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Original article

The effect of atorvastatin on cardiometabolic risk factors in women with non-classic congenital adrenal hyperplasia: A pilot study

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ABSTRACT

Background: Individuals with non-classic congenital adrenal hyperplasia (NC-CAH) often show evidence of hyperandrogenism, including premature pubarche, accelerated linear growth velocity, short final height, hirsutism, acne, alopecia, impaired ovulation, menstrual dysfunction and subfertility. Although statins were found to reduce elevated levels of androgens in subjects with this disorder, no previous study has investigated whether 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors affect cardiometabolic risk factors in patients with NC-CAH.

Methods: We studied 12 women with NC-CAH, 6 of whom because of coexisting hypercholesterolemia received atorvastatin (20–40 mg daily). Circulating levels of lipids, glucose homeostasis markers, plasma levels of androgens, 17-hydroxyprogesterone, high-sensitivity C-reactive protein (hsCRP), uric acid, fibrinogen, homocysteine and 25-hydroxyvitamin D, as well as urinary albumin-to-creatinine ratio (UACR) were determined at the beginning of the study and 12 weeks later.

Results: Beyond affecting plasma lipids, atorvastatin reduced circulating levels of testosterone, dehydroepiandrosterone sulphate, androstenedione and 17-hydroxyprogesterone, and decreased free androgen index. Moreover, atorvastatin caused a decrease in plasma levels/urinary loss of uric acid, hsCRP, homocysteine and UACR, and insignificantly increased circulating levels of 25-hydroxyvitamin D. The drug produced no effect on plasma fibrinogen. The effect of atorvastatin on hsCRP, uric acid, homocysteine, 25-hydroxyvitamin D and UACR correlated with the magnitude of reduction in 17-hydroxyprogesterone and androgens.

Conclusion: Our results suggest that statin therapy reduces cardiometabolic risk in women with NC-CAH.

Introduction

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders, each of which is associated with a deficiency of an enzyme playing a role in the synthesis of cortisol [1]. The most common form of CAH is a deficiency of 21-hydroxylase resulting from mutations or deletions of *CYP21A2* gene [2]. The degree to which the activity of this enzyme is diminished correlates with the severity of CAH and therefore the clinical presentation of 21-hydroxylase deficiency is characterized by a wide spectrum of abnormalities [1]. A partial enzyme defect leads to the development of non-classic congenital adrenal hyperplasia (NC-CAH), which is characterized by enhanced precursor accumulation prior to the enzyme block, contrasting in most cases with sufficient cortisol production [3,4]. This mild form of CAH seems to occur in 0.1–0.2% of the European population and 1–2% of women with elevated androgen levels [3,4]. Individuals with NC-CAH often show evidence of hyperandrogenism, including premature pubarche, accelerated linear growth velocity, short final height, hirsutism, acne, alopecia, impaired ovulation, menstrual dysfunction and decreased fertility [5,6].

Simvastatin, being one of the commonly used 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, decreased elevated androgen levels in women with NC-CAH [7]. Moreover,

Abbreviations: CAH, congenital adrenal hyperplasia; DHEA-S, dehydroepiandrosterone sulphate; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HOMA2-IR, the homeostasis model assessment 2 of insulin resistance index; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NC-CAH, non-classic congenital adrenal hyperplasia; SD, standard deviation; SHBG, sex hormone-binding globulin; UACR, urinary albumin-to-creatinine ratio.

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simvastatin potentiated the effect of metformin [8], which was found to be another agent known to produce an androgen-lowering effect in women with this disorder [9]. Statins are proven to prevent major cardiovascular events and mortality [10,11]. Apart from lowering lipid levels, the clinical benefits associated with statin use seem to be secondary to their extra-lipid (pleiotropic) effects, such as inhibition of inflammatory responses, regulation of smooth muscle cell migration and proliferation, improvement of endothelial function, antioxidant properties, as well as the effect on platelet function, coagulation and fibrinolysis [12–14]. However, despite reducing coronary events, statin therapy results in a slight increase in the incidence of type 2 diabetes [15,16]. In light of these findings, it seems interesting that the results of a few studies, including heterogeneous patient populations, suggest an increased cardiometabolic risk in CAH. Patients with this disorder were characterized by a small increase in the body mass index and fat mass, as well as more frequently developed insulin resistance and hypertension [17]. Moreover, the presence of CAH led to excess cardiovascular and metabolic morbidity [18], and resulted in an increase in carotid intima-media thickness [19].

