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Lower risk of stress fractures in young adults with ADHD under chronic treatment with methylphenidate

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ABSTRACT

Introduction: Methylphenidate (MP) use is highly prevalent among children and young adults. Previous basic and epidemiological research demonstrated an adverse effect of MP on bone mass. Studies in military recruits have shown that history of MP use before conscription was a risk factor for stress fractures (SF) during the service.

Methods: This study is part of the project in which the association between MP use and incidence of SF was retrospectively investigated in a cohort of healthy conscripts aged 18–25, who served for at least 12 months between 2008 and 2017. Baseline information included sex, age, weight, height, geographic origin, socio-economic status, and education. Subjects were divided into five groups: subjects without ADHD; untreated subjects with ADHD; and subjects with ADHD and prescriptions of 1–90, 91–180, or 181+ tablets during the study period. The primary outcome was at least one diagnosis of stress fracture during the study.

Results: Among 682,110 subjects (409,175 men [60%]), 29,888 (4.4%) had fractures. MP was used by 1681 (0.4%) men and 2828 (1%) women. In both men and women, SF incidence was significantly higher among subjects with untreated ADHD (7.9% and 5.4%, respectively) and significantly lower in subjects with treated ADHD (1.9–3%; 0.3–4.3%), compared to healthy controls (5.3% and 2.9%). After multivariate adjustment, subjects with untreated ADHD remained at an increased risk of fracture (men OR = 1.66, $p < 0.001$ and women OR = 1.33, $p = 0.007$), whereas only subjects with highest exposure to MP (180+ tablets) had significantly lower chances for fracture (men OR = 0.49, $p = 0.08$ and women OR = 0.09, $p = 0.02$), compared to healthy controls.

Discussion: The study has demonstrated lower risk of stress fractures with concurrent MP use. The findings in this population challenge our understanding of the MP effect on bone integrity and prompt further basic research.

1. Introduction

Stress fractures (SF) affect many young and physically active individuals [1]. They result from cumulative sub-maximal stress to bone, that exceeds the bone capacity for repair. High volumes of concurrent physical activity are therefore the primary cause of stress fractures. Within the group of subjects exposed to the same level of physical activity, risk factors for stress fractures include female sex, white ethnicity, older age, taller stature, lower aerobic fitness, prior physical inactivity, thinner bones, cigarette smoking, and inadequate intake of vitamin D and/or calcium [2].

Previous exposure to methylphenidate (MP) has been recently documented as a risk for stress fractures among military recruits [3,4]. One retrospective case-control study has shown an increased odds of MP use among combat recruits with bone-scan diagnosed SF compared to recruits without any limb complaints [3]. Another large retrospective cohort of 100,000 combat recruits showed that subjects who used MP were at an increased risk of SF compared to subjects with ADHD who did not use MP and subjects without ADHD [4].

Possible effect of MP on SF risk requires further investigation, because this medication use have been increasing over the last decades, reaching about 35% among US college students [5]. Basic and clinical research demonstrated an adverse effect of MP on bone density [6–8]. Large epidemiologic studies showed ADHD itself is a risk factor for

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fractures [9,10], whereas ADHD treatment in fact reduces fracture risk [11]. Perry et al. have compared fracture incidence between subjects with ADHD who received no medications and subjects with ADHD who received either stimulant or non-stimulant treatment. Both of the latter groups had a reduced incidence of fractures, compared to subjects who received no treatment. The authors suggested that an improved control of ADHD symptoms resulted in this positive effect on fracture risk [12]. For a fracture to occur, both propensity to fall or other accident and bone fragility are required. At younger age, the former is a far stronger determinant of fracture risk, unless a specific metabolic disorder undermined bone health. However, this may not be the case with SF that develop due to repetitive submaximal loading of the bone, which leads to micro fractures that are unable to heal [13], and not from accidents. We hypothesized that MP treatment of ADHD would not have a protective effect on stress fractures as it has for traumatic fractures.

