Effects of Oral Albuterol on Serum Lipids and Carbohydrate Metabolism in Healthy Men

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β_2-Selective adrenergic agonists are used in the management of bronchial asthma and preterm labor. Due to their ability to increase muscle strength and size in animal models, new applications for these agents are also being explored for neuromuscular disorders and in rehabilitation. However, the effects of long-term β_2-agonist administration on lipoprotein and carbohydrate metabolism are incompletely understood. This investigation evaluated the effects of a β_2-agonist, albuterol, on serum lipids and carbohydrate homeostasis in eight healthy nonsmoking men aged 24 to 61 years. Collection of fasting blood samples was completed in duplicate on separate days at baseline, during 14 days of oral albuterol administration (Proventil Repetabs, 8 mg twice daily; Schering Pharmaceuticals, Kenilworth, NJ) and during a 7-day washout period. Carbohydrate homeostasis was evaluated using the minimal model technique at the end of the baseline and albuterol periods. Fasting glucose and insulin, intravenous glucose tolerance, acute insulin response to intravenous glucose (AIRg), insulin sensitivity (Si), and glucose effectiveness (Sg) were not significantly changed during albuterol administration. Significant alterations ($P \leq .02$) were observed in total cholesterol ([TC] −9.1% ± 2.5%), low-density lipoprotein cholesterol ([LDL-C] −15.0% ± 2.9%), and high-density lipoprotein cholesterol ([HDL-C] +10.4% ± 3.2%) concentrations, as well as the TC/HDL-C (−17.4% ± 2.6%) and LDL-C/HDL-C (−22.9% ± 2.4%) ratios. During washout, TC and LDL-C returned to baseline levels, whereas HDL-C remained elevated by 5.8% ± 2.4% ($P < .05$). Thus, albuterol administration was associated with favorable changes in the serum lipid profile without marked impairment of glucose tolerance or its physiologic determinants.

THE β_2-selective adrenergic agonists are used clinically for the management of bronchial asthma and preterm labor. Due to their well-documented effects on skeletal muscle strength and size in animal models,[1-2] additional therapeutic applications are being explored for these agents in rehabilitation and in conditions associated with muscle weakness and atrophy.[3-4] Short-term administration of β_2-adrenergic agonists has been associated with notable metabolic side effects including elevation of plasma glucose, insulin, and free fatty acids, insulin resistance, and glucose intolerance.[5-9] However, the influence of long-term β-agonist therapy on carbohydrate and lipoprotein metabolism is incompletely understood.[5-6] The purpose of the present study was to investigate the effects of 2 weeks of oral albuterol administration on serum lipids and carbohydrate metabolism in healthy men.

SUBJECTS AND METHODS

Subjects

Eight healthy, nonsmoking men aged 24 to 61 years (median, 35 y) provided written informed consent to participate. The protocol was approved by the Human Subjects Subcommittee of the Edward Hines, Jr, Veterans Affairs Hospital. Subjects were free of clinical or laboratory evidence of metabolic and atherosclerotic disease, and none were taking any medications known to affect carbohydrate or lipid metabolism. All were at a stable weight (± 3%) for at least 2 months before enrollment.

Protocol

Participants reported to the laboratory on six occasions over a period of 1 month. Two visits each were completed at baseline, during albuterol administration (treatment phase), and after discontinuation of albuterol (washout). Baseline visits were separated by 4 to 7 days. One day after the final baseline visit, subjects began taking oral albuterol (Proventil Repetabs; Schering Pharmaceuticals, Kenilworth, NJ) twice daily in an open-label fashion. To minimize side effects, the dosage was gradually increased over 3 days. By the fourth day, all subjects were taking 8 mg twice daily. During the final days of the 2 week treatment period, subjects reported for testing on two occasions separated by 2 to 3 days. Washout visits were completed after the drug had been discontinued for 3 and 7 days, respectively.

Subjects were instructed to take the morning dose of albuterol 1.5 hours before their scheduled appointment, and the time of the last dose was recorded at each visit. Caffeine consumption was prohibited during the study period starting at least 3 days before the first baseline visit. Otherwise, participants were asked not to change their usual dietary habits or physical activity during the study. In particular, two subjects who engaged in regular endurance exercise were instructed to standardize the timing of exercise so that the number of hours between workouts and clinic appointments were always the same. This was verified verbally at each visit.