To date, nothing is known about cardiovascular and metabolic effects of statins in individuals with CAH. Therefore, the purpose of the our study was to assess whether atorvastatin affects plasma levels/urinary loss of cardiometabolic risk factors in women with NC-CAH.

Materials and methods

Patients

The study protocol was approved by the local ethical committee and written informed consent was obtained from all patients before inclusion. The study population consisted of 12 women (20–40 years old) with NC-CAH diagnosed on the basis of the low-dose corticotropin stimulation test, performed from 3 to 12 months before the beginning of the study, which was supported by elevated early follicular phase 17-hydroxyprogesterone levels at the study onset. To be included, the patients were required to have: (1) maximum 17-hydroxyprogesterone levels after 250 μg cosyntropin stimulation in the early follicular phase more than 10 ng/mL; (2) non-stimulated 17-hydroxyprogesterone levels in the first day of the study above 2 ng/mL; as well as (3) symptoms of androgen excess (oligomenorrhoea, hirsutism, infertility or acne). All subjects were recruited prospectively. The exclusion criteria were as follows: other disorders associated with elevated androgen levels, premature ovarian insufficiency, thyroid disorders, diabetes, any acute and chronic inflammatory processes, coronary artery disease, impaired renal or hepatic function, concomitant treatment with other agents known either to affect circulating lipid levels or to interact with statins within 3 months before the beginning of the study, and poor patient compliance. Six women with elevated levels of LDL cholesterol (above 130 mg/dL) were then treated with atorvastatin (20 mg), administered once daily at bedtime. After 6 weeks, the control assessment of plasma levels of LDL cholesterol was carried out and if these levels still exceeded 130 mg/dL, atorvastatin was up-titrated to 40 mg daily. The remaining six patients did not receive any treatment throughout the entire study period (12 weeks), serving as a control group.

Laboratory assays

Venous blood samples were collected between 8.00 and 9.00 a.m. in the fasting state (at least 12 h after the last meal) before and at the end of the study period and assessed in duplicate. Plasma levels of glucose were also measured 2 h after the oral ingestion of 75 g of glucose. Blood samples were collected from the antecubital vein after the patients had been in a recumbent position for at least 15 min. Plasma total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides, plasma glucose and plasma uric acid, as well as

Table 1
Baseline characteristics of participants.

	Atorvastatin	Untreated women
Number of patients	6	6
Age [years; mean (SD)]	31 (6)	32 (6)
Smoking [%]	30	30
Metabolic syndrome [n (%)]	4 (67)	4 (67)
Body mass index [kg/m^2; mean (SD)]	28.5 (5.1)	28.1 (4.8)
Waist circumference [cm; mean (SD)]	90 (15)	88 (13)
Systolic blood pressure [mm Hg; mean (SD)]	134 (16)	131 (15)
Diastolic blood pressure [mm Hg; mean (SD)]	84 (10)	85 (8)
Total cholesterol [mg/dL; mean (SD)]	275 (40)[a]	178 (28)
LDL-cholesterol [mg/dL; mean (SD)]	178 (25)[a]	86 (17)
HDL-cholesterol [mg/dL; mean (SD)]	48 (13)	48 (10)
Triglycerides [mg/dL; mean (SD)]	235 (72)	212 (65)
Fasting glucose [mg/dL; mean (SD)]	93 (10)	92 (9)
2-h postchallenge glucose [mg/dL; mean (SD)]	138 (22)	134 (25)
HOMA2-IR [mean (SD)]	1.63 (0.78)	1.66 (0.72)
17-hydroxyprogesterone [ng/mL; mean (SD)]	6.4 (2.0)	6.0 (2.2)
Total testosterone [ng/dL; mean (SD)]	83 (30)	75 (41)
DHEA-S [μmol/L; mean (SD)]	9.3 (2.9)	8.5 (2.5)
Androstenedione [ng/mL; mean (SD)]	2.9 (1.1)	2.6 (1.2)
SHBG [nmol/L; mean (SD)]	50 (15)	48 (12)
FAI [%; mean (SD)]	5.8 (1.9)	5.4 (1.7)
Uric acid [μmol/L; mean (SD)]	392 (72)	378 (85)
hsCRP [mg/L; mean (SD)]	2.6 (1.1)	2.4 (1.5)
Fibrinogen [mg/dL; mean (SD)]	378 (96)	400 (98)
Homocysteine [μmol/L; mean (SD)]	32 (10)	28 (14)
25-hydroxyvitamin D [ng/mL; mean (SD)]	25 (11)	23 (10)
UACR [mg/g; mean (SD)]	22 (12)	25 (10)

