Methylphenidate Has Positive Hypocholesterolemic and Hypotriglyceridemic Effects: New Data
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Many psychotropic drugs may affect plasma lipids profile and their metabolism, with carbamazepine being the best known among them. Methylphenidate is a piperidine derivative structurally related to amphetamines and acts as a central nervous system stimulant. Its effect on lipid metabolism has not been investigated. The authors evaluated how methylphenidate affects the lipid profile in the plasma of patients diagnosed as having attention-deficit hyperactivity disorder (ADHD). All consecutive patients undergoing treatment for ADHD at the Adolescent Psychiatric Clinic (2003-2007) were enrolled. Blood samples for total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, apolipoprotein A, apolipoprotein B, and lipoprotein (a) (Lp(a)) were collected before starting treatment and after 3 months of continuous treatment. Forty-two patients (22 men), median age 16, participated. The median total cholesterol count decreased by 9 mg/dL ($P < .0002$), LDL-C decreased by 5.0 mg/dL ($P < .016$), and triglycerides decreased by 8.0 mg/dL ($P < .016$). Changes in the levels of HDL-C, apolipoprotein A, and apolipoprotein B were nonsignificant, and Lp(a) levels decreased by 2.0 mg/dL ($P < .0007$). Methylphenidate improves the lipid profile by decreasing total cholesterol, triglycerides, LDL-C, and Lp(a).

**Keywords:** methylphenidate; lipids; total cholesterol; LDL cholesterol; atherosclerosis; lipoprotein (a)


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Atherosclerosis is a slowly progressive process starting at a young age. Therefore, many effective measures are taken early in life to prevent future cardiovascular disease worldwide, the most important being the awareness of a proper lifestyle, including physical activity, a proper diet, and abstaining from drugs and habits that may increase the likelihood of atherosclerosis through the development of different risk factors (eg, hyperlipidemia). Many drugs are known to cause secondary hyperlipidemia, especially psychotropic drugs used for different disturbances, such as carbamazepine, which was found to increase levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C). Tricyclic antidepressants, especially amitriptyline, induce weight gain and dyslipidemia in correlation with dosage and duration of treatment. Methylphenidate is a piperidine derivative structurally related to amphetamines and acts as a central nervous system (CNS) stimulant. Methylphenidate has been widely used since 1937 for a number of indications, such as attention-deficit hyperactivity disorder (ADHD), narcolepsy, cataplexy, and conduct disorder in children and adolescents as well as adults. Although it has been indicated for ADHD since 1957, it has had widespread use during the past 2 decades. Methylphenidate was found to affect brain sterol metabolism in mice by inhibiting the incorporation of its precursors, acetate and glucose, into the brain and by reducing the brain’s sterol levels. This reduction was found to occur within 24 hours in the brain.

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tissue cellular membrane, the site of methylphenidate’s action.9 Because of its rapidly growing use, especially in youngsters,10 it is important to examine the effect of this medication on blood lipid levels.

MATERIALS AND METHODS

Patients were recruited for this study from the Child and Adolescent Psychiatric Outpatient Clinic of the Tel-Aviv Sourasky Medical Center. They had all been referred to the clinic for suspected ADHD. Those who suffered from other psychiatric or neurologic diseases, endocrinopathies, mental retardation, or any other chronic illnesses or who were taking other medication were excluded. Suitable candidates who were finally diagnosed as having ADHD and needed treatment by methylphenidate (Ritalin) received a complete explanation about the nature of this study. Consenting patients or those with consenting guardians were enrolled. The study was approved by the local ethics committee of the Tel Aviv Sourasky Medical Center and the Israeli Ministry of Health.

Before starting treatment, a medical history was taken, and each patient underwent a physical examination and measurement of blood pressure, weight, and height. Blood samples were taken for a lipid profile that included total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, apolipoprotein A (apoA), apolipoprotein B (apoB), and lipoprotein (a) (Lp(a)) before treatment and after 3 months of continuous treatment. The period of 3 months was considered as being sufficient time for Ritalin to have had an impact on the lipid profile, if any. In addition, the participants could be expected not to undergo significant constitutional changes within that short period.

Statistics

The effect of methylphenidate treatment on various parameters was tested using the paired nonparametric Wilcoxon test. Significance was set at \( P < .05 \). All statistical analyses were performed using SAS for Windows, Version 9.1.3.

RESULTS

A total of 53 consecutive outpatients with an established diagnosis of ADHD were eligible for participation in this prospective study according to the exclusion and inclusion criteria. Of them, 11 were excluded for technical reasons, noncompliance, or lack of sufficient follow-up. The remaining 42 patients comprised the final study cohort.

