

Statin Use and the Development of Acute Mountain Sickness

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- INTRODUCTION:** Our prior publication suggested that elevated serum concentrations of low-density lipoprotein (LDL) was protective against the development of acute mountain sickness (AMS) while an inflammatory response was contributory to its development. The use of 3-hydroxy-3-methylglutaryl-coenzyme-A-reductase inhibitors ("statins") may be of interest to those traveling to altitude—these medications will lower serum LDL concentrations, but are also reported to have anti-inflammatory properties.
- METHODS:** Prior to flying from sea level to the South Pole (~10,498.7 ft or 3200 m) during the austral summer months of 2005-2006 and 2006-2007, the 248 subjects provided informed consent. Questionnaires related to AMS symptoms, acetazolamide use, personal history, and anthropometrics were paired with results from blood samples. Statin use was reported by six subjects who were matched for age, sex, altitude of residence, and acetazolamide use with seven subjects not using a statin.
- RESULTS:** No significant differences were identified in any of the matched variables between the groups. No statin users reported symptoms of AMS while 57% of participants not using a statin did report AMS symptoms ($P = 0.03$). No significant difference was noted between LDL levels in the statin group (108.3 ± 61.0) as compared to the group not taking statins (104.6 ± 22.1) ($P = 0.88$).
- DISCUSSION:** Our previous results suggested that elevated LDL was protective while an inflammatory response was contributory with respect to AMS development. The present results suggest that statin use may provide protection against AMS symptoms, possibly through an anti-inflammatory property, despite its lipid-lowering capacity.
- KEYWORDS:** LDL, cholesterol, altitude sickness, South Pole.

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In many disease processes ranging from acute mountain sickness (AMS), a benign and self-limiting condition, to sepsis, perhaps the acme of inflammatory conditions, tissue hypoxia results in an acute phase inflammatory process, including up-regulation of inflammatory markers such as interleukins and C-reactive protein.^{6,12,19} The available literature has not reached a consensus with respect to factors other than rate of ascent, hypoxia, and inflammation that either increase the risk of or provide protection against the development of AMS.^{4,16,34} However, our recent publication with a large sample of adults who were rapidly transported to altitude at the South Pole identified a unique variable, low-density lipoprotein (LDL), that was protective against AMS development.¹⁷ To the best of our knowledge, this variable has not been previously discussed as being positively or negatively related to AMS.

Literature has demonstrated an inverse relationship between serum LDL concentrations and the risk of experiencing fever or sepsis³⁵ and the severity of the septic insult.⁸ The protective mechanism is attributed to LDL's ability to bind lipopolysaccharide and thus modulate the downstream inflammatory response by decreasing the production of cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor α (TNF- α).³⁹ Serum LDL levels greater than $70 \text{ mg} \cdot \text{dl}^{-1}$ are identified as the level at

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which protection begins.³⁵ Alternatively, serum LDL greater than approximately $125 \text{ mg} \cdot \text{dl}^{-1}$ is associated with numerous cardiovascular risks for increased morbidity and mortality.³⁶ A decrease in LDL in conjunction with an increase in serum high-density lipoprotein (HDL) levels is associated with reduced risk and, as such, these changes are often brought about with either lifestyle modification or pharmaceutical agents.

The first-line pharmaceutical treatment of hyperlipidemia and atherosclerosis is 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, generically referred to as statins.²⁴ Statin therapy not only decreases serum LDL concentrations, but also has plaque stabilization, vasodilatory, antioxidant, and anti-inflammatory effects that may occur rapidly and independent from the LDL lowering effects.^{1,10,26} Animal models further suggest that statins may have an impact on the occurrence and progression of hypoxia-induced pulmonary hypertension,¹⁴ a factor thought to play a role in the development of high altitude pulmonary edema.^{2,19} In animal models, it has been described as a rescue agent in the setting of pulmonary artery hypertension.²⁵ Statins inhibit the synthesis of mevalonate, thereby inhibiting vascular smooth muscle growth, one of the prominent features of pulmonary hypertension development, while upregulating the production of prostacyclin, an eicosanoid with vasodilator and anti-inflammatory properties, and downregulating the production of endothelin, a vasoconstrictor associated with the development of pulmonary artery hypertension.²⁰ These findings make statins of significant interest in the study of AMS given the presence of subclinical pulmonary edema diagnosed by ultrasonography among AMS sufferers³⁰ and multiple sources suggesting an inflammatory component to AMS.^{4,12,16}