We decided to further investigate the effect of concurrent MP use and SF in a large cohort of military recruits was investigated. The study group, included mainly non-combat soldiers and was representative of civilian population of respective age. Moreover, the dose-response effect of MP on stress fracture incidence was investigated, allowing for deriving conclusions about causation.

2. Methods

After receiving approval by the IRB, an automated query of the military medical records was performed. The resulting study cohort was subsequently used for research of the association between methylphenidate and stress and non-stress (traumatic) fractures. The results of the study on association between MP and traumatic fractures are presented in another paper, due to the differences in pathophysiology and the role of MP in the incidence of traumatic fractures and SF [14].

Initial study sample included all subjects ages 18–25 who served in IDF between 2007 and 2017 for at least 12 months. For subjects who became older than 25 during the study period, only data related to the period of age 18 to 25 was queried. Subjects with severe chronic medical conditions or history of recent malignancy who volunteered to service were excluded. Likewise subjects with missing baseline data (age, weight and height) were regarded as false or error entries in the database, and were therefore excluded.

Baseline subject information included age (at the time of the first fracture diagnosis), gender, height (cm), weight (kg), BMI (kg/m^2), education level ($\leq$12 years, above 12 years), socio-economic level (a measure used by the state Central Bureau of Statistics, that is calculated from mean income of subject's area of residence and includes 1–10 grades), origin (defined as father's country of birth; grouped as developed countries (North America, Europe and former Soviet Union), developing countries (Africa, Middle East and South America) and Israel (including subjects with missing origin data)), occupation (combat and non-combat), duration of follow-up in months and diagnosis of ADHD.

MP exposure was calculated using medication prescription data. It was presented as a total number of tablets consumed throughout the study period, with cut-offs set at 90 and 180 tablets, similar to the method described bu. Chen et al. [11].

All International Classification of Disease (ICD-9) stress fracture diagnoses (codes starting with M84.3*) were counted once per subject during the study period. This choice of outcome was considered optimal because higher number of repeated diagnoses of SF does not necessarily indicate the severity of the condition. Moreover, some of the diagnoses were due to administrative entries and renewal of referral notes, and did not represent a new fracture or even a face-to-face encounter between the subject and the physician.

Statistical analyses included descriptive statistics (rates), the unadjusted dose-dependent risk estimates, and multivariate logistic regression. Men and women were evaluated separately considering the inherently distinct risk of stress fractures and the evidence of gender-dependent effect of MP on bone metabolism [6]. Categorical data (education, origin, socio-economic level and type of service) was presented as percentages and was analyzed using the chi-square test. Continuous data (age, height, weight, BMI, fitness test grade and duration of follow-up) was presented as mean ± standard deviations and analyzed using Student's *t*-test.

For the purpose of estimating the unadjusted dose-dependent risk of fractures, subjects were divided into five groups: subjects without ADHD (No ADHD), subjects with ADHD who did not receive MP treatment (Untreated), and subjects who had a total of 0 to 90 (ADHD 0–90), 91–180 (ADHD 91–180) or > 180 tablets (ADHD 180+) prescribed during the study period. Incidence of fractures in these five groups was presented as overall percentage of subjects who fractured within each group. In addition, the unadjusted odds ratio (OR) of fractures were calculated for each group using an exploratory logistic regression model. In the regression, the above grouping variable was the only predictor of diagnosis of fractures, with “No ADHD” subjects representing the reference group. The 95% confidence intervals (95%CI) of each diagnosis were calculated using bootstrapping.

Finally, a multivariate logistic regression was fitted to adjust prediction of fracture risk for possible confounding variables. Those variables that differed significantly between study groups were included in the model. Relationship between predictors was reviewed to exclude correlation above 0.8. Odds ratios (OR) were calculated from the regression coefficients, and their respective confidence intervals (95%CI) were estimated using bootstrapping.

