Seasonal regulation of the growth hormone-insulin-like growth factor-I axis in the American black bear (*Ursus americanus*)

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Blumenthal S, Morgan-Boyd R, Nelson R, Garshelis DL, Turyk ME, Unterman T. Seasonal regulation of the growth hormone-insulin-like growth factor-I axis in the American black bear (*Ursus americanus*). *Am J Physiol Endocrinol Metab* 301:E628–E636, 2011. First published July 5, 2011; doi:10.1152/ajpendo.00082.2011.—The American black bear maintains lean body mass for months without food during winter denning. We asked whether changes in the growth hormone/insulin-like growth factor-I (GH-IGF-I) axis may contribute to this remarkable adaptation to starvation. Serum IGF-I levels were measured by radioimmunoassay, and IGF-binding proteins (IGFBPs) were analyzed by ligand blotting. Initial studies in bears living in the wild showed that IGF-I levels are highest in summer and lowest in early winter denning. Detailed studies in captive bears showed that IGF-I levels decline in autumn when bears are hyperphagic, continue to decline in early denning, and later rise above predenning levels despite continued starvation in the den. IGFBP-2 increased and IGFBP-3 decreased in early denning, and these changes were also reversed in later denning. Treatment with GH (0.1 mg·kg<sup>−1</sup>·day<sup>−1</sup> × 6 days) during early denning increased serum levels of IGF-I and IGFBP-3 and lowered levels of IGFBP-2, indicating that denning bears remain responsive to GH. GH treatment lowered blood urea nitrogen levels, reflecting effects on protein metabolism. GH also accelerated weight loss and markedly increased serum levels of free fatty acids and β-hydroxybutyrate, resulting in a ketoacidosis (bicarbonate decreased to 15 meq/l), which was reversed when GH was withdrawn. These results demonstrate seasonal regulation of GH/IGF-I activity in black bears. Diminished GH activity may promote fat storage in autumn in preparation for denning and prevent excessive mobilization and premature exhaustion of fat stores in early denning, whereas restoration of GH/IGF activity in later denning may prepare the bear for normal activity outside the den.

wers: The American black bear is a “metabolic marvel” (24). Each winter, these bears survive up to 7 mo without food or water while maintaining nitrogen balance and lean body mass (23), yet the mechanisms responsible for this remarkable adaptation to prolonged starvation are poorly understood. To prepare for this extended period of caloric deprivation, the bear acquires an enormous fat reserve by consuming 15,000–20,000 kcal/day from late summer until October or November, when denning and the winter sleep begin (24). In the den, despite the expenditure of roughly 4,000 kcal/day and the loss of 15–30% of its body weight, the bear does not eat, drink, urinate, or defecate until its emergence from hibernation in April. Oxygen consumption decreases ∼50%, but a heavily insulated pelt, a relatively low body surface area-to-body mass ratio, and a reduction in peripheral blood flow limit the decline in body temperature from 37–39°C in summer to 31–35°C (23, 26, 30). The respiratory quotient decreases to values approaching 0.6, indicating not only that lipid oxidation has become the principal source of energy but also that metabolic CO<sub>2</sub> is utilized in synthetic processes, as, for example, in the replenishment of Krebs cycle intermediates via the pyruvate carboxylase reaction. Lean body mass, calculated using measurements of total body water based on the dilution of deuterated water, is preserved in part because the ammonia nitrogen liberated by protein catabolism or by the breakdown of urea is reincorporated into new protein. Thus, in denning bears, 14C label from injected [U-<sup>14</sup>C]glycerol was found in alanine, arginine, glycine, tyrosine, phenylalanine, and threonine (1, 24, 25). Since urea is a major determinant of urinary volume and since there is no net synthesis of urea, urine is not excreted. Nonurinary water losses, as in expired air, are replaced by metabolic water arising from fatty acid oxidation. Blood chemistries, including glucose, amino acids, plasma proteins, electrolytes, and urea nitrogen, remain relatively stable (26, 34).

Previous studies have shown that growth hormone (GH) has important effects on fat and protein metabolism (22), yet its role in the preparation for and adaptation to winter denning has not previously been explored. In states of caloric restriction, increased GH secretion promotes lipolysis in adipose tissue and fatty acid metabolism in animal models and human studies (22, 42). Norrelund et al. (28) have reported that this effect of GH on fatty acid metabolism is important for protein-sparing effects. Thus, during periods of nutritional restriction, increased GH secretion might promote increased fatty acid metabolism and thereby help to protect protein stores. In contrast, obesity is associated with a diminution in both basal and stimulated GH secretion, which may facilitate fat deposition (22), whereas little change in levels of IGF-I is noted. Multiple factors, including increased insulin levels and bioavailability of IGFs, may contribute to the suppression of GH secretion in obesity (10, 15).