The relationships between serum LDL concentration, statin therapy, and inflammation influenced our hypothesis that statin therapy would be associated with a decreased risk of AMS development following rapid passive transport to the South Pole as compared to individuals not on statin therapy. Based on the LDL levels in our previous publication,¹⁷ we hypothesized that subjects taking a statin would have two protective mechanisms: a serum LDL level greater than $70 \text{ mg} \cdot \text{dl}^{-1}$ and the anti-inflammatory benefit provided by statin therapy.

METHODS

Data was collected during two austral summer expeditions to Amundsen-Scott South Pole Station. Ethical approval was obtained from Mayo Clinic, Rochester, MN, and all participants provided written informed consent. Participants were included in the study if their duties at Amundsen-Scott South Pole Station exceeded 1 wk in duration. During 2006–2007, data was only collected from those who had not been a participant during the 2005–2006 expedition.

Participants

Participants ($N = 248$) remained at McMurdo Station for ~2 wk. Participants flew to the South Pole in an airplane that was pressurized after takeoff, but depressurized during the flight so

that cabin pressure had equilibrated with ambient atmospheric pressure at the time of arrival. During the initial 2 wk at sea level, participants underwent baseline testing and education related to high altitude illness. Acetazolamide was made available to any participant who wished to employ AMS prophylaxis. Baseline questionnaire collection included Lake Louise Symptom Score questionnaires and further questionnaire data included information related to past medical history and chronic medical conditions, current medication use, lifestyle assessment (i.e., tobacco and alcohol use; exercise habits), and previous experience with altitude and/or Antarctic expeditions. Baseline anthropometric and physiological measurements included height, weight, heart rate, blood pressure, arterial oxygen saturation (S_aO_2), and blood draw. Blood draws were performed in the morning after acclimatizing to sea level. A repeat blood draw was performed in the morning on the second day after arrival at altitude. Blood samples were analyzed for hemoglobin concentration and hematocrit, serum electrolyte and progesterone levels, circulating catecholamine levels, and thyroid, liver, and kidney function. Changes in plasma volume were calculated using Dill and Costill's method.¹¹

Participants completed the same questionnaire reporting AMS symptoms, including the Lake Louise Symptom Score form, on nine separate occasions. Questionnaires were completed at baseline, on the plane to Amundsen-Scott South Pole Station, and daily for the first 7 d following arrival. The completion of the first questionnaire at the Amundsen-Scott South Pole Station occurred prior to sleep on the first night and each of the subsequent questionnaires were completed upon waking. An individual was determined to be suffering from AMS if their Lake Louise Symptom Score was ≥ 3 concurrent with a headache at any time during the first 7 d at altitude.

Of the 248 participants studied, 6 reported using a statin medicine to treat elevated serum cholesterol concentrations. These 6 subjects were matched by gender, age, elevation of place of residence prior to traveling to Antarctica, and acetazolamide use to participants who were not on statin therapy ($N = 7$). In both groups, two participants reported daily use of 81 mg of acetylsalicylic acid. No other medications, including beta-blockers or hypoglycemic agents, were reported.

Statistical Analysis

Statistical analyses were performed with SPSS 21.0 (IBM Corporation, Armonk, NY). Chi-square test was performed to analyze rates of AMS occurrence between statin users and nonusers. A Mann-Whitney *U*-test completed the non-parametric analysis of the other data. Significance was set as $P \leq 0.05$.

RESULTS

Participant characteristics are presented in **Table I**. No significant differences were observed for any of the variables by which the two groups (Statin vs. No Statin) were matched. The only significant difference was the rate at which AMS was reported.

Table I. Subject Characteristics and Rate of AMS Occurrence.

