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Effects of methylphenidate on height, weight and blood biochemistry parameters in prepubertal boys with attention deficit hyperactivity disorder: an open label prospective study

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Abstract

Background: Adverse effects of stimulants on growth in children have long been studied, but the results remain to be clarified, because metabolic changes or predictors accompanying the growth deviations were not sufficiently studied.
Objective: This open label-prospective study investigated the effects of methylphenidate (MPH) on weight, height, blood biochemistry in children with attention deficit hyperactivity disorder (ADHD).
Method: Prepubertal boys treated with MPH in Child and Adolescent Psychiatry Clinic at Antalya Training and Research Hospital in Health Sciences University, Turkey were recruited. Height and weight z-scores and fasting blood samples were taken at baseline and 6th month. Changes were compared by paired-samples t-test or Wilcoxon signed-rank test. Any association between the changes in growth and biochemical values was analyzed by Spearman's Rank-Order Correlation. The statistical significance threshold was $p<0.01$.
Results: 31 boys aged 74 to 104 months were enrolled in the study sample (mean=87.6, Standard Deviation (SD)=9.2). Osmotic release oral system-MPH (18 mg/day) was used in 77.4% (N=24) and immediate release-MPH (5 mg three times a day) in 22.5% (N=7). Average daily drug dose was 0.66 mg/kg (SD=0.12). Baseline weight z-score was 0.63 (SD=1.12), decreased significantly at 6 months (0.24 [SD=1.04]) (Z=-4.44, p=0.000, r=0.5) (median z-score was 0.53 at baseline, -0.11 at 6 months). Baseline height z-score (0.23[SD=0.87]) was not suppressed significantly at 6 months (0.28[SD=0.85])(t(30) =-1.50, p=0.14).
Glucose (t(30) = -4.33, p=0.000, r=0.6), creatinine (t(30)=-3.28, p=0.003, r=0.5) and 25OH-VitD (N=29, Z=-3.98, p=0.000, r=0.5) increased but alkaline phosphatase (ALP) decreased (t(28)=3.63, p=0.001, r=0.5). The differences in W-SDS and ALP were positively correlated (r=0.47, p=0.009).
Conclusions: Our results indicate the importance of monitoring blood variables that may accompany growth changes early in MPH treatment and should be further assessed in larger samples.

Keywords: Methylphenidate; weight; height; blood biochemistry; ADHD

Introduction

Attention deficit hyperactivity disorder (ADHD) is a frequent neurodevelopmental disorder typical with the primary symptoms as inattention, hyperactivity, and impulsivity in children (1). The worldwide prevalence in children is 7.2 % (6.7-7.8 %)(2), and ADHD studies report 2 to 10 times more frequency in boys than in girls (3).

Stimulants are the most widely used pharmacological agents in ADHD treatment (1), and methylphenidate (MPH) is the first choice among them according to the leading algorithms and the metaanalysis studies (4, 5). MPH acts as indirect dopamine (DA) agonist by disinhibiting D2 autoreceptors on the presynaptic dopaminergic neuron, and activating D1 receptors on the postsynaptic neuron (6). It principally increases the extracellular synaptic dopamine and norepinephrine by inhibiting their reuptakes via specific transporters in striatal and cortical areas (7), and mediates the

redistribution of the vesicular monoamine transporter-2 (7). MPH improves attention deficit and executive function, lowers uncontrolled hyperactivity and impulsivity, and suppresses disruptive behaviors (1). As a result, family and peer relations, learning skills, and school success become much better in children with ADHD.

Adverse effects of MPH on expected growth in children have long been claimed and studied (8, 9). MPH may usually suppress height and weight gain in the first year (9-11), and this suppression disappears (12) or attenuates slowly, over time (9, 10). Weight is affected earlier (11, 13, 14), but height later and at higher doses (9, 15), and more in those who started the drug at prepuberty (16, 17). Not every study, to date, yielded similar and consistent results. A recent study from Thailand reported weight suppression only in the first year and no significant deviation for height throughout 1 to 5 years in the retrospective records of children and adolescents aged 5 to 18 (18). As against, only height gain decreased in the first months with no weight loss in the studies of Zhang et al. (19), Moungnoi and Maipang (20), Lisska and Rivkees (21). Harstad et al. (22) revealed that children who used stimulants in the past caught their peers at adulthood in height but the studies of Greenhill et al. (23) and Swanson et al (24) indicated the long-term MPH users to be shorter than their peers in adulthood. Furthermore, several studies reported no significant loss in height or weight despite long-term MPH treatment (25-28).

Growth deviations may lead to metabolic changes in bone structure and alterations in related blood biochemistry parameters as indicatives of these disturbances, but studies on this subject are very scarce.