3. Results

A total of 826,742 recruits were identified after an automated search of medical records between 2008 and 2017. After exclusion of subjects who served for less than one year, those who were older than 25 at any time point during the study period, those who volunteered to service and those missing baseline data (1%), the remaining 682,110 recruits constituted the final cohort (Fig. 1).

There were 409,175 men (21,740 fractures, 5.3%) and 272,935 women (8148 fractures, 3.0%). ADHD was prevalent among 2.2% of men and 2.5% of women. MP was used by 1681 (0.4%) men and by 2828 (1.0%) women.

Baseline characteristics of study subjects are presented in Table 1. There were several significant and substantial differences between persons with and without fractures. SF were associated with combat service in both genders ($p < 0.001$ and $p < 0.001$), and with lower education ($p < 0.001$) and high socio-economic level ($p < 0.001$) in men.

The comparison of SF incidence between the five treatment groups within each gender, highest incidence was found in the untreated ADHD group (7.9% men, 5.4% women). Increasing use of MP was associated with lower frequency of stress fractures, going far below the baseline SF risk of healthy subjects (Table 2).

In multivariate analysis, two separate models were fitted for men and women. An interaction between MP-ADHD exposure status and combat service was added to the model. The model output confirmed that subjects with highest exposure to MP were at lowest risk of stress fractures adjusted to age, weight, origin (Israeli-born vs South America, North Africa and Middle East vs North America, Europe and Former USSR), education (higher education vs high school or less), socio-economic level (lower vs middle vs higher) and combat service vs non-combat service (Table 3).

4. Discussion

This study investigated the effect of MP use on stress fracture risk in a large cohort of young healthy adults. It showed that subjects with ADHD were at significantly higher risk of SF compared to healthy controls. However, subjects with ADHD who used 180 or more tablets during the study period were at lower risk of SF compared to subjects

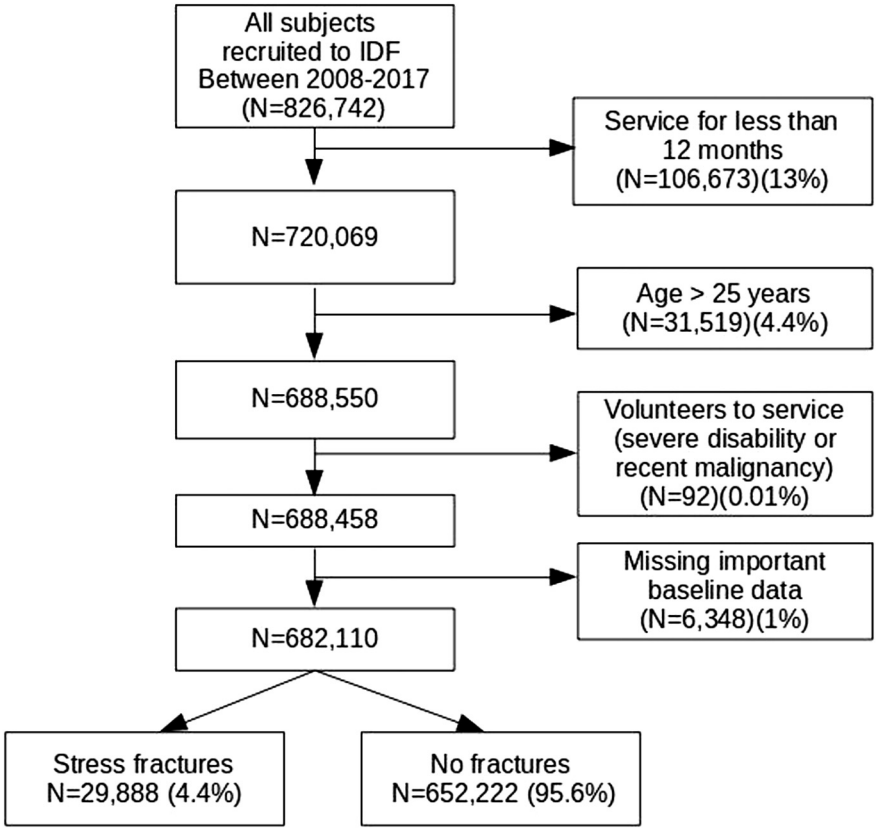

Fig. 1. Study flowchart.