VARIABLE	STATIN	NO STATIN	P-VALUE	T-SCORE/X ²	DEGREES OF FREEDOM
Age (yr)	48.5 ± 6.7	47.9 ± 5.1	1.00	0.20	11
Gender (M)	6/6	7/7	1.00	0	1
Res Alt (m)	1269.8 ± 586.1	1435.9 ± 543.4	0.63	0.53	11
Acetazolamide Use	0/6	0/7	1.00	0	1
AMS	0/6	4/7	0.03*	4.49	1
AMS Severity	1.5 ± 1.9	2.1 ± 1.2	0.37	0.72	11
Height (m)	1.8 ± 0.1	1.8 ± 0.1	0.73	0.35	11
Weight (m)	88.9 ± 11.9	85.7 ± 16.6	0.53	0.40	11
BMI (kg · m ⁻²)	27.7 ± 4.6	26.0 ± 4.8	0.45	0.63	11
Heart Rate (bpm)					
Sea Level	79.5 ± 12.1	68.4 ± 11.4	0.10	1.70	11
Altitude	91.2 ± 12.6	87.0 ± 7.8	0.66	0.86	9
Blood Pressure (mmHg)					
Sea Level					
Systolic	119.8 ± 14.3	116.6 ± 11.2	0.84	0.46	11
Diastolic	73.3 ± 7.3	69.7 ± 8.4	0.45	0.82	11
Altitude					
Systolic	111.0 ± 15.2	108.6 ± 11.7	0.30	1.46	11
Diastolic	68.7 ± 10.9	73.2 ± 10.4	0.33	0.70	9
Oxygen Saturation (%)					
Sea Level	97.3 ± 1.0	96.6 ± 1.0	0.23	1.37	11
Altitude	88.0 ± 3.9	90.4 ± 3.0	0.43	1.13	9

*Significant difference between Statin and No Statin groups.

Table II summarizes the sea-level metabolic and hematological results, including liver function tests. **Table III** details the lipid profiles of our two groups at sea level and **Table IV** provides the changes in absolute values of the hormonal and neurotransmitter results between sea level and altitude.

DISCUSSION

In our previous publication, significant differences were observed between serum LDL concentrations in individuals who did and did not develop AMS.¹⁷ Our review of available literature in the realm of altitude research suggests this is a novel finding. In this present study of a population of adults

rapidly transported from sea level to the South Pole, statin therapy was associated with a decreased incidence of AMS as compared to matched controls. The incidence of AMS among the nonstatin controls, 57%, was comparable to our larger population as a whole, 52%,³ and to our other small group analysis, 51%.¹⁷ Interestingly, no significant differences were observed in the lipid profile (Table III) between individuals in the current analysis despite, or perhaps because of, statin therapy. However, participants in the statin group were taking simvastatin in doses ranging from 20 mg to 40 mg daily with one individual also taking niacin. This dose has been associated with a 35–40% decrease in serum LDL concentrations,²⁹ suggesting that serum LDL level in our statin group would have been significantly higher pretreatment.

Table II. Analysis of Metabolic and Hematological Results at the South Pole.

VARIABLE	STATIN	NO STATIN	P-VALUE	T-SCORE	DEGREES OF FREEDOM
Sodium (mEq · L ⁻¹)	137.8 ± 2.4	137.4 ± 2.4	0.77	0.30	11
Potassium (mEq · L ⁻¹)	4.1 ± 0.3	4.2 ± 0.3	0.62	0.51	11
Chloride (mEq · L ⁻¹)	101.7 ± 2.8	100.6 ± 1.7	0.41	0.86	11
Glucose (mg · dl ⁻¹)	93.7 ± 6.4	93.6 ± 7.0	0.98	0.03	11
Creatinine (mg · dl ⁻¹)	1.0 ± 0.1	1.1 ± 0.1	0.16	1.50	11
Calcium (mEq · L ⁻¹)	9.5 ± 0.3	9.7 ± 0.3	0.36	0.96	11
AST (U · L ⁻¹)	25.2 ± 8.6	32.0 ± 14.6	0.34	1.00	11
ALT (U · L ⁻¹)	32.0 ± 4.7	34.0 ± 17.8	0.80	0.27	11
Alkaline Phosphatase (U · L ⁻¹)	70.3 ± 15.8	71.4 ± 13.9	0.90	0.13	11
Hemoglobin (g · dl ⁻¹)	15.7 ± 0.4	16.2 ± 1.0	0.23	1.26	11
Hematocrit (%)	45.8 ± 1.2	47.4 ± 2.5	0.16	1.50	11
Leukocytes (x109/L)	5.6 ± 0.9	6.2 ± 2.1	0.61	0.53	10
Platelets (x109/L)	255.8 ± 38.3	233.4 ± 78.8	0.54	0.63	11
Eosinophils (x109/L)	4.0 ± 2.3*	1.1 ± 0.4*	0.01	3.29	11

*Significant difference between Statin and No Statin groups.