In addition to effects on fat metabolism, GH stimulates the production of insulin-like growth factor-I (IGF-I), which mediates major effects of GH on body growth and anabolism and provides a useful serum marker that reflects integrated levels of
GH secretion (31). Adequate nutrition also plays a critical role in regulating IGF-I, and protein nutrition is particularly important in maintaining the ability of GH to regulate IGF-I levels (37). Since the denning bear is remarkably efficient in maintaining lean body mass (19, 20) and derives the bulk of its energy from fatty acid oxidation, we asked whether changes in the GH-IGF axis might contribute to seasonal regulation of metabolism and the adaptation of Ursus americanus to winter denning.

MATERIALS AND METHODS

Materials. Recombinant human IGF-I was purchased from Bachem (Torrance, CA). Recombinant human growth hormone was generously provided by Genentech (South San Francisco, CA). C-2 silica cartridges were obtained from Varian (Harbor City, CA). Endoglycosidase F and staphylococcal protein A (Pansorbin) were purchased from Calbiochem. Reagents for sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) were purchased from Bio-Rad (Richmond, CA), and pretained molecular weight standards were obtained from Amersham (Arlington Heights, IL). Polyclonal rabbit antiserum against human IGF-II was provided by the National Hormone and Pituitary Program (Baltimore, MD), and polyclonal antiserum, which recognizes human IGF-binding protein (IGFBP)-2, was kindly provided by Dr. Ron Rosenfeld.

Animals and blood collection. Studies were limited to adult male bears to avoid confounding effects of age-related changes in blood levels of IGF-I and effects of pregnancy on circulating levels of IGFBPs and/or IGFs. Studies on wild black bears were approved by the Minnesota Department of Natural Resources, and studies on captive bears were approved by the Carle Foundation and the University of Illinois at Chicago Institutional Animal Care and Use Committees.

Wild radio-collared bears in north-central Minnesota were studied between December 1998 and February 1999. Animals were captured temporarily in barrel traps during the summer months and handled in dens during winter. These bears were immobilized by intramuscular injection with ketamine-xylazine (4.4/1.8 mg/kg) in the summer and ketamine-promazine (12.0/0.6 mg/kg) in the winter. Blood was drawn from the femoral vein per vacutainer in glass tubes and then placed on ketamine-promazine (12.0/0.6 mg/kg) in the winter. Blood was drawn temporarily in barrel traps during the summer months and handled in captives.

Captive male and female bears were housed outdoors and were provided with a cement curl, where they den in winter months. Denning was initiated in mid-late November by withdrawal of food, and animals were allowed access to food again in mid-March. After emerging from the den, animals consumed ≤3.6 kg/day of dog chow (“Generic Chunk Style;” Wells Pet Food, Monmouth, IL) until midsummer, when food intake was increased, until they were consuming 5.5–6.4 kg/day before denning. Animals were allowed free access to water, although spontaneous water intake does not occur during denning. For blood drawing, captive animals were immobilized by administration of 2 mg/kg ketamine with 2 mg/kg im zolazepam (Elkins-Sinn, Cherry Hill, NJ). Blood was drawn from the femoral vein by syringe and then transferred to plain or heparinized glass tubes and centrifuged at 4°C. Serum and plasma were stored in aliquots at −20°C.

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GH secretion was measured by immunoassay as described previously (40). For studies of IGFBP-2, immunoprecipitation and Western blotting studies were performed as reported previously (27). In brief, staphylococcal protein A was washed in Tris-saline and then incubated with serum was preincubated with fresh protein A in Tris-saline to remove proteins that bind nonspecifically and then microfuged, and the supernatant then was incubated with antibody-coated protein A. Washed pellets were heat-denatured and then digested and IGFBPs identified by autoradiography at −80°C with enhancing screens. Relative levels of IGFBPs were determined by densitometry, as described previously (40).