Testing

Fasting (12 to 14 hours) blood was drawn for determination of serum lipoproteins, insulin, glucose, potassium, magnesium, and uric acid at every visit. In addition, three flow-volume loop procedures were completed (Morgan Auto-Link Spirometer; Morgan Instruments, Kent, UK) for determination of forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), and forced vital capacity (FVC). The best of three trials was recorded. Weight was measured with subjects in light clothing without shoes, using a calibrated balance-beam scale. Height was measured only at the first baseline visit. Body mass index was calculated as weight in kilograms divided by height in meters squared.

At the final baseline and treatment visits, body composition was

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estimated using the bioimpedance method (Spectrum Lightweight II; RJL, Detroit, MI).[10] Supine abdominal circumference was measured at the umbilicus after normal expiration. Additionally, at each of these visits, an insulin-modified intravenous glucose tolerance test (IVGTT) was performed.[11] Intravenous lines were established for injection and blood sampling, respectively. These were kept patent with a slow normal saline drip. Two basal samples, separated by 5 minutes, were drawn into heparinized syringes and immediately transferred to tubes containing sodium fluoride. An injection of dextrose 0.3 g/kg body weight (50% wt/vol) was then administered within 2 minutes, and a bolus injection of regular human insulin (0.02 U/kg body weight) was given 20 minutes after the start of the dextrose injection. Additional blood samples were obtained following the start of the dextrose injection at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 23, 24, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 minutes.

Plasma insulin and glucose concentrations were measured in the samples from each IVGTT as described later, and these data were submitted to the MINMOD 2.0 program (copyright R.N. Bergman, 1986), which generates minimal model estimates of insulin sensitivity (Si) and glucose effectiveness (Sg).[11] Si represents the increase in the fractional disappearance of glucose per unit increase in plasma insulin concentration.[11] Sg represents the increment in the fractional disappearance of glucose per unit increase in plasma glucose concentration. Sg is independent of changes in plasma insulin level, but includes the effect of basal insulin concentration.[11]

Glucose effectiveness at theoretical zero insulin (GEZI) was obtained by subtracting the basal insulin effect from Sg.[11] Basal insulin effect was taken to be the product of basal insulin concentration and Si. The glucose disappearance constant ([K_g] percent per minute) was calculated as $-100 \times$ the slope of ln plasma glucose concentration on time from 10 to 19 minutes. The acute insulin response to intravenous glucose (AIRg) was defined as the incremental area under the insulin curve for the period 0 to 10 minutes.

Because IVGTTs were performed only during the baseline and albuterol treatment periods, an additional method of assessing insulin sensitivity was used, the fasting insulin sensitivity index (FISI),[12] FISI = 100/(ln G · ln I), where G and I are glucose and insulin concentrations in milligrams per deciliter and milliunits per liter, respectively. In the Insulin Resistance and Atherosclerosis (pilot) Study, FISI was the best fasting index for predicting glycemic clamp–derived Si.[12] In addition, FISI was strongly correlated with Si ($P < .001$) for the eight subjects in the present study during both the baseline ($r = .94$) and albuterol treatment ($r = .97$) periods. We believe this measure is superior to fasting insulin concentration as a marker for Si because it takes into account the glucose concentration and the nonlinear relationship between fasting insulin and Si.[13]

Biochemical Analyses

Serum or plasma from each study was frozen at −20°C and stored until analysis. Serum lipid levels were measured using a Paramax analyzer (model 720ZX; Baxter Scientific, Deerfield, IL). Total cholesterol (TC) and triglycerides (TG) were determined enzymatically. High-density lipoproteins cholesterol (HDL-C) level was measured after precipitation of lower-density lipoproteins by phosphotungstate. Low-density lipoprotein cholesterol (LDL-C) level was calculated using the Friedewald equation, LDL-C = TC − HDL-C − (TG/5). To minimize laboratory variance, lipid profiles from thawed serum were measured in the same run for each subject's baseline, albuterol treatment, and washout samples. In addition, lipid profiles were also determined on fresh serum for baseline samples on the day of collection. Results did not differ when frozen or fresh baseline serum samples were used, indicating that differences in the time samples were stored did not materially alter the study's findings.

Serum or plasma glucose measurements were completed with a Glucose Analyzer II (Beckman Instruments, Fullerton, CA) by the glucose oxidase method. Plasma insulin was assessed by double-antibody radioimmunoassay (Pharmacia Human Insulin Assay; SmithKline Beecham Clinical Laboratories, St Louis, MO). Serum potassium, magnesium, and uric acid levels were measured with an automated analyzer (Paramax model 720ZX; Baxter Scientific).