Poulton et al. (29) studied the tissue growths in the body and the changes in blood variables in children aged 4 to 9 years with significant weight and height loss after MPH or dexamphetamine over three years. Leptin and P1NP reduced, and albumin increased at 3 months, but osteocalcin, C telopeptides, Insulin-like growth factor-1 (IGF-1), Insulin-like growth factor-binding protein 3 (IGFBP-3) increased in the 3rd year. Fat mass decreased and lean tissue, total bone mineral content, body mass density (in the arms) elevated at 3 months, but the growths of all the tissues increased in the 3rd year. In another study, Poulton et al. (30) revealed no delay in bone maturation during three years despite weight and height loss in MPH or dexamphetamine-treated children compared with their healthy siblings. Additionally, several blood parameters as fasting insulin, glucose, prealbumin, albumin, transferrin, IGF-1, IGFBP-3, and ghrelin had no predictive value on growth suppression. Feuer et al. (31) compared stimulant-treated children and adolescents with nonuser controls and found that height, weight, body mass index (BMI), weight z-score, BMI z-score were lower in boys; height, weight, and BMI were lower in girls, and bone mineral content and bone mineral density (BMD) were lower in both genders. 25OH-VitD levels were also higher in a small group of stimulant users (31). Lahat et al. (28) found no significant difference in expected height and weight, BMD, blood bone-specific alkaline phosphatase (B-ALP), and urinary deoxypyridinoline levels between the healthy group and the MPH-treated children in 12 to 24 months. Kim et al. (32) reported no difference in height and weight between the drug-naive ADHD group, the MPH-treated ADHD group, and the healthy group in children aged 7-11 with both genders over six months to 3 years. Only TSH was lower in the MPH-treated group among blood variables.

Why the results of previous studies are controversial, have various causes: Firstly, the pathophysiological mechanisms underlying the impact of MPH on growth are not evident yet even though several hypotheses as apathy loss, growth hormone reduction via dopaminergic activity, damage to cartilage tissue were suggested (33). Also, predictors or metabolic alterations that could contribute to or accompany the outcomes have not been proven consistently or investigated.

Our first aim was to measure the heights and weights at baseline and 6 month in prepubertal boys treated with MPH. Secondly, we intended to measure the blood biochemistry parameters, simultaneously. Baseline and 6 month values of all variables were compared to see the probable changes from baseline. Whether there is an association between the changes in blood parameters and the changes in growth values was also investigated. Our hypothesis was that: If MPH treatment causes any growth deviation, absolute changes from baseline values in the relevant blood parameters should be measurable. Also, it will be much more meaningful to obtain significant findings in the short term and at relatively low therapeutic doses. There is no doubt that pubertal maturation drives both genders into different phenotypical features in growth, and the outcomes with stimulants also differ in preschool, prepubertal and postpubertal ages. Moreover, it is not always possible to deal with all the factors related to growth in wide age ranges and long-term treatments. Therefore, our study sample included the boys at only prepubertal ages, and the follow-up was limited to six months.

Methods

Study design

This study was conducted in Child and Adolescent Psychiatry Clinic of Antalya Training and Research Hospital in Health Sciences University, Turkey for six months in 2015. The study proposal was approved by Internal Review Board of Clinical Studies according to the Declaration of Helsinki of the World Medical Association (March 12, 2015-56 /7).

Inclusion criteria were male gender, 6 to 9 years of age, ADHD diagnosis based on DSM-5 criteria, and MPH treatment. Exclusion criteria were psychotropic drug history, other mental disorders (autism, bipolarity, intellectual disability, and depression), parental psychiatric disorders, the onset of puberty, physical diseases, and drug treatments likely to impact growth, symptoms and blood abnormalities referring to any disease.

A child psychiatrist completed the baseline and follow-up examinations, using the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5)(34). DSM-5 defines ADHD in five steps: Step A includes two symptom clusters: inattention and hyperactivity/impulsivity, each with nine items. Step B asks for whether some symptoms present before age 12, step C about the symptom presence in more than one setting, step D about the functional impairment, step E about the presence of another psychiatric disorder that could explain the symptoms. ADHD has three different subtypes: predominantly inattentive, predominantly hyperactive/impulsive, and combined, depending on the presence of at least six items from one of each symptom cluster or the combination of both. DSM-5 also describes the disorder severity as mild, moderate, and severe based on the symptom excess or functional impairment. At our follow-up, disappearance of the symptoms or decrease to the subclinical threshold in DSM-5 items and improvement in functionality were considered as symptomatic remission. Comorbid psychiatric conditions were also diagnosed by DSM-5. A child endocrinologist examined all the boys at baseline and 6 months for growth measurements, pubertal maturation, and other pathological conditions. Minimal hairy pigmentation at the base of the penis and increase in either long axis (2.5 to 3.2 cm) or volume (more than 4 ml) in the testicles were accepted as the onset of puberty, according to Stage 2 of Tanner's scaling.