Abbreviations: DHEA-S, dehydroepiandrosterone sulphate; FAI, free androgen index; HDL, high-density lipoprotein; HOMA2-IR, the homeostatic model assessment 2 of insulin resistance ratio; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NC-CAH, non-classic congenital adrenal hyperplasia; SD, standard deviation; SHBG, sex hormone-binding globulin; UACR, urinary albumin-to-creatinine ratio.

[a] $p < 0.001$ *vs.* untreated women.

urinary albumin and creatinine were assayed by routine laboratory techniques using reagents obtained from Roche Diagnostics (Basel, Switzerland). LDL cholesterol was determined directly. Plasma levels of 17-hydroxyprogesterone were determined by enzyme-linked immunosorbent assay using a EUROIMMUN analyzer I (Euroimmun, Wrocław, Poland). Circulating levels of insulin, total testosterone, dehydroepiandrosterone sulphate (DHEA-S), sex-hormone-binding globulin (SHBG) and homocysteine were determined by direct chemiluminescence using acridinium ester technology (ADVIA Centaur XP Immunoassay System, Siemens Healthcare Diagnostics, Munich, Germany). Plasma levels of androstenedione and high-sensitivity C-reactive protein (hsCRP) were measured by immunoassay with chemiluminescent detection (Immulite 2000XPi, Siemens Healthcare, Warsaw, Poland). Fibrinogen was measured by the Clauss technique in an automated BCS XP analyzer (Siemens Healthcare, Warsaw, Poland). Plasma levels of 25-hydroxyvitamin D levels were detected by competitive immunoassay using Roche Diagnostic commercial kits and a multichannel automatic analyzer (Roche Cobas e 411, Mannheim, Germany). The homeostatic model assessment 2 of insulin resistance (HOMA2-IR) was calculated from plasma glucose and insulin levels using an online calculator downloaded from http://www.dtu.ox.ac.uk. Free androgen index (FAI) was calculated as follows: FAI = 100 × total testosterone (nmol/L)/SHBG (nmol/L). The urinary albumin-to-creatinine ratio (UACR) was calculated by dividing the amount of urinary albumin (mg) by the amount of urinary creatinine (g).

Statistical analyses

The distributions of variables were evaluated for normality using the Kolmogorov-Smirnov test. Before statistical analysis, all non-normal variables (hormones, hsCRP, fibrinogen, 25-hydroxy vitamin D, homocysteine, triglycerides, HOMA2-IR, FAI and UACR) were log-transformed to achieve a normal distribution. Student's unpaired *t*-tests were used to compare both groups of women, while Student's paired *t*-tests were applied to compare values within the same group. Dichotomized or nominal variables were compared using χ^2 tests. Pearson's *r*-tests were used to evaluate the existence of correlations. *P*-values of below 0.05 were considered significant.

Results

The mean age, smoking status and body mass index, as well as the number and percentage of patients fulfilling the criteria of metabolic syndrome were similar or the same in both study groups (Table 1). As expected, the groups differed from each other in total and LDL cholesterol levels. Baseline values of HDL cholesterol, triglycerides, fasting and 2-h postchallenge glucose, HOMA2-IR, uric acid, 17-hydroxyprogesterone, testosterone, DHEA-S, androstenedione, FAI, hsCRP, fibrinogen, homocysteine, 25-hydroxyvitamin D and UACR were comparable between both groups (Table 1). Atorvastatin treatment was well tolerated and all participants completed the study. The mean daily dose of atorvastatin was 27 ± 10 mg.