Statistical Analysis

Anthropometric, pulmonary-function, and fasting serum or plasma values from two visits were averaged for the baseline, treatment, and washout periods. ANOVA for repeated measures was used to test for changes in these variables. Where appropriate, this was followed by Scheffe's post hoc test. Because changes in K_g, Si, and Sg were not normally distributed, the Wilcoxon signed-rank test was used to assess possible differences in IVGTT-generated data between the baseline and treatment periods. Two-tailed P values not greater than .05 were considered statistically significant. All analyses were completed on a Macintosh personal computer (Apple, Brea, CA) with the Statview 4.0 statistical analysis package (Abacus Concepts, Berkeley, CA).

RESULTS

Compliance, Side Effects, and Pulmonary Function

Compliance was excellent, as estimated by interview and pill count, ranging from 93% to 100% of all scheduled doses. None of the subjects reported missing a dose of albuterol on a test day, and all pretest doses were reported to have been consumed between 1 and 2 hours before arriving at the laboratory. Seven subjects experienced tremor and/or a feeling of "jitteriness" after starting to take albuterol, but these disappeared or were substantially reduced within a few days and did not necessitate discontinuation of the medication in any subject.

FVC and FEV_1 were significantly increased ($P < .01$) during albuterol administration. Both returned to baseline values after discontinuation of the drug, further supporting a high degree of compliance. FVC and FEV_1 were as follows (mean ± SEM): baseline, 5.16 ± 0.21 and 4.28 ± 0.13 L; during albuterol, 5.38 ± 0.19 and 4.60 ± 0.14 L; posttreatment, 5.23 ± 0.17 and 4.40 ± 0.12 L. PEF remained steady throughout the study period. Baseline PEF was 10.5 ± 0.42 L/s, and albuterol and washout values were 10.6 ± 0.51 and 10.6 ± 0.61 L/s, respectively.

Serum Lipids

Mean fasting serum lipid values throughout the study are shown in Table 1. Significant changes were observed in serum lipoproteins during albuterol treatment ($P \leq .02$). TC and LDL-C decreased by 9.1% ± 2.5% and 15.0% ± 2.9%, respectively. HDL-C increased by 10.4% ± 3.2%, with all but one subject displaying some increase. As a result of higher HDL-C and/or reduced TC (seven subjects) and LDL-C (all subjects), the TC/HDL-C (17.4% ± 2.6%) and LDL-C/HDL-C (22.9% ± 2.4%) ratios were reduced in every participant (Fig 1). Serum TG was also lower in six subjects, but the mean change did not

Table 1. Fasting Serum Lipid Concentrations (mg/dL, mean ± SEM) According to Study Phase

Lipid Variable	Baseline	Albuterol Treatment	Washout Period	P (ANOVA)
TC	179.1 ± 8.8	162.1 ± 6.5*	182.9 ± 7.6	.0003
LDL-C	115.3 ± 7.6	97.4 ± 5.9*	116.6 ± 7.8	<.0001
HDL-C	43.7 ± 4.0	47.9 ± 3.9†	46.1 ± 4.2†	.0085
LDL-C/HDL-C	2.85 ± 0.38	2.19 ± 0.30*	2.76 ± 0.42	<.0001
TC/HDL-C	4.36 ± 0.47	3.61 ± 0.44*	4.25 ± 0.49	<.0001
TG	100.2 ± 13.5	84.1 ± 18.2	101.6 ± 10.3	.2745

*Significantly different from baseline and washout values.
†Significantly different from baseline value.

reach statistical significance (mean change, −16.6% ± 8.9%). During the washout period, serum lipid concentrations were nearly identical to baseline values, except for HDL-C, which remained elevated (5.8% ± 2.4%, $P < .05$ *v* baseline).

IVGTT

Median values for K_g (1.40 *v* 1.36%/min), Si (5.05 *v* 4.85 × $10^{-4} \cdot min^{-1} \cdot [mU/L]^{-1}$), Sg (1.91 *v* 1.66 × $10^{-2} \cdot min^{-1}$), GEZI (1.56 *v* 1.36 × $10^{-2} \cdot min^{-1}$), and AIRg [184.9 *v* 198.3 mU/L · min) did not vary significantly from the baseline to albuterol treatment period (Table 2).

