Analysis of Insulin Resistance Among Children and Adolescents in Slovenia With Hypercholesterolemia After Treatment With Statins

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Introduction

Statins are the first-line treatment for lowering atherogenic low-density lipoprotein cholesterol (LDL-C) in children with familial hypercholesterolemia (FH).1,2 Clinical trials have demonstrated the efficacy, safety, and good tolerability of statins among children with FH.3 The number of adolescents with FH needed to treat to prevent 1 heart attack is approximately 2.4 In adults, statins are associated with increased insulin resistance, insulin secretion, and type 2 diabetes risk.5,6 Data on the effects of statins on glucose homeostasis are lacking for children, who require lifelong lipid-lowering treatment (LLT).1,2,4 We assessed the association between treatment with statins and changes in insulin resistance markers in children and adolescents in Slovenia.

Methods

The National Medical Ethics Committee of Slovenia approved this cohort study. Written informed consent was obtained from participants or their parents/caregivers. The study followed the STROBE reporting guideline.

Children and adolescents diagnosed with FH were included if they met the criteria for LLT initiation1 and had fasting insulin and glucose measurements for 2 consecutive visits between 2016 and 2021. The treatment group comprised individuals who were prescribed 5 mg of rosuvastatin at baseline, had unmodified therapy between consecutive visits, and had a 20% or greater reduction in LDL-C from baseline. Control participants were those receiving no therapy despite intention to treat. Race and ethnicity were self-reported by participants or their parents/caregivers. Median values are reported with IQRs. Nonparametric statistical tests (all 2-tailed) were used; P < 0.05 was considered significant. Data were analyzed using IBM SPSS Statistics, version 26.0 (IBM).

Table. Changes in Cholesterol and Indirect Parameters of Insulin Resistance Among the Study Cohort

<table>
<thead>
<tr>
<th>Marker</th>
<th>Rosuvastatin, 5 mg (n = 20)</th>
<th>Control (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
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<tr>
<td></td>
<td>Baseline Follow-up</td>
<td>Baseline Follow-up</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>209 (189-267)</td>
<td>174 (160-193)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>292 (266-341)</td>
<td>255 (234-264)</td>
</tr>
<tr>
<td>Insulin, μIU/mL</td>
<td>7.6 (3.2-11.0)</td>
<td>3.3 (2.4-13.9)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>84 (80-87)</td>
<td>79 (77-83)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.5 (0.63-2.1)</td>
<td>0.75 (0.47-2.80)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.3 (5.2-5.4)</td>
<td>5.2 (5.1-5.4)</td>
</tr>
</tbody>
</table>

Abbreviations: HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance index; LDL-C, low-density lipoprotein cholesterol.

* P values were calculated for between-visit differences among groups. SI conversion factors: To convert LDL-C to millimoles per liter, multiply by 0.0259; to convert total cholesterol to micromoles per liter, multiply by 6.945; to convert glucose to millimoles per liter, multiply by 0.0555; and to convert HbA1c to proportion of total hemoglobin, multiply by 0.01.

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Results

This study included 35 participants: 20 in the treatment group (8 girls [40.0%], 12 boys [60.0%]; median [IQR] age at baseline, 10.0 [8.7-11.6] years) and 15 in the control group (7 girls [46.7%], 8 boys [53.3%]; median [IQR] age at baseline, 10.2 [8.8-13.2] years). Eighteen treatment group (90.0%) and 9 control group (60.0%) participants had a positive genetic test result for FH. All participants were White. Treatment and control group follow-up visits were performed at a median of 7.4 (6.4-12.6) and 13.4 (11.5-19.6) months \( (P = .03) \) from baseline, respectively.

Although median baseline LDL-C was higher among treatment group vs control group participants \( (209 \text{ [189-267]} \text{ vs } 174 \text{ [160-193]} \text{ mg/dL}) \) \( (P = .01) \), glucose homeostasis parameters at baseline were comparable \( (Table) \). Participants taking rosuvastatin had median reductions of 40.2% \( (34.6\%-47.0\%) \) in LDL-C \( (P < .001) \) \( (Figure) \) and 32.6% \( (24.9\%-39.2\%) \) in total cholesterol \( (P < .001) \). No changes in LDL-C and total cholesterol were observed among control participants; end-of-study LDL-C levels were lower in the treatment group \( (Table) \). No changes in median body mass index \( z \) scores were observed among treatment or control participants. Rosuvastatin was not associated with increased fasting glucose, fasting insulin, or HOMA-IR \( (Table) \). HbA1c levels remained unchanged.

Discussion

Children with FH who sustain a lifetime reduction in LDL-C with LLT have a lower risk of cardiovascular disease.\(^1\)\(^2\)\(^4\) In this cohort study, substantial reductions in LDL-C among children and adolescents taking rosuvastatin were not accompanied by increased fasting glucose, fasting insulin, HOMA-IR, and HbA1c levels after 7 months. In contrast, studies of adults suggest that changes can be observed 10 weeks after statin initiation.\(^6\)

Study limitations include the small sample size, short follow-up, low rosuvastatin dose, and lack of data on family history and pubertal status. Short-term treatment with rosuvastatin was not associated with changes in insulin resistance markers in this cohort of children with FH.
ARTICLE INFORMATION

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Critical revision of the manuscript for important intellectual content: Groselj, Sikonja, Kotnik, Battelino, Knowles.

Statistical analysis: Sikonja.

Obtained funding: Groselj, Battelino.

Administrative, technical, or material support: Groselj, Mlinaric, Knowles.

Supervision: Groselj, Battelino, Knowles.

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REFERENCES