RESULTS

Radioimmunoassay of IGF-I in bear serum. To measure immunoreactive IGF-I in bear serum, we first removed IGFBPs by acid treatment and solid-phase extraction, as reported pre-
viously (33). We confirmed that bear IGFBPs were removed based on measurement of IGF-binding activity (Fig. 1A) and Western ligand blotting (Fig. 1B). Next, we tested bear serum extracts for the presence of immunoreactive IGF-I. As shown in Fig. 1C, bear serum extracts compete in parallel with recombinant human IGF-I for binding by antiserum against human IGF-I. Recombinant human IGF-II is not detected in this assay (Fig. 1C), indicating that this assay is specific for IGF-I. Serum collected from a bear in December during early winter denning (Fig. 1C, ◊) was less potent than a sample collected from the same bear in October (Fig. 1C, □) before denning, suggesting that levels of IGF-I might be lower during denning.

**IGF-I levels in wild bears.** We next examined IGF-I levels in serum samples collected during different times of the year from radio-collared bears living in the wild. As shown in Fig. 2A, IGF-I levels in individual bears were higher during the active season (May–August) than during early (December and January) or later denning (February and March). When levels for all bears were combined for each season (Fig. 2B), levels of IGF-I were significantly higher in bears during the active season compared with levels during early denning. Interestingly, levels of IGF-I tended to rise in bears in later compared with early denning despite continued starvation, suggesting that IGF-I levels may not be regulated primarily by nutrition in late denning.

**IGF-I levels in captive bears.** To better define seasonal changes in circulating levels of IGF-I in black bears, we next examined IGF-I levels in captive bears, where more frequent measurements were possible. Figure 3A shows IGF-I levels in serum samples collected from three adult male black bears over the course of 3 yr. Figure 3B shows the results for all three bears combined according to the month of the year. Figure 3C compares IGF-I levels measured in spring (post-denning; April and May), summer (June–August), autumn (September–November), early denning (December and January), and later denning (February and March). As shown in Fig. 3A, serum levels of IGF-I followed a similar pattern of regulation in each of the three bears over the course of several years. IGF-I levels were high in bears in the spring and summer and then decreased in the autumn, when bears increase food intake in preparation for denning. IGF-I levels tended to fall further in early denning but increased later during denning, exceeding predension levels despite prolonged starvation. Taken together, these results indicate that circulating levels of IGF-I decline in autumn, when bears are in preparation for denning.
before their food intake is reduced, and increase during late denning despite prolonged starvation.

Circulating IGFBPs. We also examined levels of IGFBPs in serum collected from captive bears (Fig. 4). Western ligand blotting demonstrates that bear serum contains IGFBPs with molecular weights of 40 – 48, 36, 30, and 24 kDa (Fig. 4A, lane 1). As shown in Fig. 4A, lane 2, the 36-kDa IGFBP in bear serum is recognized by antibody against human IGFBP-2 (lane 2), but not nonimmune IgG (lane 3), indicating that this represents bear IGFBP-2. The 24-kDa IGFBP is similar in size to IGFBP-4 found in other species, suggesting that it represents bear IGFBP-4. The 30-kDa IGFBP in bear serum is similar in size to human IGFBP-1 and -5 and to proteolytic fragments of IGFBP-3 but is not recognized by antibodies against the human forms of these IGFBPs, limiting our ability to identify the 30-kDa IGFBP in bear serum. As shown in Fig. 4B, treatment with endoglycosidase F reduces the apparent molecular weight of the 40- to 48-kDa IGFBPs in bear serum, indicating that they are N-glycosylated, similar to IGFBP-3 found in human serum (9), indicating that they represent bear IGFBP-3.

Figure 4, C and D, shows IGFBPs in serum samples collected at different times of year from a representative bear living in captivity. As shown in Fig. 4C, IGFBP-2 and -3 are the predominant forms of IGFBPs detected in bear serum after brief (12 h) exposure of membranes to autoradiography. Levels of IGFBP-3 are low in early denning (December and January)
and increase during late denning (March) and remain high in animals living during the active season, paralleling changes seen in serum levels of IGF-I (Fig. 3). In contrast, levels of IGFBP-2 are highest during early denning, decline during later denning, and remain low during active living. As shown in Fig. 4D, more prolonged autoradiography (48 h) of the sample Western blot revealed that 24- and 30-kDa IGFBP levels also increase during early denning and decrease during later denning and throughout the active season.