Table III. Analysis of Lipid Panel Results at the South Pole.

VARIABLE	STATIN	NO STATIN	P-VALUE	T-SCORE	DEGREES OF FREEDOM
Total Cholesterol (mg · dl ⁻¹)	207.2 ± 30.6	179.1 ± 22.5	0.08	1.90	11
Low Density Lipoprotein (LDL) (mg · dl ⁻¹)	108.3 ± 61.0	104.6 ± 22.1	0.88	0.15	11
High Density Lipoprotein (HDL) (mg · dl ⁻¹)	46.3 ± 10.3	55.1 ± 6.2	0.08	1.90	11
Very Low Density Lipoprotein (VLDL) (mg · dl ⁻¹)	25.3 ± 6.4	20.7 ± 9.5	0.48	0.75	11
Triglycerides (mg · dl ⁻¹)	146.2 ± 51.5	97.7 ± 46.0	0.12	1.72	10

Our statin and nonstatin populations both had serum LDL concentrations that were comparable to the concentration we had previously found to be associated with decreased risk of AMS³ while the statin group had the additional anti-inflammatory benefit associated with statin therapy. LDL concentrations greater than 70 mg · dl⁻¹ are associated with decreased inflammatory response in a variety of acute inflammatory processes along the spectrum ranging from fever to severe sepsis and septic shock,³⁵ and similar protective properties against sepsis-related mortality is offered by increases in serum HDL cholesterol concentrations,⁹ an event that occurs concurrently with the initiation of statin therapy.²⁴ No differences were noted between the hemodynamic variables of blood pressure and heart rate between the two groups at either sea level or altitude despite the vasodilatory properties of statins,^{22,27} though this may have been due to the small population included in the analysis.

Multiple sources suggest an influential role of systemic inflammation in the development of AMS.^{12,17,18} Statin use has been demonstrated to downregulate the production of multiple inflammatory markers, including TNF- α and C-reactive protein (CRP).^{26,31} Statins have also been demonstrated to have a potent antioxidant effect²¹ and hypothesized to have therapeutic benefit in autoimmune conditions.¹⁵ The decrease in CRP concentration during a 5-yr follow-up in a population of postmyocardial infarction patients on statin was significant and independent to decreases in LDL concentration³¹ while decreased inflammation was noted independent of decrease in plaque size in patients with carotid stenosis.¹⁰ Our current results include patients on low to moderate dose simvastatin; while anti-inflammatory effects of

statins are considered to be a class effect,²³ high-dose atorvastatin is associated with a greater decrease in CRP as compared to simvastatin.³⁷ It is possible our results underestimate the potential benefit of statin therapy in ameliorating the symptoms of AMS.

Aside from the differences in rate of AMS development, statistically significant differences were noted in three variables: eosinophil, progesterone, and norepinephrine concentrations. Eosinophil levels were associated an increased risk of AMS development in our prior publication¹⁷ and have been associated with increased inflammatory responses, including cytokine and proinflammatory marker production.³³ The eosinophil concentration was higher in the statin group and, given the decreased rate of AMS development in this group despite the proinflammatory role of these cells, these individuals may have benefited from the anti-inflammatory properties of both serum LDL and statin therapy.