Table 1
Subjects baseline characteristics.

	Men (n = 409,175)			Women (n = 272,935)		
	Stress fracture (n = 21,740; 5.3%)	No fractures (n = 387,435; 94.7%)	p-Value	Stress fracture (n = 8148; 3%)	No fractures (n = 264,787; 97%)	p-Value
Age	18.5 ± 0.8	18.9 ± 1.2	< 0.001	18.3 ± 0.6	18.4 ± 0.8	< 0.001
Weight	71.9 ± 13.8	72.2 ± 15.3	0.01	60.7 ± 10.5	59.9 ± 12.4	< 0.001
Height	174.4 ± 6.6	174.4 ± 6.8	0.35	162.5 ± 6	162.2 ± 6.3	< 0.001
BMI	23.6 ± 4.1	23.7 ± 4.5	0.01	23 ± 3.7	22.7 ± 4.3	< 0.001
Education						
< 12 years	638 (3%)	17,223 (4.5%)	< 0.001	55 (1%)	4275 (1.6%)	< 0.001
12 years	20,651 (96%)	351,025 (92%)		8030 (98%)	256,844	
> 12 years	232 (1%)	12,708 (3.5%)		55 (1%)	(97.4%)	
					2568 (1%)	
Origin						
North Africa	3305 (15%)	61,409 (16%)	< 0.001	1128 (14%)	39,075 (15%)	< 0.001
Asia and South America	2761 (13%)	56,461 (15%)		981 (12%)	36,306 (14%)	
Middle East	339 (2%)	9627 (2%)		49 (1%)	4756 (2%)	
Ethiopia	1773 (8%)	29,834 (7%)		568 (7%)	16,203 (6%)	
Israel	7235 (33%)	118,872 (31%)		3401 (42%)	93,809 (35%)	
Other	1923 (9%)	47,138 (12%)		606 (7%)	31,839 (12%)	
Former USSR North America and Europe	4404 (20%)	64,094 (17%)		1415 (17%)	42,799 (16%)	
Socio-economic						
Level	640 (3.3%)	14,731 (5.3%)	< 0.001	86 (1.2%)	3082 (1.3%)	< 0.001
Low	13,979 (72.9%)	255,492		5159 (71.5%)	174,286	
Middle		(92.2%)		1966 (27.3%)	(74.9%)	
High	4562 (23.8%)	6941 (2.5%)			55,337 (23.8%)	
Occupation						
Combat	11,111 (59.7%)	96,932 (29.7%)	< 0.001	904 (13.7%)	4415 (2%)	< 0.001
Non-combat	7503 (40.3%)	229,083 (70.3%)		5673 (86.3%)	214,995 (98%)	
Follow-up (months)	58.9 ± 19.7	54.8 ± 19.8	< 0.001	57.1 ± 21.4	57.9 ± 20.5	0.002

BMI: body mass index.

Table 2
Unadjusted dose-response association between methylphenidate and risk of fracture.

		Men		Women	
		Stress fracture incidence during the study period (%)	Odds of stress fracture with 95%CI[a]	Stress fracture incidence during the study period (%)	Odds of stress fracture with 95%CI[a]
No ADHD		21,181 (5.3%)	Reference group	7843 (2.9%)	Reference group
Untreated ADHD		487 (7.9%)	1.54 (1.41:1.69)	222 (5.4%)	1.87 (1.63:2.14)
Treated ADHD	1–90 doses	54 (3%)	0.55 (0.41:0.71)	74 (4.3%)	1.49 (1.17:1.87)
	91–180 doses	7 (1.7%)	0.3 (0.13:0.59)	7 (1.5%)	0.51 (0.22:0.99)
	180+ doses	11 (1.9%)	0.34 (0.18:0.59)	2 (0.3%)	0.1 (0.02:0.3)