Study sample

Parents of boys who were newly diagnosed with ADHD and had been an indication to use OROS-MPH were invited for their boys to enroll in the study by giving informed consent if eligible to the study inclusion criteria. Of 98 boys invited during six months, parents of 21 boys refused to join (see Table 1). Eight boys were not taken into the study after the first clinical exam based on the exclusion criteria. Sixty-nine were recruited to the study sample. Eight boys discontinued the drug in a few days or weeks due to some adverse effects and 30 quitted the treatment due to various causes in subsequent months. Finally, 31 boys completed six months of MPH treatment (see Table 1). The age range of our sample was 74 to 104 months (mean=87.6, SD=9.2). The combined subtype was the most common diagnosis (N=18), seven boys had the inattentive subtype, and six had the hyperactive/impulsive subtype. Clinical severity was mild in fifteen boys, moderate in twelve, and severe in four. Six boys had comorbidities as one specific learning disorder, one oppositional defiant disorder, two anxiety disorders (specific phobia, separation anxiety), one somnambulism, and one phonological disorder.

Twenty-four boys completed 6 months with 18 mg/day OROS-MPH (77.4 %) (Concerta, Janssen-Cilag Manufacturing LLC, Gurabo, Puerto Rico). Those who could not use it due to inability to swallow or other excuses were not excluded from the study with the informed consents, switched to an equivalent dose of IR-MPH (5 mg three times a day) (N=7, 22.5 %) (Ritalin, Novartis Pharmaceuticals Corporation, USA), in a few days (35). Average daily dose was 0.66 mg/kg (SD=0.12, min-max=0.37-0.90). A fixed drug dose was preferred during six months because of two reasons: Consuming the first days or weeks to individualize MPH doses could lead to a waste of time in our short-term treatment. Individualization of drug dose for each child could cause the study sample to split into smaller groups and bias in interpreting the analysis results.

Growth assessment

At baseline and 6th month, heights were recorded by Harpenden stadiometer to the nearest 1 millimeter and weights by a calibrated electronic scale to the nearest 10 gram with measurements taken without shoes and only with underwear. These raw scores then were converted to z-scores. Z-score is calculated by subtracting the age and sex corrected population mean from the actual value of each child and then dividing the result by standard deviation score. Z-score calculation shows how many standard deviations the measurement is away from the mean. For the conversion from raw score to z-score; ChildMetrics (36, 37) was used, a computer-based algorithm that converts raw scores to z-scores based on the age and gender-matched population norms (38).

TABLE 1. Study participants

Subjects	N
Prepubertal boys with ADHD	98
Parents who rejected	21
Excluded at baseline exam	8
Intellectual disability (N=2)	
Pubertal signs (N=2)	
Very high levels of TSH (N=1) and transaminases (N=1)	
Severe anemia (N=1)	
Very low growth percentile (N=1)	
Recruited subjects	69
Drop-outs due to adverse effects	8
Appetite loss and insomnia (N=2)	
Nausea and appetite loss (N=1)	
Stomachache and irritability (N=1)	
Syncope (N=1)	
Headache (N=1)	
Insomnia, irritability, and appetite loss (N=1)	
Headache, stomachache, and insomnia (N=1)	
Drop-outs due to other causes	30
Weak compliance (N=6)	
Parental disagreement (N=6)	
Summer holiday (N=6)	
Surgical operation (N=2)	
City change (N=3)	
Pubertal signs (N=2)	
Unknown (N=5)	
Sample size	31

Blood sample collection and analysis

Just before the drug treatments, fasting blood samples were drawn into BD Vacutainer (Becton-Dickinson, USA) SSTTM II Advance tubes coated with micronized silica particles, which activate clotting. Blood samples were checked for hemolysis or other interfering substances, and then were separated from the cells by centrifugation at 1500×g for ten minutes. The same process was repeated at 6 months, and all the blood samples were stored at –80°C until analyses. Glucose, blood urine nitrogen (BUN), creatinine, calcium, magnesium, phosphate, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), iron, total iron-binding, transferrin were measured with conventional spectrophotometer in Beckman Coulter AU5800 Autoanalyzer; hemogram in Beckman Coulter LH780 Autoanalyzer; ferritin, vitamin B12, thyroid-stimulating hormone (TSH), fT3 (free triiodothyronine), fT4 (free tetraiodothyronine), parathyroid hormone (PTH) with chemiluminescence method in Beckman Coulter DxI800 Analyzer; OSC, B-ALP, 25-hydroxy vitamin D (25OH-vitD) with chemiluminescence method in Liason Analyzer. Procollagen type 1 N-propeptide (P1NP, measurement range: 5-2000 ng/mL, sensitivity: 2.51 ng/mL) and Type 1 Collagen Cross-linked N-telopeptide (Ntx, measurement range: 15.6-1000 pg/mL, sensitivity: 5.51 pg/mL) were measured with commercial ELISA kits (YH Biosearch, Shanghai, China).