Fasting Insulin and Glucose

Fasting serum glucose and insulin concentrations did not differ significantly during the three test periods (Table 3). FISI was not different between the baseline and treatment periods, but was higher during the washout period than during the baseline ($P < .06$) and albuterol ($P < .03$) phases. Insulin concentration during the washout phase was not measured for one subject, because an insufficient volume of serum was available for analysis.

Serum Potassium, Magnesium, and Uric Acid

Serum potassium declined significantly during albuterol treatment and returned to baseline after discontinuation of the drug. Serum magnesium also declined. The concentration during treatment was significantly less than during washout, but was not different from the baseline value. Uric acid concentration was unchanged during the study.

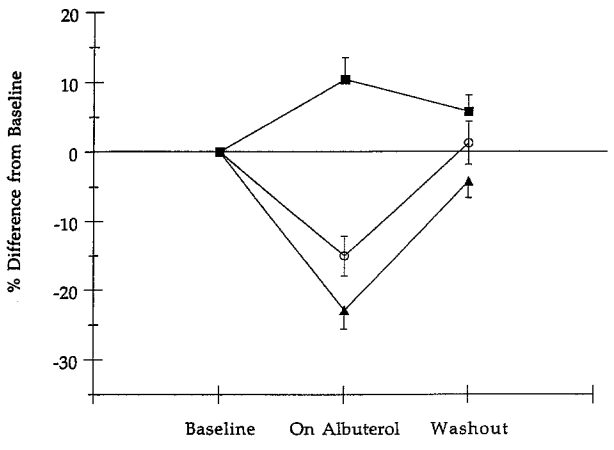

Fig 1. Percent difference from baseline concentration (mean ± SEM) for (■) HDL-C, (○) LDL-C, and (▲) the HDL-C/LDL-C ratio according to study phase.

Table 2. Values for Variables Derived From the IVGTT According to Study Phase

Variable	Baseline Median	Baseline Range	Albuterol Treatment Median	Albuterol Treatment Range	P (Wilcoxon signed-rank test)
K_g (%/min)	1.40	1.12-3.90	1.36	0.75-1.80	.327
Si ($10^{-4} \cdot min^{-1} \cdot$ [mU/L])	5.05	0.30-12.80	4.85	0.60-11.90	.889
AIRg ($10^2 \cdot$ [mU/L] · min)	1.89	0.74-2.93	1.98	0.97-4.04	.161
Sg (10^{-2}/min)	1.91	0.56-2.54	1.66	1.39-3.65	.674
GEZI (10^{-2}/min)	1.56	0.18-2.37	1.36	0.93-2.33	.575

NOTE. Median and range are reported because the distribution of values was not Gaussian.

Anthropometry and Body Composition

Body weight, abdominal circumference, and body composition were not significantly altered during the course of the study (Table 4). However, a nonsignificant increase in lean body mass and a reduction in fat mass were observed. As a result, mean percent body fat was 2.1% lower at the end of the treatment period ($P = .07$, n = 7). Body composition data were not obtained for one subject, due to a technical problem.

DISCUSSION

In this sample of healthy men, 2 weeks of oral albuterol administration decreased mean serum TC and LDL-C by 9% to 16% and increased HDL-C by 10%. As a result, TC/HDL-C and LDL-C/HDL-C ratios decreased in every subject (mean changes, −17% and −23%, respectively). Intravenous glucose tolerance and its physiologic determinants were not substantially altered.

Serum Lipids

Hooper et al[14] found that 3 weeks of oral terbutaline (5 mg three times daily) increased HDL-C by 10% in 15 healthy men, without altering TC, LDL-C, or TG. One week after discontinuation, HDL-C was still elevated by 5% in comparison to the baseline value. In contrast, albuterol administration produced reductions in TC and LDL-C, as

Table 3. Fasting Values (mean ± SEM) for Metabolic Variables According to Treatment Phase

Variable	Baseline	Albuterol Treatment	Washout	P (ANOVA)
Glucose (mg/dL)	92.2 ± 2.1	94.9 ± 2.3	90.2 ± 2.1	.078
Insulin (mU/L)*	10.8 ± 1.8	11.0 ± 1.7	8.1 ± 1.0	.055
FISI	9.9 ± 0.7	9.5 ± 0.5†	11.2 ± 0.8	.019
K (mEq/L)	4.39 ± 0.10	4.14 ± 0.08‡	4.44 ± 0.07	.007
Mg (mEq/L)	1.71 ± 0.04	1.64 ± 0.05†	1.77 ± 0.07	.013
Uric acid (mg/dL)	5.98 ± 0.49	5.95 ± 0.58	6.30 ± 0.55	.103

*n = 7 for fasting insulin and FISI.
†Significantly different from washout period, $P < .05$.
‡Significantly different from baseline and washout periods, $P < .05$.