95%CI – 95% confidence interval.
[a] Odds of stress fracture when subjects without ADHD as reference group.

without ADHD. The results contradict our study hypothesis according to which the well-documented effect of MP on bone mass should have resulted in higher risk of SF. Laboratory studies have suggested that MP may have an adverse effect on bone density through adrenergic activation of osteoclasts [8]. A recent study has confirmed that there is a dose- and sex-dependent effect of MP on osteoclast differentiation, activity and resorption, as well as on bone mechanical integrity in rats [6]. Several epidemiologic studies have shown that MP is associated with osteopenia in children [7,8]. However, there is no evidence that this deterioration of bone integrity translates into higher risk of fracture. In fact, the opposite was demonstrated by Chen et al.: subjects with ADHD who were not treated had a higher traumatic fracture risk compared to those who received medication for 180 days or more [11]. Chou et al. demonstrated that children treated for ADHD did not have an increased traumatic fracture risk compared to children without ADHD, whereas children who did not receive treatment for ADHD had higher fracture risk than healthy controls [9]. Perry et al. suggested that better control of ADHD symptoms reduces traumatic fracture risk [12].

The presented study is a large and heterogeneous cohort of healthy subjects. Due to the compulsory conscription law, almost all country population groups are represented by the study. Risk estimates were adjusted for multiple characteristics and known determinants of SF risk. This valid and actual data prompts further investigation of the pathophysiology of stress fracture risk.

One explanation for the findings is the effect of MP on behavior, which is close to explanation of the traumatic fracture reduction documented in other studies. The difference is that instead of impulsive or risk-taking behavior that leads to accidents and stress fractures, the risk of SF must be modified by the effect of MP in the whole routine of the subject: the ability to manage rest-effort cycles and to distribute effort evenly. In every training routine, whenever strict it is, there is considerable variation between subjects in the total amount of activity they perform and the actual way they perform. Alternative explanation, is that MP does not affect bone mass in young adults. All of the previous literature documenting decrease in bone density following MP treatment related to children and adolescents up to age of 20 [7,8]. In this study, individuals at ages 18–25 were included. Two other studies that found positive association between SF and MP use in military recruits of same age group related to MP use prior to conscription. It is probable that exposure to MP in earlier years is more critical to bone mass compared to older age. Finally, an explanation proposed by the author OC is that the amount of bone mineral content does not reflect the bone resilience to stress. In fact, only 50–70% of variability in bone strength is explained by bone mineral content [15]. According to Hart et al., "*Bone strength is … a sophisticated and multifactorial proposition specific to the complex interplay of macroscopic tissue (trabecular and cortical), material properties (organic and inorganic) and structural properties (geometry and distribution); and is modulated by neighbouring muscle as a key osteogenic stimulant and modifier of mechanical behaviour*" [15]. MP as a stimulant may modify gait and muscle tone, and affect strains exerted on the bone. A recent bio-mechanical research showed variable effect of calf and thigh muscle fatigue on tibia strain [16]. MP was shown to improve gait rhythmicity in children [17] and reduce gait errors in older adults [18]. It is possible that MP has additional, presently

Table 3
Adjusted odds stress fractures for methylphenidate use, ADHD and other risk factors.

