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Seasonal Variation in Lipoprotein Lipase and Plasma Lipids in Physically Active, Normal Weight Humans*

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ABSTRACT

Adipose tissue lipoprotein lipase (ATLPL) provides free fatty acids (FFA) for storage in adipocytes, whereas in skeletal muscle LPL (SMLPL) provides FFA for oxidation. In hibernating animals, the level of SMLPL is relatively higher in summer than winter (promoting fat oxidation), whereas the opposite is seen with ATLPL. A patient-controlled study was designed to determine whether such seasonal variation occurs in normal weight humans.

Eighteen subjects were studied in the summer and winter. After 2 days of a standardized diet, they underwent muscle and adipose biopsies for LPL activity, assessment of fitness by $\dot{V}O_2$ max, and determination of body composition by hydrostatic weighing. The percentages of body fat, body mass index, $\dot{V}O_2$ max, insulin, glucose, FFA, glycerol, and leptin were not affected by the season. Total cholesterol was higher in the winter than in the summer (157 ± 5.5 *vs.* 148 ± 4.2 mg/dL respectively; $P = 0.03$). The ATLPL activity was also higher in the winter than in the summer (4.4 ± 0.8 *vs.* 2.3 ± 0.6 nmol FFA/10^6 cells·min; $P = 0.04$). SMLPL activity trended to be higher in the winter than in the summer (1.9 ± 0.5 *vs.* 1.0 ± 0.1 nmol FFA/g·min; $P = 0.06$).

In summary, ATLPL is seasonally regulated. It appears that SMLPL is similarly regulated by season. For physically active lean subjects, this increase in SMLPL may be a compensatory mechanism to help protect from seasonal weight gain. (*J Clin Endocrinol Metab* **85:** 3065–3068, 2000)

HIBERNATING mammals are able to store large amounts of energy-rich lipids before hibernation, and part of the mechanism by which this is accomplished is through an increase in adipose tissue lipoprotein lipase (ATLPL) (1). Some studies have shown humans to also have a seasonal fluctuation in weight, with winter body mass index being almost 0.5 kg/m^2 greater than that in summer (2). In an uncontrolled retrospective analysis of ATLPL activity, Persson (3) found a seasonal variation, with activity being the highest in the winter and the lowest in the summer. However, this analysis did not control for patient differences or for seasonal changes in diet or activity levels.

In addition to seasonal differences in weight and potential differences in lipoprotein lipase (LPL) activity, plasma lipids are known to vary seasonally. Numerous studies have demonstrated total cholesterol to be higher in the winter than the summer by an average of about 4% (4–7). Additionally, low density lipoprotein (LDL) cholesterol (or apolipoprotein B) appears to increase in the winter (5, 8, 9), as does high density lipoprotein (HDL) cholesterol (5, 8, 10). Although triglycerides may vary seasonally and may be less in the winter than the summer (8, 11, 12), the variation in triglycerides does not appear to be related to the variation in cholesterol (2). The mechanism for these lipid changes with season is unknown. It does not appear to be due to diet (2), although one study has been able to abolish the seasonal effect with high dose vitamin C (13). Additionally, the lipid changes do not appear to be due simply to changes in temperature (2). The changes described above in LPL activity may also play a role.

This study was designed to evaluate these questions in a prospective, patient-controlled manner. Specifically, the hypotheses tested were: ATLPL will be highest in the winter (promoting storage) and lowest in the summer (promoting mobilization); SMLPL will be seasonally reciprocal to adipose tissue LPL; the variation will be due to seasonal differences in activity and/or body composition; and the variation in LPL will account (in part) for the seasonal variation in lipids.

Subjects and Methods

The institutional review board of the University of Colorado Health Sciences Center approved the study, and all patients were studied after obtaining informed consent. Eighteen normal weight subjects (12 women and 6 men) were recruited by advertising on the campus of University of Colorado Health Sciences Center. For the purposes of this study, summer was defined as May through August, and winter was November through February. Subjects underwent baseline testing at each season, consisting of underwater weighing for determination of body composition and determination of fitness level by exercise treadmill testing using Full Bruce Protocol with determination of fitness by maximal oxygen uptake ($\dot{V}O_2$ max). On the 2 days before the acute study, subjects consumed a standardized diet consisting of 50% carbohydrate, 35% fat, and 15% protein. Subjects were admitted for the acute study after an overnight fast of at least 12 h. Blood was drawn for lipid determination, free fatty acids (FFA), glucose, insulin, and leptin. Subjects then underwent an adipose tissue biopsy and a skeletal muscle biopsy. The adipose tissue was obtained from the sc gluteal region using aspiration as previously described (14). Skeletal muscle was obtained from the vastus lateralis using a Bergstrom biopsy needle as previously described (15). Subjects were then discharged to usual activity and diet

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until approximately 6 months later, when they again underwent the procedures described above.