In the control women, plasma lipids, fasting and postchallenge plasma glucose and HOMA2-IR, as well as the assessed hormones and cardiometabolic risk factors remained at the similar level throughout the study (Table 2). Beyond reducing total and LDL cholesterol levels, twelve weeks of atorvastatin treatment decreased circulating levels of 17-hydroxyprogesterone, total testosterone, DHEA-S and androstenedione. Moreover, the drug decreased FAI, reduced plasma levels of hsCRP, uric acid, homocysteine and UACR, and insignificantly increased circulating levels of 25-hydroxyvitamin D ($p = 0.098$). Post-treatment values

Table 2
The effect of atorvastatin on plasma lipids, glucose homeostasis markers, as well as on the investigated hormones and cardiometabolic risk factors in women with non-classic congenital adrenal hyperplasia.

	Atorvastatin Mean (SD) [Δ%]	Untreated women Mean (SD) [Δ%]
Total cholesterol [mg/dL]		
Baseline	275 (40)[c]	178 (28)
After 12 weeks	194 (36) [−29][e]	183 (34) [3]
LDL-cholesterol [mg/dL]		
Baseline	178 (25)[c]	86 (17)
After 12 weeks	98 (18) [−45][f]	89 (15) [3]
HDL-cholesterol [mg/dL]		
Baseline	48 (13)	48 (10)
After 12 weeks	53 (10) [10]	50 (12) [4]
Triglycerides [mg/dL]		
Baseline	235 (72)	212 (65)
After 12 weeks	198 (74) [−16]	202 (69) [−5]
Fasting glucose [mg/dL]		
Baseline	93 (10)	92 (9)
After 12 weeks	94 (11) [1]	92 (8) [0]
2-h postchallenge glucose [mg/dL]		
Baseline	138 (22)	134 (25)
After 12 weeks	141 (24) [2]	132 (28) [−2]
HOMA2-IR		
Baseline	1.63 (0.78)	1.66 (0.72)
After 12 weeks	1.74 (0.67) [7]	1.59 (0.69) [−4]
17-hydroxyprogesterone [ng/mL]		
Baseline	6.4 (2.0)	6.0 (2.2)
After 12 weeks	3.2 (1.4) [−50][b,e]	6.7 (2.3) [12]
Total testosterone [ng/dL]		
Baseline	83 (30)	75 (41)
After 12 weeks	46 (24) [−46][a,d]	82 (31) [9]
DHEA-S [μmol/L]		
Baseline	9.3 (2.9)	8.5 (2.5)
After 12 weeks	5.8 (2.5) [−38][a,d]	8.9 (2.3) [5]
Androstenedione [ng/mL]		
Baseline	2.9 (1.1)	2.6 (1.2)
After 12 weeks	1.6 (0.8) [−44][a,d]	3.1 (1.4) [19]
SHBG [nmol/L]		
Baseline	50 (15)	48 (12)
After 12 weeks	58 (20) [16]	51 (16) [6]
FAI [%]		
Baseline	5.8 (1.9)	5.4 (1.7)
After 12 weeks	2.8 (1.0) [−52][b,e]	5.6 (1.4) [4]
Uric acid [μmol/L]		
Baseline	392 (72)	378 (85)
After 12 weeks	302 (62) [−23][a,d]	406 (93) [7]
hsCRP [mg/L]		
Baseline	2.6 (1.1)	2.4 (1.5)
After 12 weeks	1.4 (0.7) [−46][a,d]	2.7 (1.0) [13]
Fibrinogen [mg/dL]		
Baseline	378 (96)	400 (98)
After 12 weeks	397 (82) [5]	385 (64) [−4]
Homocysteine [μmol/L]		
Baseline	32 (10)	28 (14)
After 12 weeks	19 (10) [−41][a,d]	34 (18) [21]
25-hydroxyvitamin D [ng/mL]		
Baseline	25 (11)	23 (10)
After 12 weeks	34 (10) [36]	22 (13) [−4]
UACR [mg/g]		
Baseline	22 (12)	25 (10)
After 12 weeks	10 (5) [−55][a,d]	29 (15) [16]