Table 4. Anthropometric and Body Composition Values (mean ± SEM) According to Treatment Phase

Variable	Baseline	Albuterol Treatment	P
Body mass index (kg/m²)	26.2 ± 1.1	26.2 ± 1.2	.87
Abdominal girth (cm)	87.8 ± 3.7	87.7 ± 3.8	.71
Lean body mass (kg)	61.5 ± 2.8	62.4 ± 3.4	.36
Fat mass (kg)	17.0 ± 2.3	15.9 ± 1.9	.27
Body fat (%)	21.3 ± 1.5	19.2 ± 1.7	.07

well as an increase in HDL-C, in our subjects. Chazan et al[15] administered oral albuterol (8 mg twice daily) to 10 patients with chronic bronchitis. They also showed an elevation of HDL-C (6.9%). In addition, TC (15.9%) and the TC/HDL-C ratio (18.3%) were significantly reduced. These investigators[15] also studied the acute effects of a single parenteral dose of albuterol on plasma lipids in patients not recently treated with β-agonists. No changes in HDL-C or the TC/HDL-C ratio were noted over a 24-hour period, suggesting that the lipid changes are a long-term effect of the medication.

Additional evidence for a favorable influence of β_2-agonism on serum lipids has been provided by studies of β-antagonists. Nonselective ($\beta_1 + \beta_2$) blockade (eg, propranolol) causes a depression of serum HDL-C and an elevation of TG.[16] These effects are less pronounced with β_1-selective agents such as metoprolol.[16] Several reports also indicate that β-blockers with β_2-stimulatory activity (eg, dilevalol and celiprolol) reduce TC and/or TG and increase HDL-C.[17-19] Moreover, among 615 male participants in the Normative Aging Study, urinary epinephrine excretion was positively correlated with HDL-C and inversely related to TG concentration and the LDL-C/HDL-C ratio[20] after adjustment for several potential confounders. Norepinephrine and dopamine excretion were not related to any aspect of the lipid profile. Taken together, these findings are consistent with a role for chronic β_2-receptor agonism in modulating lipoprotein metabolism.

Dietary changes can influence serum lipids. We did not attempt to document dietary stability in our subjects, because it was believed that estimates from self-reported dietary records are not sufficiently precise to provide an accurate assessment of individual changes in a study of this size.[21] Nevertheless, we believe altered diet to be an unlikely explanation for the lipid alterations observed. TC/HDL-C and LDL-C/HDL-C ratios were reduced in all eight subjects, whereas body weight was unaltered. Large differences in dietary fatty acid composition would need to have occurred in all subjects to account for lipid changes of this magnitude.

Although no differences were observed in body weight, changes in body composition may have contributed to the lipid shifts, since bioimpedance measurements suggest that fat mass may have decreased slightly while lean mass increased to a similar degree. However, with the exception of HDL-C, lipid values had returned to baseline levels within 3 days after discontinuation of the drug, suggesting that altered body composition was not of primary importance. The small changes in body composition estimated with bioimpedance might have been related to fluid redistribution (discussed in more detail below), which could also influence serum lipid concentrations. We are unable to exclude the possibility that fluid shifts influenced serum lipid measurements during albuterol treatment. Nevertheless, since LDL-C and HDL-C changed to similar degrees but in opposite directions, differences in the LDL-C/HDL-C ratio cannot be explained by alterations in serum volume. Since lipid concentrations within each phase were averaged from two blood samples drawn on separate days, the influence of regression to the mean was also minimized. Thus, we believe that the pharmacologic actions of albuterol provide the most probable explanation for our findings.