Statistical analysis

Data was analyzed on Statistical Package for the Social Sciences, Version 22 for Windows. Normality assumptions were checked by sample size, Shapiro-Wilk Test (SWT), histograms, Q-Q plots, outlier determinations. Normally distributed variables (SWT>0.05) were compared by parametric paired-samples t-test, not-normally distributed variables (SWT<0.05) by non-parametric Wilcoxon signed-rank test. Then, whether there is an association between the changes in blood variables and growth measurements was examined by Spearman's Rank-Order Correlation. The threshold for statistical significance was set as $p<0.01$ in all calculations.

Results

Height and weight measurements

The mean time interval from the first visit to last was 6.5 months (SD=0.4, min-max=5.6-7.7, median=6.4). Raw scores of heights were 114.7 cm to 138.8 cm (mean=124.6, SD=6.8, median=123.6) at baseline and 117.8 cm to 140.9 cm (mean=127.7, SD=6.8, median=126.2) at 6 months. Baseline height z-score (mean=0.23, SD=0.87, min-max=-1.64-2.05) increased at 6 months (mean=0.28, SD=0.85, min-max=-1.46-2.55) but not to significant extent, in paired samples t test (t (30) =-1.50, p=0.142) (see Table 2). Raw scores of weights were 19.1 kg to 48.5 kg (mean=27.10, SD=7.22, median=25.20) at baseline and 19.5 kg to 50.4 kg (mean=26.93,

SD=7.02, median=25.90) at 6 months. Wilcoxon signed-rank test indicated that weight z-score at 6 month (mean=0.24, SD=1.04, min-max=-1.11-2.74) was significantly lower than baseline weight z-score (mean=0.63, SD=1.12, min-max=-1.13-3.13) and the effect size was large (N=31, Z=-4.44, *p*=0.000, *r*=0.5) (median z-score was 0.53 at baseline, -0.11 at 6 months) (see Table 3).

Mean growth velocity in height per half-year was 2.89 cm (SD=0.78, min-max=1.21-5.04, median=2.90) for the total sample, 3.03 cm (SD=0.91, min-max=1.70-5.04, median=2.90) for age 6 (N=11), 2.82 cm (SD=0.79, min-max=1.21-3.94, median=2.92) for age 7 (N=13) and 2.81 cm (SD=0.59, min-max=1.98-3.56, median=2.73) for age 8 (N=7).

Alterations in blood biochemistry parameters

Paired samples t test revealed significant increase in glucose (t(30)=-4.33, *p*=0.000, *r*=0.6) and creatinine (t(30)=-3.28, p=0.003, r=0.5) and significant decrease in ALP (t(28)=3.63, *p*=0.001, *r*=0.5) at 6 month (see Table 2). Wilcoxon signed-rank test revealed significant increase in 25OH-vitD (N=29, Z=3.98, p=0.000, r=0.5) (median z-score was 19.75 at baseline and 26.70 at 6 month) (see Table 3). No significant change from baseline was measured in other blood variables.

TABLE 2. Comparisons of baseline and 6 months values in paired samples t-test

Variable	Baseline M (SD)	6 months M (SD)	T value	df	Significance (*p*)*	Effect size (*r*)
Height z-score	0.23 (0.87)	0.28 (0.85)	-1.50	30	0.142	
Hemoglobin	12.57 (0.87)	12.47 (0.86)	0.89	29	0.380	
Hematocrit	38.22 (2.52)	37.850 (2.26)	0.91	29	0.368	
Platelet	331.53 (91.91)	311.50 (59.96)	1.37	29	0.179	
Glucose	82.54 (6.21)	88.09 (6.66)	-4.33	30	0.000*	0.6
Creatinine	0.56 (0.08)	0.60 (0.06)	-3.27	30	0.003*	0.5
Calcium	9.46 (0.51)	9.51 (0.45)	-0.46	29	0.648	
Phosphate	4.71 (0.45)	4.66 (0.42)	0.56	28	0.578	
AST	29.26 (6.23)	29.60 (3.98)	-0.33	29	0.738	
ALP	243.06 (47.07)	215.24 (44.33)	3.63	28	0.001*	0.5
Vitamin B12	306.72 (121.66)	288.41 (115.31)	1.10	28	0.278	
TSH	2.64 (0.98)	2.38 (1.03)	1.68	28	0.104	
fT3	3.96 (0.65)	3.73 (0.46)	1.93	28	0.063	
fT4	0.87 (0.10)	0.86 (0.09)	0.60	28	0.553	
B-ALP	84.44 (25.58)	82.98 (23.25)	0.32	28	0.750	