Assays

Leptin was assayed using a human leptin RIA kit (Linco Research, Inc., St. Charles, MO). The intra- and interassay coefficients of variance for the leptin assay were 7.7% and 6.8%, respectively. Serum glucose, insulin (16), FFA (17), glycerol (18), and plasma lipids (19, 20) were measured as described in the literature. Lipoprotein lipase was analyzed using a radiolabeled substrate as previously described (15). For quality control, all assays included a postheparin plasma (PHP) standard that was kept at −70 C and aliquoted at the time of each assay. The coefficient of variation between the summer and the winter for PHP was 3.65% in the summer and 4.48% in the winter, and there were no significant differences between the summer and winter PHP lipase assays. All tissue samples were run in duplicate, and then a duplicate of the postheparin lipase was used with substrate to determine LPL activity. Progesterone was measured in women using a solid phase RIA (Diagnostics Products, Los Angeles, CA); the interassay coefficient of variation was less than 10% (36).

Statistics

Statistical analysis was performed using SigmaStat for Windows (version 2.0, Jandel Scientific, San Rafael, CA). Comparisons between summer and winter were made using Student's paired *t* test. If normality or equal variance failed, a Wilcoxon signed rank test was performed. Linear correlation was used to test the relationship between change in LPL activity and change in lipid parameters. Significance was set at $P < 0.05$. Data are presented as the mean ± SEM.

Results

Table 1 shows the baseline characteristics of the subjects for summer and winter. There were no significant differences in BMI, percent body fat, or level of fitness by $\dot{V}O_2$ max by season. Additionally, there was no difference in physical activity by season when assessed using a physical activity recall questionnaire in a subset of subjects (196 ± 20 *vs.* 201 ± 22; $P = 0.21$; n = 5). There were also no differences in total calories or macronutrient composition of the diet by 2-day dietary recall in a subset of subjects (n = 11; data not shown).

Table 2 demonstrates the effect of season on metabolic parameters. Glucose, insulin, FFA, and glycerol were not significantly different between summer and winter. Additionally, as a marker for change in adiposity (21), plasma leptin levels were obtained. As would be predicted from the body composition data, there were no changes in leptin between summer and winter. Total cholesterol was significantly higher in the winter than the summer (157 ± 5.5 *vs.* 148 ± 4.2 mg/dL; $P = 0.03$). This was due primarily to a nearly significant increase in LDL cholesterol in the winter *vs.* the summer (81 ± 5.9 *vs.* 75 ± 5.1 mg/dL; $P = 0.06$). Triglycerides and HDL cholesterol were not significantly different between summer and winter.

Figure 1 shows the effect of season on ATLPL and SMLPL activities. There was a significant increase in ATLPL from summer to winter (2.3 ± 0.6 *vs.* 4.4 ± 0.8 nmol FFA/10^6 cell·min; $P = 0.04$). There was also a nearly significant increase in skeletal muscle LPL activity from summer to winter (1.0 ± 0.2 *vs.* 1.9 ± 0.5 nmol FFA/g·min; $P = 0.055$).

There was no control for menstrual cycle timing in the women. However, using progesterone as a marker of the phase of the menstrual cycle, there was no change in progesterone levels between the studies overall. Second, when the women were evaluated separately, the seasonal effect persisted for adipose tissue, albeit at a weaker level statis-

TABLE 1. Baseline characteristics by season

	Summer	Winter
Gender	12 women + 6 men	
Age (yr)	31.5 ± 1.3	
BMI (kg/m^2)	22.4 ± 0.7	22.5 ± 0.7
% Body fat	24.0 ± 1.4	24.1 ± 1.4
$\dot{V}O_2$ max. (mL/kg·min)	42.0 ± 1.8	43.1 ± 2.0

TABLE 2. Metabolic characteristics by season

	Summer	Winter
Glucose (mg/dL)	84 ± 2	84 ± 2
Insulin (μU/mL)	6.5 ± 0.6	6.7 ± 1
FFA (μEq/L)	576 ± 64	518 ± 51
Glycerol (μmol/L)	99 ± 10	81 ± 6
Leptin (ng/mL)	5.9 ± 1.1	7.1 ± 2.1
Total cholesterol (mg/dL)	148 ± 4	157 ± 5[a]
LDL cholesterol (mg/dL)	75 ± 5	81 ± 6[b]
HDL cholesterol (mg/dL)	56 ± 3	56 ± 3
Triglycerides (mg/dL)	87 ± 8	99 ± 12

[a] $P = 0.03$, summer *vs.* winter.
[b] $P = 0.06$, summer *vs.* winter.