Abbreviations: DHEA-S, dehydroepiandrosterone sulphate; FAI, free androgen index; HDL, high-density lipoprotein; HOMA2-IR, the homeostatic model assessment 2 of insulin resistance ratio; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NC-CAH, non-classic congenital adrenal hyperplasia; SD, standard deviation; SHBG, sex hormone-binding globulin; UACR, urinary albumin-to-creatinine ratio.

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$ *vs.* untreated women.
[d] $p < 0.05$.
[e] $p < 0.01$.
[f] $p < 0.001$ *vs.* baseline value.

of 17-hydroxyprogesterone, androgens, FAI, hsCRP, uric acid, homocysteine and UACR were lower in atorvastatin-treated than atorvastatin-naïve women, while plasma levels of 17-hydroxyvitamin D was insignificantly higher ($p = 0.071$) in subjects receiving atorvastatin than in the control group. The drug produced a neutral effect on HDL cholesterol, triglycerides, fasting and 24-h postchallenge glucose levels, HOMA2-IR, SHBG and fibrinogen (Table 2).

At baseline, circulating levels of total and LDL cholesterol positively correlated with levels of 17-hydroxyprogesterone, testosterone, DHEA-S, androstenedione and FAI (r values between 0.30 [$p < 0.05$] and 0.59 [$p < 0.01$]). The reduction in total and LDL cholesterol moderately correlated with statin-induced changes in plasma levels of 17-hydroxyprogesterone, testosterone, DHEA-S, androstenedione and FAI (r values between 0.32 [$p < 0.05$] and 0.47 [$p < 0.01$]). There were correlations between the impact of atorvastatin on hsCRP, uric acid, homocysteine, 25-hydroxyvitamin D and UACR and the degree of reduction in 17-hydroxyprogesterone and androgens (r values between 0.35 [$p < 0.05$] and 0.56 [$p < 0.01$]). Moreover, atorvastatin-induced reduction in hsCRP, plasma uric acid, homocysteine and UACR and atorvastatin-induced increase in 25-hydroxyvitamin D correlated with baseline plasma levels of 17-hydroxyprogesterone and androgens (r values between 0.30 [$p < 0.05$] and 0.49 [$p < 0.01$]). There were no significant correlations between the impact on cardiometabolic risk factors and the effect of atorvastatin on plasma lipids, fasting and postchallenge plasma glucose and HOMA2-IR.

Discussion

Unlike individuals with classic CAH, only some groups of patients with the non-classic form of this disorders (children with accelerated linear growth velocity and women planning pregnancy [3,4]) need to be treated with exogenous glucocorticoids and sometimes also with fludrocortisone. The inclusion and exclusion criteria used in our study enabled us to select a population of drug naïve-patients. This means that all effects observed in the study seem to result from statin therapy and cannot be interpreted as a time-dependent effect of glucocorticoids and/or as a result of an interaction between glucocorticoids and atorvastatin.

In line with our previous studies [7], statin therapy reduced circulating levels of total testosterone, DHEA-S and androstenedione. The only difference was a stronger impact of atorvastatin on 17-hydroxyprogesterone levels compared with simvastatin. This difference may be explained either by a larger number of a statin-treated patients in the present study (6 *vs.* 4) and/or by a greater strength of action of atorvastatin than simvastatin [7].

However, the most important finding of our study was that atorvastatin treatment of women with NC-CAH reduced circulating levels of uric acid, hsCRP and homocysteine, increased plasma levels of 25-hydroxyvitamin D, as well as decreased UACR. Interestingly, uric acid, hsCRP, homocysteine and UACR are positive predictors, while 25-hydroxyvitamin D is a negative predictor of cardiometabolic disorders [20–25]. Considering their role as risk factors, statin therapy may inhibit the development of atherosclerosis and its complications in patients with NC-CAH partially by altered production of these biomarkers. The effect of therapy on the assessed cardiometabolic risk factors was lipid-independent and probably resulted from the inhibitory impact on the production of non-sterol isoprenoids, such as farnesyl and geranylgeranyl pyrophosphates and possibly also other mevalonate derivatives, which stimulate protein prenylation [26].