Notes. *< 0.01 (two-tailed).
Abbreviations: M=mean, SD=standard deviation, df=degree of freedom, AS=aspartate aminotransferase, ALP=alkaline phosphatase, TSH=thyreoid stimulating hormone, fT3=free triiodothyronine, fT4=free tetraiodothyronine, B-ALP=bone specific alkaline phosphatase.
Measurement units: cm for hight, mg/dL for glucose, creatinine, calcium, phosphatate; pg/mL for vitamin B12, free T3; U/L for ALP, AST, 10^ for platelet; g/dL for hemoglobin, % for hematocrite, ulU/ml for TSH, ng/dl for free T4, ug/L for B-ALP

TABLE 3. Comparisons of baseline and 6 months values in Wilcoxon signed-rank test

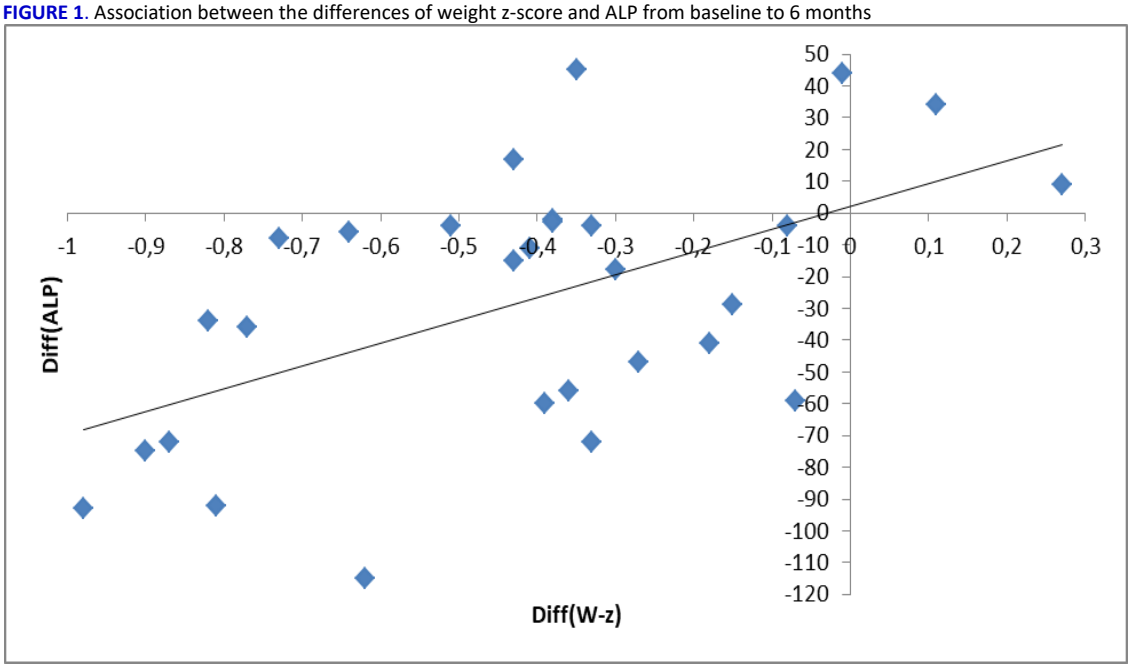
Variables	Measurements M, (SD)		Negative ranks			Positive ranks					Statistics	
	Baseline	6 months	N	mean rank	sum of ranks	N	mean rank	sum of ranks	Ties	Z	Significance (*p*)*	Effect size (*r*)
Weight z-score	0.63 (1.12)	0.24 (1.04)	29	16.83	488	2	4	9	0	-4.704	0.000*	0.5
P1NP	471.15 (264.24)	648.30 (507.60)	14	13.14	184	17	18.35	312	0	-1.254	0.210	
NTx	248.48 (228.69)	250.29 (256.86)	21	14.33	301	10	19.50	195	0	-1.039	0.299	
WBC	8.31 (2.68)	7.65 (1.70)	21	15.29	321	9	16	144	0	-1.822	0.069	
RBC	4.84 (0.52)	4.78 (0.51)	12	16.29	195.5	13	9.96	129.50	5	-0.896	0.370	
BUN	11.20 (2.80)	12.06 (2.51)	11	11.18	123	15	15.20	228	4	-1.339	0.181	
Magnesium	2.07 (0.16)	2.01 (0.18)	11	12.36	136	8	6.75	54	11	-1.676	0.094	
ALT	16.66 (13.38)	16.46 (8.55)	12	15.83	190	15	12.53	188	3	-0.024	0.981	
Ferritin	23.34 (11.57	19.72 (8.56)	19	13.18	250.50	8	15.94	127.50	2	-1.479	0.139	
Transferrin	266.06 (51.58)	270.31 (30.90)	17	13.47	229	11	16.09	177	1	-0.592	0.554	
Iron	79.10 (31.90)	75.37 (34.01)	16	15.38	246	12	13.33	160	1	-0.979	0.327	
PTH	38.09 (14.52)	35.41 (24.25)	21	15.88	333.50	8	12.69	101.50	0	-2.509	0.012	
OSC	67.25 (18.75)	60.18 (19.07)	19	16.39	311.50	10	12.35	123.50	0	-2.033	0.042	
25OH-vit D	18.42 (7.15)	27.22 (7.18)	4	8.25	33	25	16.08	402	0	-3.989	0.000*	0.5