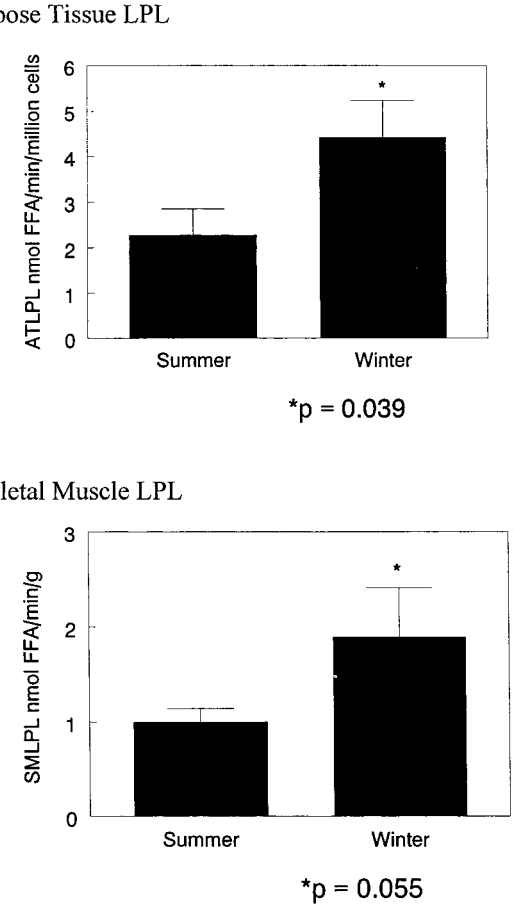

FIG. 1. Effect of season on LPL activity. Subcutaneous gluteal adipose tissue LPL activity was significantly higher in the winter than in the summer. Vastus lateralis skeletal muscle LPL activity was also higher in the winter than in the summer; however this failed to reach statistical significance ($P = 0.055$).

tically due to the decrease in sample size (6.65 nmol FFA/10^6 cell·min summer *vs.* 13.22 nmol FFA/10^6 cell·min winter; $P = 0.07$). There was also a significant seasonal effect on SMLPL in women (1.04 nmol FFA/g·min summer *vs.* 2.63 nmol FFA/g·min winter; $P = 0.03$). Third, when only women in the follicular phase of the menstrual cycle were studied (*i.e.* progesterone <1 ng/mL; n = 6) the significant increase in ATLPL persisted (2.73 ± 0.79 nmol FFA/10^6 cells·min in the summer *vs.* 5.92 ± 1.6 nmol FFA/10^6 cells·min in the winter; $P = 0.03$). In this subgroup, the trend for increased SMLPL in the winter was present as well (1.07 ± 0.17 nmol FFA/g·min in the summer *vs.* 3.10 ± 1.17 nmol FFA/g·min in the winter; $P = 0.12$). Finally, there were no relationships seen between progesterone and LPL activity in women, either during a given season or when evaluated by the correlation between the change in serum progesterone and the change in LPL activity (*i.e.* change in progesterone *vs.* change in ATLPL: r = 0.076; $P = 0.8$; change in progesterone *vs.* change in SMLPL: r = 0.019; $P = 0.96$).

There was no significant correlation between the change in total cholesterol and the change in ATLPL (r = 0.07; $P = 0.79$) or the change in SMLPL (r = 0.25; $P = 0.36$). Likewise, there was no correlation between the change in LDL cholesterol and the change in ATLPL (r = 0.03; $P = 0.9$) or the change in SMLPL (r = 0.25; $P = 0.17$). However, there was a correlation between the change in triglycerides and the change in ATLPL (r = −0.55; $P = 0.02$). The change in HDL and the change in ATLPL were also significant (r = 0.58; $P = 0.01$). There was a trend for the change in HDL cholesterol to correlate with the change in SMLPL (r = 0.46; $P = 0.07$), but not for the change in triglycerides to do so (r = 0.39; $P = 0.14$).

Discussion

Retrospective and unpaired data reported by Presson (3) indicate that ATLPL increases in the winter relative to the summer. However, retrospective analysis is fraught with potential confounding variables, foremost the intersubject variations. Thus, this study was undertaken to control for the variation between subjects using a paired study design. Prospectively, there persisted a significant increase in ATLPL in the winter compared to the summer. In contrast to our initial hypothesis, however, there were no differences in activity, body composition, or other metabolic parameters.

The etiology of the increased ATLPL could be due to either environmental or physiological changes. Environmental changes include changes in food supply macronutrients, physical activity alterations due to weather, temperature, and light. Physiological changes include changes in body composition or hormone levels. Although changes in dietary composition in winter compared to summer are a possible explanation for the change in ATLPL, other studies of the effect of season on lipid levels have failed to show a significant difference in diet between summer and winter (7). Additionally, we have shown that 6 weeks of a high fat (30% carbohydrate and 50% fat) *vs.* high carbohydrate (55% carbohydrate and 25% fat) diet fails to alter fasting ATLPL (22).