	Men		Women	
	OR (95%CI)	p-Value	OR (95%CI)	p-Value
Untreated ADHD[a]	1.66 (1.41:1.95)	< 0.001	1.33 (1.07:1.63)	0.007
ADHD 1–90 doses[a]	0.67 (0.41:1.03)	0.09	1.29 (0.90:1.78)	0.14
ADHD 91–180 doses[a]	0.39 (0.09:1.04)	0.11	0.68 (0.24:1.49)	0.39
ADHD 180+ doses[a]	0.49 (0.19:1.01)	0.08	0.09 (0.01:0.40)	0.02
Age	0.89 (0.87:0.92)	< 0.001	0.93 (0.87:0.99)	0.02
Weight	1.002 (1.00:1.003)	0.01	1.005 (1.002:1.007)	< 0.001
Origin: North Africa, South America and Middle East[b]	0.87 (0.81:0.92)	< 0.001	0.84 (0.76:0.93)	0.001
Origin: Northern America and Europe, former Soviet Union[b]	0.99 (0.92:1.05)	0.67	0.86 (0.77:0.95)	0.004
Education > 12 years[c]	1.30 (1.17:1.46)	< 0.001	2.46 (1.76:3.57)	< 0.001
Middle socio-economic level[d]	1.32 (1.17:1.49)	< 0.001	0.99 (0.73:1.31)	0.92
High socio-economic level[d]	1.56 (1.38:1.77)	< 0.001	1.2 (1.12:1.29)	< 0.001
Combat service[e]	3.7 (3.55:3.86)	< 0.001	8.53 (7.71:9.44)	< 0.001
Duration of follow-up	1.0004 (1.0003:1.0005)	< 0.001	1.0001 (1.00:1.0002)	0.008

The models were adjusted for age, weight, origin, education, socio-economic level, type of service, duration of follow-up and for the interaction between exposure (ADHD and MP use) and type of service.
[a] Subjects without ADHD as reference group.
[b] Reference group – Israeli born.
[c] Education of 12 years or less as reference group.
[d] Low socioeconomic level as reference.
[e] Non-combat service as reference group.

unknown effects on bones and surrounding tissues, resulting in higher resistance to fractures. This will be further investigated in a study on an animal model.

The study has several limitations. First, the exposure information could be imprecise due to potential for MP misuse by non-ADHD subjects and due to ability to purchase medication in private pharmacies, or by unreported MP use by subjects with ADHD. However, this limitation would be common to any type of study attempting to investigate the effects of MP use in large populations. It is still likely that most subjects who had a documented use of 180+ tablets during service actually used more medication than subjects who had no documented MP use. Second, the way of measuring exposure is arguable. Although exact dosing information was available, we considered that dosing would reflect subjects' weight, severity of ADHD symptoms and metabolic factors that may not be accounted for in multivariate analysis, and therefore considered that duration of treatment (derived from number of tablets prescribed) may be a simple and reliable indicator of MP exposure that is subject to the above bias to a lesser extent. Third serious limitation is lack of bone density measures, that of course was not possible for a cohort of this size, but could contribute tremendously to explanation of the findings in the discussion above. Lastly, stress fracture diagnosis was obtained from medical records and did not have strict case definition criteria. The diagnosis was done clinically by a primary care physician, based on the IDF clinical guidelines. Criteria for SF diagnosis therefore included history of pain with activity, local tenderness or swelling and positive provocative tests (fulcrum test and jumping on one leg). With about 20,000 bone scans performed in IDF during the study period, 25% of which were positive [3], it is clear that most of the clinical diagnoses were false positive. Whether the diagnosis is biased or not, the bias would have affected all study groups equally.

The multivariate analysis yielded several interesting findings. Higher socio-economic level was associated with higher SF risk. This is probably explained by tendency of people with high socio-economic status to lead a healthier lifestyle and be involved in recreational activity. Moreover, particularly in IDF, subjects with favorable socio-economic background choose combat service, which is associated with higher incidence of SF. One explanation for this is relative prestige of combat service in Israel. Second is the general policy of IDF to allow non-combat conscription and simultaneous employment for conscripts with economical difficulties. The finding of higher SF risk with higher education is probably explained by older age, tendency towards recreational activity and overall sedentary employment. The effect of ethnicity on SF risk in this study is mostly non-genetic but cultural, because all subjects are Jewish coming from different diaspora. The information therefore may not be generalizable to other populations.

As a conclusion, the findings of this study represent a valid estimate of the negative association between MP use and the incidence of SF. The pathophysiology behind this association is not completely understood and should prompt further investigation.

Declarations of interest

None.

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