A second variable that differed between the two groups was serum levels of progesterone. The relationship between serum progesterone levels and AMS, as influenced by the use of oral contraceptive pills, was the subject of one of our other earlier publications.¹⁸ Progesterone is a cholesterol hormone that is a respiratory stimulant, a smooth muscle relaxant, and a powerful anti-inflammatory in the central nervous system (CNS).²⁸ Numerous sources suggest the development of AMS has a large contributory CNS component,^{6,16,34} while progesterone levels have been shown to increase during exposure to high altitude.⁵ Statins are also associated with decreased lesion size in both hemorrhagic events in the CNS and after traumatic brain injury.³⁸ Statin use does not interfere with the production of progesterone²⁵ and our results would suggest the statin

Table IV. Analysis of Absolute Change in Hormone and Neurotransmitter Concentrations from Sea Level to the South Pole.

VARIABLE	STATIN	NO STATIN	P-VALUE	T-SCORE	DEGREES OF FREEDOM
Progesterone (ng · ml ⁻¹)	0.3 ± 0.3*	-0.1 ± 0.4*	0.02	2.33	11
TNF- α (pg · ml ⁻¹)	-0.4 ± 0.4	0.2 ± 0.4	0.07	1.59	11
VEGF (pg · ml ⁻¹)	11.7 ± 10.6	50.9 ± 27.6	0.39	0.29	11
Leptin (ng · ml ⁻¹)	2.3 ± 6.8	-0.4 ± 0.9	0.31	0.51	11
EPO (μ U · ml ⁻¹)	19.5 ± 14.4	25.0 ± 15.4	0.53	0.08	11
Norepinephrine (pg · ml ⁻¹)	120.0 ± 79.9*	250.6 ± 104.8*	0.03	2.10	11
Epinephrine (pg · ml ⁻¹)	-7.5 ± 16.7	4.3 ± 11.2	0.16	1.04	11
Dopamine (pg · ml ⁻¹)	-3.7 ± 22.5	19.1 ± 21.2	0.09	1.43	11

* Significant difference between Statin and No Statin groups.

group may have benefited from a combination of increased progesterone and statin therapy. However, this variable warrants further investigation in a sample population that includes female participants.

The final variable that differed was norepinephrine. The statin group demonstrated a smaller increase in levels after rapid transportation to altitude. Catecholamine surges, in particular increases in circulating levels of norepinephrine, are associated with exposure to high altitude in attempts to increase cardiac output, peripheral vascular tone, and pulmonary perfusion.¹³ However, elevations in norepinephrine during hypoxic exposure, even at low altitude, is a potential predictor of altitude sickness, including AMS and high altitude pulmonary edema.^{7,32} Statin therapy is associated with a decrease in norepinephrine levels as compared to placebo.^{22,27} While no differences were noted in systemic blood pressures at sea level and altitude between groups, perhaps the combination of effects of statin therapy on the pressures within the pulmonary vasculature and circulating norepinephrine levels were sufficient to provide protection against AMS.

An obvious weakness of the present study is the size and composition of the population. Our intervention population of six individuals was matched based on sex, age, acetazolamide use, and elevation of place of residence while blinding ourselves to rates of AMS development in selecting our controls. We included seven subjects in the control group due to near identical similarities between two individuals with respect to these variables with respect to each other and to the individual in the intervention group to whom they were being compared. Additionally, our subjects were all men. However, the small all-male sample is countered by the rigorous methodology with which the data was collected—all subjects acclimatized at sea level for comparable period of time, rapidly traveled to the same altitude via the same passive method, and had the same blood samples drawn at the same time at both sea level and altitude.

A number of differences were noted that demonstrated a trend toward statistical significance (i.e., $P < 0.10$) in four variables: HDL, total cholesterol, TNF- α , and dopamine concentrations. These factors have been linked to inflammatory response and have been associated with beneficial responses to statin therapy. Larger sample sizes may provide more information about their specific roles and relationships with respect to AMS.

In conclusion, in our population of adults rapidly transported to altitude from sea level, statin therapy was associated with a decreased risk of AMS development. The precise protective mechanism is not clearly identified in our study, but a number of possible options make a multifactorial physiological response very likely. Further research efforts should investigate the exact mechanism(s) and dose-response relationship by which this occurs on a larger scale. Our subjects were all being treated with simvastatin and research suggests other statin medications, e.g., atorvastatin, may have even more anti-inflammatory properties of interest to altitude research. Regardless, our results have provided findings that may guide numerous future hypotheses.

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