Dzau and Sacks[22] suggest that β-adrenergic stimulation may influence the lipid profile by inhibiting hepatic very–low-density lipoprotein synthesis and stimulating lipoprotein lipase activity. This would be expected to produce a reduction in circulating TG concentration with a reciprocal increase in HDL-C.[23] Reduced TC and LDL-C might also result from a decline in very–low-density lipoprotein synthesis. Belahsen and Deshaies[24] found that 7 days of clenbuterol feeding increased lipoprotein lipase activity in skeletal muscle and brown adipose tissue but reduced the activity in white adipose tissue of Dawley rats. Serum TG was reduced by 23%, but no change was observed in hepatic TG secretion.[24] Further investigation of the metabolic pathways responsible for the lipid changes we and others have observed appears to be indicated.

Glucose Homeostasis

No significant changes in fasting or dynamic aspects of carbohydrate metabolism were found between the baseline and treatment phases. With eight subjects, our study had a power to detect changes of approximately $2.3 \times 10^{-4} \cdot \text{min}^{-1} \cdot (\text{mU/L})^{-1}$ and 0.55%/min in Si and K_g, respectively ($\alpha = .05$, $\beta = .80$). Thus, we can only rule out relatively large albuterol-induced changes in carbohydrate metabolism. However, our results are consistent with data reported by Wager et al,[25] who found that 10 to 45 days of oral albuterol treatment did not alter K_g or the early insulin response in women during the last trimester of pregnancy. Haenni and Lithell[17] also found that Si, K_g, and AIRg were unchanged after 6 months of antihypertensive treatment with dilevolol, a β-blocker with β_2-agonist activity.

Short-term administration of epinephrine or large-dose β_2-agonists induce marked insulin resistance and may precipitate glucose intolerance.[26-28] β_2-receptor stimulation appears to be essential for the reduction in insulin-mediated glucose disposal.[29] Tolerance to many of the metabolic actions of β_2-stimulation develops with longer-term exposure,[27,30-31] which might account for the lack of adverse influence on carbohydrate metabolism observed in our subjects.

Scheidegger et al[32] studied the effects of 1 to 2 weeks of oral terbutaline (5 mg three times daily) in seven healthy young men. Using the hyperinsulinemic-euglycemic clamp technique with indirect calorimetry, they found increased total (29%) and nonoxidative (45%) glucose disposal after

terbutaline treatment. This was due to greater insulin action in peripheral tissues (presumably skeletal muscle), since hepatic glucose production was shown to be completely suppressed. Our protocol used the minimal model approach, which does not distinguish between insulin's actions to enhance glucose disposal and to suppress hepatic glucose production. Thus, we cannot exclude the possibility that peripheral glucose uptake and hepatic glucose production were simultaneously increased.

An additional possibility is that the timing of albuterol ingestion before testing is responsible for the disparate findings. The subjects in their study[32] took their last dose of terbutaline the evening before testing. Our subjects took a longer-acting preparation and received a dose of albuterol 2 to 3 hours before the IVGTT. Thus, our subjects, but not theirs, were likely to have had therapeutic blood concentrations of β_2-agonist at the time Si was assessed.[33] The elevated FVC and FEV_1 values observed at the same visit corroborate this assumption. Glycogen depletion induced by a prior injection of epinephrine has been shown to enhance sensitivity to insulin-mediated glucose transport in washed (to remove epinephrine) rat skeletal muscle.[34] A similar mechanism may have been operative in the subjects reported by Scheidegger et al.[32] Our study also provides some indirect evidence for this possibility, in that fasting glucose and insulin concentrations were lower after discontinuation of albuterol. As a result, FISI was elevated during the washout period as compared with baseline and treatment phases.

Serum Potassium and Magnesium

Changes in serum cations were small and consistent with the previously demonstrated actions of β_2-agonists.[6,7,30] Reductions of this magnitude are unlikely to be of clinical significance in healthy subjects. However, because decreases of serum potassium and magnesium have been linked to the development of cardiac dysrhythmias, they may be of greater importance for patients on concurrent therapy with diuretics, corticosteroids, theophylline, or digoxin and for persons with ischemic heart disease.[7]

Body Composition

Although not a primary objective of the present investigation, a trend was noted for increased lean body mass and reduced fat mass. The magnitude of observed changes was similar to that reported during 2 weeks of terbutaline treatment[35] and is in the direction that would be predicted based on the known effects of β_2-agonists on body composition.[1-2] The significant decline observed in serum potassium concentration suggests an increase in cellular Na-K exchange, which, in turn, may have altered the ratio of intracellular to extracellular fluid. Body weight and abdominal circumference were stable throughout; thus the possibility must be considered that differences in estimated lean and fat masses were due to fluid redistribution, since bioimpedance measurements are sensitive to such shifts.[36]

Potential Clinical Implications

Interest in β_2-agonists has increased substantially over the past few years, largely due to the profound influence these agents exert on body composition.[1-2] Randomized clinical studies have reported increased muscle strength in humans treated with albuterol or clenbuterol.[4,37] Moreover, β_1-adrenergic antagonists that also stimulate β_2-receptors may be useful for the management of hypertension without producing undesirable metabolic consequences (eg, dyslipidemia).