Notes. *< 0.01 (two-tailed).
Abbreviations: N=sample size, P1NP: procollagen type 1 N-propeptide, NTx: type 1 Collagen Cross-linked N-telopeptide, WBC: white blood cell, RBC: right blood cell, BUN: blood urine nitrogen, ALT: alanine aminotransferase, PTH: parathormone, OSC: osteocalcin, 25OH-vit D: 25OH-vitamin D.
Measurement units: kg for weight, ng/mL for P1NP, pg/mL for NTx and PTH, 10^3/mm for WBC, 10^6/mm^3 for RBC, mg/dL for BUN, magnesium and transferrin, U/L for ALT, ug/dL for iron, ng/ml for OSC, 25OH-vitamin D and ferrerin.

Associations between growth deviations and the changes in blood variables

Baseline values of weight z-score, glucose, creatinine, ALP, and 25OH-Vit D were subtracted from 6 months values to calculate the differences they created (Diff(variable)). Then, whether an association of weight z-score change at 6 months with the changes from baseline in biochemical variables was calculated. A moderate positive correlation was found between ALP difference (Diff(ALP)) and weight z-score difference (Diff(W-z)) at 6 months on Spearman's rank-order correlation (r=0.47, p=0.009) (see Figure 1). No association was seen between Diff(W-z) and Diff(glucose) (r=-0.03, p=0.844), Diff(creatinine) (r=0.27, p=0.133) or Diff(25OH-it D) (r=0.29, p=0.121), respectively.

FIGURE 1. Association between the differences of weight z-score and ALP from baseline to 6 months



Notes. Diff (ALP)= mean values of the differences from baseline for ALP (6 months- baseline);
Diff (W-z)=mean values of the differences from baseline for W-SDS (6 months-baseline)

To predict the possible effects of drop outs on the results, "the sample who dropped out" (N=38) and "the study sample" (N=31) were compared in terms of ages and education levels of children and the parents, ADHD symptoms, baseline blood measurements in Mann Whitney. Only hyperactivity/impulsivity symptoms were lower in "the sample who dropped out" (U=367, p=0.044, median=4) than in "the final sample" (median=6). Since the baseline measurements could not be obtained from the records, we could not predict whether there are differences in baseline growth values between the two groups.

Discussion

We investigated the outcomes of methylphenidate treatment on growth and blood biochemistry parameters in prepubertal boys. All the study variables were measured at baseline and 6 months of the treatment. Our hypothesis was to see the changes in height and weight, and the changes in blood variables that will associate with the predicted growth loss.

Weight z-score decreased significantly at 6 months in our sample. In Gurbuz et al.'s study (14), weight-SDS (standard deviation score) decreased significantly at 3 months with OROS-MPH in boys, height-SDS also decreased but not to significant extent. Drug dose was low (0.5 mg/kg/day), the age range was wide as from 7 to 14, the expected pubertal changes were not considered, baseline heights and weights were in the population norms in contrast to our heavier and slightly taller sample. Spencer et al. (39) revealed weight-SDS decrease at 5 months in

boys and girls aged 6 to 13 treated with OROS-MPH, the drug dose was high (1.2 mg/kg/day), and the sample was slightly shorter and heavier than healthy peers at baseline. Schachar, Cunningham, and Corkum (13) reported reducement in weight raw scores but no loss in height raw scores at 4 months in boys and girls aged 6 to 12. They used IR-MPH (Ritalin) in a daily dose of 0.7 mg/kg and analyzed absolute measures, not SDSs. The distinctive feature of our study was the appearance of the loss in weight within low therapeutic doses and in the first months and may be suggested the result of the decreased appetite (40).