Effects of GH treatment on IGF-I and IGFBP levels in denning bears. Changes in circulating levels of IGF-I and IGFBPs may reflect differences in GH secretion and/or action. We were not able to measure circulating levels of GH in bears using immunoassays for human or bovine GH. To determine whether bears remain responsive to GH during early denning, when IGF-I levels are lowest, we treated three adult male bears living in captivity with recombinant hGH for 6 days beginning 30 days after the onset of denning and studied effects on IGF-I and IGFBP level at baseline, 24 h after the last GH injection, and 7 days later.

As shown in Fig. 5A, left, serum levels of IGF-I increased approximately fourfold with GH treatment and declined after GH was discontinued in all three bears, demonstrating that bears remain responsive to GH during early denning. We also examined effects of GH treatment on IGFBPs by Western ligand blotting. As shown in Fig. 5, A and B, levels of IGFBP-3 increased with GH treatment and declined after GH treatment in all three bears, whereas levels of IGFBP-2 declined with GH treatment and increased after GH was discontinued. Levels of 30-kDa IGFBPs also increased with GH treatment and declined after GH was discontinued.

Effects of GH on body weight and metabolism. We also examined metabolic effects of GH treatment in denning bears. As shown in Fig. 6, GH treatment decreased serum levels of urea nitrogen in all three bears, and this effect was reversed after GH was discontinued. In contrast, GH treatment had no effect on serum creatinine levels, indicating that GH lowered blood urea nitrogen (BUN) levels due to an effect on protein metabolism and/or ureagenesis and not kidney function.

We also considered the effects of GH on body weight and metabolism in denning bears. As shown in Fig. 7A, denning bears lose 1–1.5 kg/day, and this increased to ≥2 kg/day during GH treatment. This accelerated weight loss was accompanied by a marked increase in circulating levels of free fatty acids (Fig. 7B) and β-hydroxybutyrate (Fig. 7C). Serum levels of bicarbonate were reduced (Fig. 7D), whereas the anion gap (the difference between measured cations and measured anions, usually reflecting the increased accumulation of lactate or keto acids) was increased (Fig. 7E). As shown in Fig. 7F, GH treatment did not result in a significant change in lactate levels, indicating that the decline in bicarbonate level and increase in anion gap reflected the accumulation of excessive keto acids. Effects on weight loss and levels of free fatty acids, β-hydroxybutyrate, bicarbonate, and unmeasured anions were all reversed after GH was discontinued.

As shown in Fig. 7G, effects on glucose levels were more variable and were not statistically significant. In contrast, insulin levels increased markedly in all three bears during GH

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Fig. 4. Bear IGFBPs. A: immunoreactive IGFBP-2. IGFBPs in bear serum were analyzed by Western ligand blotting either before (lane 1) or after immunoprecipitation with antibody against human IGFBP-2 (anti-BP-2; lane 2) or nonimmune IgG (lane 3). B: treatment with endoglycosidase F (Endo F). Bear IGFBPs were analyzed by Western blotting either before (lane 1) or after incubation at pH 5.0 with (lane 3) or without (lane 2) Endo F. The apparent MW of the major IGFBPs visualized after brief autoradiography was reduced by treatment with Endo F, indicating that they are N-glycosylated, similar to IGFBP-3 identified in other species. C and D: seasonal regulation of IGFBPs. IGFBPs in serum samples collected from captive bears at different times of year were analyzed by Western ligand blotting, and representative results for a single bear are shown. IGFBPs were visualized after brief (12 h) or more prolonged (48 h) autoradiography.
treatment, whereas levels of glucagon were not significantly affected by GH. Together, these results indicate that GH treatment of denning bears results in accelerated weight loss and the accumulation of significant amounts of keto acids, reflecting accelerated lipolysis and ketogenesis, despite accompanying hyperinsulinemia.

**DISCUSSION**

In this study, we examined seasonal changes in the GH-IGF-I system in black bears living in the wild and in captivity. Donahue et al. (7) reported that circulating IGF-I levels are decreased in denning bears compared with pre- and post-denning levels, but they did not examine changes during the course of denning. Our initial studies in wild bears indicated that serum levels of IGF-I are high in the spring and summer and lower in early denning (December and January) and may rise during later denning (February and March). More detailed studies in captive bears revealed that serum levels of IGF-I decline in autumn, when bears are hyperphagic and gaining weight in preparation for winter, reach a nadir in early denning, and increase later in the den, exceeding predenning levels despite continued starvation. This pattern was highly reproducible in three individual bears studied over the course of 3 yr. Previous studies in humans and other species show that circulating IGF-I levels are strongly regulated by nutrition and are suppressed by fasting and malnutrition (22, 36). However, our results indicate that factors other than nutrition also play a major role in determining levels of IGF-I in the bear during the course of the year, since IGF-I levels decline in autumn despite adequate nutrition, and IGF-I levels increase later in the den despite prolonged fasting.