Previous studies investigating the acute actions of β_2-agonists have shown them to induce hyperglycemia, hyperinsulinemia, and elevation of free fatty acids, raising the possibility that these agents might adversely influence glucose and lipoprotein metabolism with long-term administration. Our findings are therefore encouraging, since carbohydrate homeostasis was not substantially impaired and the influence of albuterol treatment on serum lipids appeared to be favorable. Nevertheless, extrapolation of these findings to patients with glucose intolerance or pronounced dyslipidemia would be premature.

Conclusion

In this sample of healthy men, 2 weeks of oral albuterol administration reduced TC and LDL-C, increased HDL-C, and reduced the TC/HDL-C and LDL-C/HDL-C ratios. Neither fasting nor postload indicators of glucose homeostasis were markedly altered during albuterol administration. Taken in conjunction with previous reports, these findings support the concept that chronic β_2-stimulation modulates lipoprotein metabolism. Further study with larger groups and longer treatment periods should be undertaken to explore the mechanisms responsible for these actions, and to clarify the influence of β_2-agonist administration on carbohydrate metabolism and body composition.

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REFERENCES

1. Kim YS, Sainz RD: B-Adrenergic agonists and hypertrophy of skeletal muscles. Life Sci 50:397-407, 1992

2. Yang YT, McElligott MA: Multiple actions of β-adrenergic agonists on skeletal muscle and adipose tissue. Biochem J 261:1-10, 1989

3. Maltin CA, Delday MI, Watson JL, et al: Clenbuterol, a β-adrenoceptor agonist, increases relative muscle strength in orthopaedic patients. Clin Sci 84:651-654, 1993

4. Signorile JF, Banovac K, Gomez M, et al: Increased muscle strength in paralyzed patients after spinal cord injury: Effect of beta-2 adrenergic agonist. Arch Phys Med Rehabil 76:55-58, 1995

5. Bressler P, DeFronzo RA: Drugs and diabetes. Diabetes Rev 2:53-84, 1994

6. Haffner CA, Kendall MJ: Metabolic effects of β_2-agonists. J Clin Pharm Ther 17:155-164, 1992

7. Phillips PJ, Vedig AE, Jones PL, et al: Metabolic and cardiovascular side effects of the β_2-adrenoceptor agonists salbutamol and rimiterol. Br J Pharmacol 9:483-491, 1980

8. Skorodin MS, Freebeck PC, Yetter B, et al: Magnesium sulfate potentiates several cardiovascular and metabolic actions of terbutaline. Chest 105:701-705, 1994

9. Tantucci C, Santeusanio F, Beschi M, et al: Metabolic and hormonal effects of preferential beta 1- and beta 2-adrenoreceptor stimulation in man. J Endocrinol Invest 11:279-287, 1988

10. Lukaski HC, Johnson PE, Bolunchuk WW, et al: Assessment of fat-free mass using bioelectrical impedance measurements of the human body. Am J Clin Nutr 47:7-14, 1988

11. Bergman RN, Ader M: Concepts emerging from the minimal model approach. Curr Top Diabetes Res 12:39-65, 1993

12. Anderson RL, Hamman RF, Savage PJ, et al: Exploration of simple insulin sensitivity measures derived from frequently sampled intravenous glucose tolerance tests. Am J Epidemiol 142:724-732, 1995

13. Kahn SE, Prigeon R, McColloch DK, et al: Quantification of the relationship between insulin sensitivity and β-cell function in human subjects. Diabetes 42:1663-1672, 1993

14. Hooper PL, Woo W, Visconti L, et al: Terbutaline raises high-density-lipoprotein-cholesterol levels. N Engl J Med 305:1455-1457, 1981

15. Chazan R, Droszcz W, Bobilewicz D, et al: Changes in plasma high density lipoprotein (HDL) levels after salbutamol. Int J Clin Pharmacol Ther Toxicol 23:427-429, 1985