Interestingly, unlike subjects belonging to the general population [15,16] or diagnosed with polycystic ovary syndrome [27], in women with NC-CAH simvastatin [7] or atorvastatin therapy produced a neutral effect on glucose homeostasis. These differences in results may be a consequence of different inclusion criteria, drugs, doses and differences in the duration of treatment periods. Taking into account the association between the investigated biomarkers and carbohydrate metabolism disorders atorvastatin may even indirectly retard the development of diabetes in subjects with NC-CAH. Although no study was carried out on patients with hyperandrogenism, it is probable that a deteriorating effect of statins on cellular glucose uptake [28] (protein prenylation up-regulates the insulin-responsive glucose transporter 4 [29]) is counterbalanced by the inhibitory impact of atorvastatin on factors known to worsen glucose homeostasis, such as free fatty acids and tumor necrosis factor-α, as it was found in other group of patients [30].

There are many similarities between NC-CAH and polycystic ovary syndrome, the latter of which is one of the commonest endocrine disorders in premenopausal women [31,32]. Polycystic ovary syndrome seems to be associated with an increased prevalence of cardiovascular disorders and type 2 diabetes, as a result of an impaired insulin receptor action, atherogenic dyslipidemia, endothelial dysfunction and prothrombotic state [33–35]. Interestingly, statin therapy of women with polycystic ovary syndrome was found to reduce circulating levels of hsCRP and vascular cell adhesion molecule 1, as well as to decrease systolic and diastolic blood pressure [36–38]. Our results support these findings, showing that a cardioprotective of statins is observed in various groups of hyperandrogenic women.

Recently, Krysiak et al. [39] have observed that the effect of atorvastatin on cardiometabolic risk factors correlated with thyroid function, being more pronounced in levothyroxine-treated and levothyroxine-naïve euthyroid women than in drug-naïve women with hypothyroidism. Because all participants of the present study remained untreated and the study included only patients with NC-CAH, it is difficult to conclude whether cardiometabolic effects of atorvastatin depend on androgen levels. However, the existence of correlations between a decrease in uric acid, hsCRP, homocysteine and UACR or between an increase in 25-hydroxyvitamin D and baseline levels of 17-hydroxyprogesterone and androgens may suggest that the strength of action of atorvastatin on the assessed biomarkers depends on the degree of 21-hydroxylase deficiency and that the impact of statins is more pronounced in more severe forms of CAH.

There are some study limitations that should be noted. The most important of them is a small sample size and a short period of atorvastatin treatment. Moreover, because the study included only women with NC-CAH, the effect of atorvastatin may be different in more severe forms of CAH. Furthermore, cut-off values for 17-hydroxyprogesterone after cosyntropin stimulation are a matter of debate. The Endocrine Society guidelines recommend 10 ng/mL in the early follicular phase, used in the study [40]. Some authors, however, suggest cut-off value of 15 ng/mL, carrying out this test at any time of day and at any time of the cycle [41]. Finally, we cannot totally exclude cases of other defects in the steroidogenic pathway (11β-hydroxylase deficiency and 17-hydroxylase deficiency) in our patients.

In conclusion, this study has shown for the first time that HMG-CoA reductase inhibitors reduced plasma levels and urinary loss of cardiometabolic risk factors in subjects with NC-CAH and this effect depended on the magnitude of reduction in 17-hydroxyprogesterone and androgens. The obtained results suggest that statins may bring some benefits to glucocorticoid-naïve patients with this disorder. Further research is, however, needed to verify our findings.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

R.K.: conception and design, analysis and interpretation of the data, the drafting of the paper; K.K.: conception and design, analysis and interpretation of the data; A.B.-C.: analysis and interpretation of the data; B.O.: conception and design, revising the manuscript critically for intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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