This group of study subjects did not have a decrease in VO_2 max in the winter, in contrast to what has been reported in the literature (23). This could account for the unexpected increase in SMLPL in the winter that, in turn, could contribute to the lack of seasonal increase in body weight (body fat). In an animal model we have shown that overexpression of LPL in skeletal muscle prevents obesity during a high fat diet (24). Thus, there is a precedent for SMLPL having a role in the regulation of body weight. Additionally, although all visible adipose tissue was dissected from the skeletal muscle, the possibility remains that im adipocytes (with regulation adipocyte of LPL) were the cause of the increased SMLPL in the winter (25).

Temperature appears to play a role in the seasonal regulation of ATLPL in animal models (26). Specifically, Mitchell *et al.* found the brown adipose tissue LPL increases with cold exposure, and that this is due to an increase in the stability of LPL messenger ribonucleic acid (26). This may be due to increased catecholamines working through β-adrenergic receptors. It is difficult to conclude that a similar mechanism is occurring in humans, especially given that humans are only exposed to temperature fluctuations for brief periods of time. None the less, this remains a possible mechanism for the increase in ATLPL.

The decreased duration of light in the winter is a major mechanism for physiological changes in many animals. These changes are due in part to changes in melatonin levels, which are higher during the shorter photoperiods of the winter. The role of melatonin in human obesity is unknown. However, in animal models, melatonin is associated with decreases in ATLPL activity (27, 28). Thus, it appears unlikely that the shorter light period (or potentially increased melatonin) is the mechanism for the increased ATLPL seen in our study.

There could have been increases in adipose tissue mass below the threshold of measurement that might account for the change in ATLPL. However, as ATLPL activity per cell and per g tissue (data not presented) both increased significantly, it is unlikely that such a change would explain these findings.

Finally, seasonal changes in hormonal systems, such as thyroid axis and glucose control, have previously been shown (29–31). Glycosylated hemoglobin has been shown to be about 0.4% lower in the summer than in the winter (32), indicating that there is a relative worsening of insulin sensitivity in the winter. To corroborate this, Behall *et al.* (31) found that fasting insulin levels were over 2-fold higher in the fall than in the spring. However, ATLPL activity is decreased in diabetic subjects (33); thus, insulin resistance in the winter would be expected to decrease, not increase, ATLPL (34). Of note, we found no significant change in fasting insulin or glucose levels in this group of subjects. Additionally, in hypothyroid patients receiving a fixed dose of L-T_4, T_3 and free T_4 concentrations have been shown to be lower in the winter, and TSH has been shown to be higher (30). However, when the thyroid axis is intact, it is unlikely that such changes occur. Additionally, a "relative" hypothyroidism in the winter would be expected to decrease and not increase LPL activity (35); thus, this is not a likely mechanism for the changes observed.

The gonadal axis also could have been responsible for these changes. Not controlling for changes in the menstrual cycle is a potential weakness of this study. However, we do

not believe that changes in sex steroids are the explanation for the seasonal changes in LPL for several reasons. First, the changes in ATLPL and SMLPL were similar in men and women. Second, there was no change in progesterone levels between the studies overall. Third, when only women in the follicular phase were evaluated the seasonal changes persisted. Finally, there were no relationships between progesterone and LPL activity in women, either during a given season or when evaluated by the correlation between the change in progesterone and the change in LPL activity.

Finally, we tested the hypothesis that the change in LPL activity might explain the seasonal change in lipids. Indeed, the change in ATLPL correlated with changes seen in triglycerides and HDL cholesterol. As would be expected, a decrease in triglycerides correlated with an increase in ATLPL between seasons. However, the seasonal changes in lipids were seen in total cholesterol, and a trend for a change was seen in LDL cholesterol, but there was no relationship to the changes in ATLPL or SMLPL activity. Thus, it appears that the increased lipase activity accounts for an increased metabolism of triglyceride-rich particles, but that the primary etiology of the seasonal change in cholesterol is due either to an overproduction of cholesterol by the liver and/or a decreased LDL receptor activity in the winter. This requires further evaluation.

In summary, in this group of lean and physically active subjects ATLPL was higher in the winter than in the summer, and SMLPL tended to be higher in the winter. The change in ATLPL was consistent with our retrospective data as well as those reported by Persson *et al.* (3). The mechanism for this remains to be elucidated, but does not appear to be due to changes in fitness or diet. The trend toward increase in SMLPL in the winter was in contrast to the retrospective data from our laboratory. This group of individuals also did not have the expected winter increase in adiposity and remained fit during the winter. Thus, the increase in SMLPL might be part of the mechanism for controlling body weight in the winter. Finally, as others have also observed, a wintertime increase in total cholesterol was seen. However, the increase in lipase activities is unlikely to be a major mechanism for the seasonal changes in cholesterol.

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