16. Lithell HO: Effects of antihypertensive drugs on insulin, glucose, and lipid metabolism. Diabetes Care 14:203-209, 1991

17. Haenni A, Lithell H: Treatment with a β-blocker with β_2-agonism improves glucose and lipid metabolism in essential hypertension. Metabolism 43:455-461, 1994

18. Herrmann JM, Mayer EO: A long-term study of the effects of celiprolol on blood pressure and lipid-associated risk factors. II. Am Heart J 116:1416-1421, 1988

19. Materson BJ, Vlachakis ND, Glasser SP, et al: Influence of beta2 agonism and beta1 and beta2 antagonism on adverse effects and plasma lipoproteins: Results of a multicenter comparison of dilevalol and metoprolol. Am J Cardiol 63:58-63, 1989

20. Ward KD, Sparrow D, Landsberg L, et al: The relationship of epinephrine excretion to serum lipid levels: The Normative Aging Study. Metabolism 43:509-513, 1994

21. Thompson FE, Byers T: Dietary Assessment Resource Manual. J Nutr 124:2245S-2317S, 1994 (suppl)

22. Dzau VJ, Sacks FM: Regulation of lipoprotein metabolism by adrenergic mechanisms. J Cardiovasc Pharmacol 10:S2-S6, 1987 (suppl)

23. Tall A: Plasma high-density lipoproteins: Metabolism and relationship to atherogenesis. J Clin Invest 86:379-384, 1990

24. Belahsen R, Deshaies Y: Modulation of lipoprotein lipase activity in the rat by the B_2-adrenergic agonist clenbuterol. Can J Physiol Pharmacol 70:1555-1562, 1992

25. Wager J, Lunell NO, Nadal M, et al: Glucose tolerance following oral salbutamol treatment in late pregnancy. Acta Obstet Gynecol Scand 60:291-294, 1981

26. Morrow LA, Morganroth GS, Herman WH, et al: Effects of epinephrine on insulin secretion and action in humans. Interaction with aging. Diabetes 42:307-315, 1993

27. Tibaldi JM, Lorber DL, Nerenberg A: Diabetic ketoacidosis and insulin resistance with subcutaneous terbutaline infusion: A case report. Am J Obstet Gynecol 163:509-510, 1990

28. Walters JM, Ward GM, Kalfas A, et al: The effect of epinephrine on glucose-mediated and insulin-mediated glucose disposal in insulin-dependent diabetes. Metabolism 41:671-677, 1992

29. Lager I, Attvall S, Eriksson BM, et al: Studies on the insulin-antagonistic effect of catecholamines in normal man. Evidence for the importance of β_2 receptors. Diabetologia 29:409-416, 1986

30. Jenne JW, Chick TW, Strickland RD, et al: Subsensitivity of beta responses during therapy with a long-acting beta-2 preparation. J Allergy Clin Immun 59:383-390, 1977

31. Martin IK, Weber KM, Boston RC, et al: Effects of epinephrine infusion on determinants of intravenous glucose tolerance in dogs. Am J Physiol 255:E668-E673, 1988

32. Scheidegger K, Robbins DC, Danforth E: Effects of chronic beta receptor stimulation on glucose metabolism. Diabetes 33:1144-1149, 1984

33. Lipworth BJ, Clark RA, Dhillon DP, et al: Single dose and steady state pharmacokinetics of 4 mg and 8 mg oral salbutamol controlled-release in patients with bronchial asthma. Eur J Clin Pharmacol 37:49-52, 1989

34. Nolte L, Gulve EA, Holloszy JO: Epinephrine-induced in vivo muscle glycogen depletion enhances insulin sensitivity of glucose transport. J Appl Physiol 76:2054-2058, 1994

35. Acheson KJ, Ravussin E, Schoeller DA, et al: Two-week stimulation or blockade of the sympathetic nervous system in man: Influence on body weight, body composition, and twenty-four-hour energy expenditure. Metabolism 37:91-98, 1988

36. Bioelectrical Impedance Analysis in Body Composition Measurement. NIH Technology Assessment Statement. Bethesda, MD, NIH, December 12-14, 1994, pp 1-35

37. Martineau L, Horan MA, Rothwell NJ, et al: Salbutamol, a β_2-adrenoceptor agonist, increases skeletal muscle strength in young men. Clin Sci 83:615-621, 1992