1	17,0	8,3	0,02
Weight Perc. [%]	19,2	27,5	7,1	10,2	0,002
Body Mass Index [/m²]	16,0	2,9	15,1	1,8	0,166
BMI Perc. [%]	32,2	32,9	27,6	28,9	0,501
BMI SDS	-0,7	1,3	-1,1	1,4	0,836

BMI: Body Mass Index; Perc.: Percentile; BP: Blood Pressure; SDS: Standard Deviation Score.
Paired t-test before and after Omega-3-fatty supplementation: *P-value<0.05; **P-value<0.01; ***P-value<0.001.

the autonomic nervous system goes ahead with a significant 50% reduction of premature ventricular contractions in children with arrhythmias. Taken together the register data from Sweden and our observation indicate a lower cardiovascular mortality in later life due to heart failure and arrhythmias that obviously depend on the autonomic nervous system.

With respect to the growth hormone therapy our data are part of a quality management data base called KIGS (Sponsor Pfizer Health AB, Sweden and Pfizer Ltd., UK). In very good accordance with the German data, we start growth hormone therapy at a mean age of 6 years and a height SDS around (-)2.8 and reach the (-)1 SDS after 4 years with a mean growth hormone dose of 34µg/kg per day. Of cause methodological limitations of this retrospective study we cannot decide if Omega-3-Fatty Acid supplementation improves growth in growth hormone treated children. However, we are able to treat children with Omega-3-Fatty Acid supplementation at a younger age and children with short stature due to heart failure who had an increased risk of complications during growth hormone therapy as recently published [16].

Moreover, our data seems to be important for the big group of children in the developing world who suffer from stunted growth. Stunting remains a major nutritional problem worldwide, especially in middle- and low-income countries. Beneath poor growth, research has documented that sufficient intakes of dietary ω-3 long-chain polyunsaturated fatty acids are important for optimal health throughout the life span, especially brain development and cognition [2]. Stunting is associated with an enhanced cardiovascular risk in later life [17]. Ongoing studies will show if omega-3-fatty supplementation will improve growth, cognitive impairments and cardiovascular prognosis in stunted children.

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