Height z-score did not decrease, even increased although not significant. Lack of loss in height gain may be related to MPH dose and the short-term treatment (15, 41). The suppression in height gain occurs later and at higher doses with stimulant treatments (15, 41). Prepubertal children with drug-naive ADHD were also proven to grow faster in height (42, 43). It can be advocated that our slightly taller children maintain the growth velocity during 6 months owing to the late onset of presumed loss in height. All these assumptions should be elucidated in future studies.

For blood variables, fasting glucose, creatinine, and 25OH-VitD increased, but ALP decreased at 6 months in our sample.

The increase in fasting glucose with MPH treatment was rarely reported in previous studies. In Wigal et al.'s study (44), 21.4 % of the children displayed significant and transient hyperglycemia, but only 8 % of their sample exceeded the physiological reference values during two years with OROS-MPH. Charach et al. (45) revealed significant hyperglycemia with a 22 % rise (88.3 mg/dL; SD=10.1) at 3 months in comparison with baseline (73.63 mg/dL, SD=7.12) in adolescents and young adults who used MPH (Ritalin). In our sample, glucose increased by 7.09 % (SD=9.33, min-max: -5.68-33.77) at 6 months, and none of the measurements were in the pathological range.

Pathophysiological mechanisms underlying the fasting glucose to increase with MPH are not clear yet. Dopamine receptor-mediated action mechanisms may be assumed to have a role in this process. Dopaminergic D2 receptor availability is essential in both the action mechanism of MPH (6) and the response to treatment (46). Also, in animal and in-vitro studies, D2 receptors were demonstrated to be essential in insulin-mediated glucose regulation, and disruption at the receptor level may cause glucose intolerance (47, 48).

Bone metabolism and glucose regulation are closely interrelated. Dysregulations in glucose homeostasis can cause blood bone marker concentrations to change and may indicate the disruption in bone turnover (49). In this context, although any significant association was not settled, concurrently increased glucose and decreased OSC are intriguing and compatible with the reported studies so far. OSC acts as an essential mediator between bone metabolism and glucose homeostasis by prompting insulin expression in the pancreas and adiponectin expression in adipocytes (50). Some studies displayed an inverse relationship between glucose and total or under-carboxylated form of OSC in overweight or prediabetic prepubertal children and other populations (50, 51). However, since we have not investigated many other mediators in these intermediate pathways and could not show significant relationships between the relevant variables, we cannot propose any prediction regarding our results.

ALP is an osteoid formation marker contributing to bone mineralization (52). Total ALP pool consists of various isoforms named according to the tissues from which it originates, such as liver, bone, intestine, spleen, kidney, and placenta but it is mostly of skeletal origin in children (52). Recently, Kim et al. (32) compared the growth markers among the drug-naive ADHD, MPH-treated ADHD, and control groups in boys and girls aged 6 to 12, and ALP levels did not differ with a daily drug dose of 1.02±0.39 mg/kg after 1.79±1.11 years of treatment. They reported this outcome in a sample in which study subjects were in a wider age range, including both sexes, and treated for longer term with the higher drug dose. Still, we believe that the ALP decrease in our study may be taken into account as a signal that could display the blood bone marker levels could change, even in short-term.

25OH-VitD is an essential micronutrient of bone mineralization. It may support bone turnover via regulating the circuit of calcium, phosphate, and PTH (53). Low blood concentrations were reported before in children with ADHD (54). An impact of MPH on 25OH-VitD level is not known so far, and its blood concentration is minimally affected by nutritional factors. The increase at 6 months may be explained by the seasonal variation from winter to summer in which the blood samples were taken. Increased bone turnover due to rapid growth in prepubertal ages may also be suggested to contribute partly to the concentration changes. However, blood 25OH-VitD levels are still below the expected physiological reference values despite increase.

Creatinine concentration is mostly regulated by the protein metabolism in the muscular mass and the filtration ability of the kidneys (55). Temporary and minimal changes in blood levels may occur depending on various reasons as drugs or

supplements, dehydration of the body (thirstiness, summer season), protein consumption, exercise, and growth. In this event, creatinine increase at 6 months in our study may be accepted as temporary and coincidental, because any notable symptom has not accompanied this change.