The baseline characteristics of the study group are presented in Table I. There were 22 males and 20 females whose median age was 16 years (range, 11-31).

Table II displays the differences in the examined parameters before and after 3-month treatment by methylphenidate. Body mass index (BMI) did not change during the study period. Significant decrease was
found in total cholesterol, LDL-C, and triglycerides levels. Nonsignificant changes were seen in HDL-C, apoA, and apoB levels. The changes in Lp(a) unexpectedly turned out to be statistically significant. There were no gender-based differences in any of these parameters after adjustment according to age or any correlations between the lipid parameters.

DISCUSSION

Many risk factors are related to atherosclerosis and cardiovascular disease. Being a neurostimulant medication, the possible linkage of methylphenidate to the cardiovascular system was investigated. The data are controversial. Samuels et al11 investigated the effect of methylphenidate on blood pressure. Their study provided evidence for a possible negative cardiovascular effect of stimulant medication on children with ADHD. Satterfield et al12 found no association between prolonged administration (1-4 years) of methylphenidate to hyperactive boys regarding hematopoietic, endocrine (including glucose levels), hepatic, or cardiovascular functions analyzed in their study. However, Gontkovsky et al13 reported a decrease of 26% in serum glucose values after methylphenidate initiation in a patient after a cerebellar tumor resection. Vitiello14 did not find clinically significant changes in cardiovascular function in the majority of cases investigated. However, in their review, Langendijk and Wilde15 elucidated an increase in blood pressure and heart rate among adults treated by methylphenidate as being a risk factor for a cardiovascular event, and Rapport and Moffitt16 described the possible increase of blood pressure and heart rate among children treated by methylphenidate for ADHD as transient, dose dependent, and easily rectified with dosage adjustment. Spivak et al17 reported a decrease in platelet-poor plasma level of norepinephrine, dopa, and serotonin in children treated 3 months with methylphenidate, which means that this medicine has an inhibitory impact on platelet activation.

Hyperlipidemia is one of the major risk factors of atherosclerosis and cardiovascular diseases.18,19 The cause of lipid metabolism abnormalities is mainly genetic. The secondary causes of dyslipidemia are well-known and include inappropriate lifestyle, liver disease, renal disease, and hypothyroidism.13 The different drugs that are known to affect lipid metabolism include hormones (glucocorticoids, estrogens, and androgens), beta-blockers, diuretics, and others.11 Many recently developed drugs were designed to be started early in childhood to improve various organ somatic, cognitive, and neuropsychiatric functions. These medications appeared to be very potent and significantly changed patients' quality of life, features that led to their widespread use all over the world.20 Weight gain has been described since the discovery and use of the first psychotropic drugs, and it seems to be intensified with some of the second-generation antipsychotic medications, such as olanzapine and clozapine.11 Rader and Hobbs20 reported that some of these drugs may affect lipid and lipoprotein metabolism and increase or decrease atherogenicity. As such, prescribing psychiatrists must be alert to the use of concomitant medications and individual factors underlying overweight and dyslipidemia. Some antiepileptic and antidepressant drugs2‑5 were found to increase LDL-C blood levels, a finding that may well have an impact on the development of atherosclerosis.

Methylphenidate is one of the drugs that has been shown to elicit behavioral sensitization.2 Its use has been increasing rapidly throughout the years and is often prescribed for many years from childhood to adolescence and even adulthood, thus facilitating the study of their effect in the human organism. Therefore, it is possible to get plenty of opportunities to study their different effects on the human organism.

Methylphenidate is the most abundantly used medication worldwide for the treatment of ADHD in all age groups.10 It is well-known that methylphenidate has an effect on brain tissue intracellular cholesterol, but its effect on plasma lipid metabolism has not yet been studied in the clinical setting.9

We believe this to be the first investigation into the impact of methylphenidate on plasma lipid profile and atherosclerosis. The results of the current study showed that methylphenidate has a significant and positive impact on the lipid and lipoprotein profile with regard to atherosclerosis. It significantly decreases total cholesterol, triglycerides, and the main atherosclerotic lipoproteins, LDL-C and Lp(a). This lipid effect is in no way an indication to use the drug for preventing atherosclerosis but rather evidence that it can be used safely without concern of accelerating the development of atherosclerosis. A careful search of the literature did not reveal any significant data about the impact of methylphenidate on plasma lipid profile and atherosclerosis.

Conclusion

The presented data support some positive effects on lipid profile by decreasing total cholesterol,
triglycerides, LDL-C, and Lp(a). No conclusions could be made concerning atherosclerosis.

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