Our results have not entirely supported our hypothesis that growth deviation with MPH treatment could lead to significant abnormalities in the relevant blood biochemistry parameters. Various opinions may be asserted for this incompetence. Data obtained from a low sample size may have been insufficient to achieve statistical and clinical significance in all variables. Alterations in blood concentrations may have been compensated by the early homeostasis mechanisms. Cumulative effects of the drug doses may not have reached the levels that could impact height and other blood variables. A single dose of 18 mg OROS-MPH (or equivalent dose of IR-MPH) was used in order not to extend the drug doses to the extremes, and clinical efficacy was regularly monitorized. However, our dose predilection may have caused the drug absorption and utilization to downward in heavier boys. To use fixed dosing, although not declared at visits, may have not met the expectations and may have caused some parents to non-comply with and even quit the treatment. Fewer disruptive behaviors in some children may have facilitated some parents to non-adhere the treatment and leave the study group as shown in the sample who dropped out.

The awareness of the treatment practices by the clinicians, patients, and caregivers may cause the patient selection, follow-up observations, and the outcomes to be subject to biases in open-label studies. To eliminate or minimize this risk, fully structured diagnosis and follow-up procedures were used, growth and blood analyses were also very trustworthy and objective, in our study. Nonetheless, it should be kept in mind that all risks may not be overcome due to uncontrollable reasons in open-label studies.

Beyond all, significant changes in blood biochemistry values should be interpreted with caution. Because their levels did not fall out of the physiological reference ranges (53, 56). Notable clinical symptoms associated with these changes were not also recorded at follow-ups.

Nonetheless, in our study, the increase in glucose which is one of the mediators between lipid (or energy) metabolism and the skeletal system may open a new window to future MPH studies that will investigate the growth deviations. In addition, alterations in 25OH-VitD and ALP levels in short-term and at low therapeutic doses may still indicate the need to measure blood bone markers as often and as early as possible from the initiation of treatment. Because, it is well known that bone remodeling requires the complex integration of bone, adipose tissue, brain, parathyroid gland, kidneys, and pancreas (57).

Limitations

Short-term treatment and study inclusion criteria as age and gender were our choices, but may also have caused the study sample to be limited. We followed the boys in regular intervals, but we could measure the study variables only two times, at baseline and 6 months due to practical and financial difficulties. Intermittent serial measurements in longer follow-ups would yield more comparable results on the courses of growth deviations and blood level fluctuations. We used two different MPH formulations, but we could not have the opportunity to study and distinguish the subtle pharmacodynamic differences of each due to methodological inadequacies.

Clinical significance and future research

Bone formation and resorption turnover may be disturbed in hyperglycemia conditions. Therefore, glucose increase with MPH in our study may indicate the interactions between bone turnover and energy metabolism, which is waiting to be elucidated in the future. It may be suggested that ALP reduction may display early stress in bone metabolism at 6 months. An increase in 25OH-Vit D and creatinine level may be due to seasonal variations or other coincidental causes. Lack of significant changes in other blood bone markers (B-ALP, P1NP, NTx) may be due to the study limitations as sample size, short-term treatment, drug dose rather than the ineffectiveness of MPH.

Methodological diversities in previous ADHD studies may be the most crucial factor in inadequacy for obtaining consistent and conclusive results. Growth features differ at every age in both genders, but these studies commonly studied girls and boys in the same sample along a broad age spectrum. Withdrawal rates from treatment were high in most, and only the results of the children who completed the studies were reported, but we believe that long-term follow-ups of children who left the treatment will also yield challenging findings. Many studies used more than one stimulant (MPH, dextro-amphetamine, pemoline) in the same sample. However, pharmacokinetic and pharmacodynamic properties unique to each stimulant may cause subtle differences in the results. Comorbid disorders in ADHD may also influence the clinical course and the pharmacotherapy, but comorbidities were hardly ever incorporated into these studies. Treatment

duration varied from 3 months to 1-3 years or even ten years. In short term, some measurements may not be sufficient to provide significant results and in long term, some confounding variables may arise that would influence the growth process and the study results.

Whether these changes are related to the pharmacodynamic properties of the drug itself or the needs of the growing body may not be explained clearly without comparing with healthy or drug-naive ADHD children. Because, the concentrations of blood parameters may show variabilities under many physiological, pathological, and even methodological conditions (age, gender, diet, medicines, diseases, diurnal or seasonal circularity, laboratory conditions) (58).

Of course, methodologically more structured studies with more selective hypotheses giving privilege to the pharmacodynamic properties of MPH, appraising both the probable growth deviations and the structural features unique to ADHD will enrich the studies published to date. Because child growth is too complex to be explained with simple cause-effect relations.

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