Serum levels of IGF-I are strongly regulated by GH, and seasonal changes in IGF-I levels in black bears may reflect alterations in GH secretion and/or action. Although we were not able to measure bear GH directly, several observations suggest that the decline in IGF-I levels in autumn and early denning and the subsequent increase during later denning are likely to be due, at least in part, to seasonal changes in GH secretion. Treatment of bears with exogenous GH during early denning, when IGF-I levels are at their nadir, resulted in a marked increase in serum IGF-I levels, and this was reversed after GH was withdrawn, indicating that black bears remain responsive to GH during early denning. One limitation of this study is that the small number of captive bears available for study (n = 3) precluded the possibility of having a separate control group, so each bear served as its control. Although it is possible that the changes we observed could be due to other factors, the marked effects of GH treatment and withdrawal on serum levels of IGF-I are consistent with well-known effects of

![Figure 5](image-url)  
*Fig. 5. Growth hormone (GH) treatment: effects on IGF-I and IGFBP levels. Three captive male bears were treated with GH (18 mg/day × 6 days) in December, 30 days after entering the den. Serum samples were collected just before the first dose of GH, 24 h after the last dose, and 1 wk later. A: serum levels of IGF-I and IGFBP-2 and -3. Serum levels of IGF-I levels were measured by immunoassay, and levels of IGFBP-2 and -3 were determined by Western ligand blotting and densitometry. Levels from individual bears are joined by solid lines. Results for individual bears are connected by lines. *P < 0.05 for GH vs. pre- or post-GH values. B: Western ligand blot of IGFBPs. Western ligand blots of IGFBPs in serum collected from all 3 bears before, during, and 1 wk after GH treatment are shown.*

![Figure 6](image-url)  
*Fig. 6. Effect of GH on blood urea nitrogen (BUN) and creatinine. The effects of GH treatment on BUN and creatinine levels in denning bears are shown. Results for individual bears are connected by lines. *P < 0.05 for GH vs. pre- or post-GH values.*
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Fig. 7. Effects of GH on weight loss and metabolism. The effects of GH treatment on weight loss (kg/day; A) and levels of free fatty acids (free FAs; B), β-hydroxybutyrate (β-OH butyrate; C), bicarbonate (bicarb; D), anion gap (E), lactate (F), glucose (G), insulin (H), and glucagon (I) are shown. Results for individual bears are connected by lines. *P < 0.05 for GH vs. pre- or post-GH values.

GH on IGF-I levels in other species (16), supporting the concept that they reflect effects of GH treatment in denning bears.

GH treatment also reversed effects of early denning on serum levels of IGFBP-2 and -3, suggesting that reduced GH effects also contribute to changes in levels of these IGFBPs during early denning. However, changes in IGFBP proteases (4, 5) may also contribute to seasonal differences in circulating levels of IGFBPs but were not studied.

We also observed other effects of GH treatment in denning bears, including effects on protein and lipid metabolism. GH treatment reduced levels of BUN but not creatinine, indicating that this change in BUN reflects an effect on nitrogen metabolism and not renal function. GH treatment may reduce levels of BUN by several mechanisms by both suppressing mobilization of protein stores (13) and reducing amino acid catabolism and urea production at the level of the liver (12). Based on levels of IGF-I, the effects of endogenous GH appear to be at their nadir during early denning, indicating that GH probably does not play a major role in maintaining nitrogen balance during this phase of winter denning. On the other hand, since protein nutrition plays an important role in maintaining GH responsiveness (36), the ability of the bear to maintain nitrogen balance may be important in maintaining tissue sensitivity to GH during winter denning.

Exogenous GH also exerted important effects on fat metabolism in denning bears. Treatment with GH during early denning resulted in accelerated weight loss and a marked increase in circulating levels of free fatty acids and β-hydroxybutyrate that was reversed after GH was discontinued, demonstrating that GH can strongly stimulate fatty acid mobilization and metabolism in bears. In contrast, GH had variable effects on glucose levels. The effect of GH on fat metabolism was not due to either insulin deficiency or glucagon excess, since insulin levels were high and glucagon levels were not altered during GH treatment. Together, these findings indicate that GH exerts important effects on fat metabolism in bears, consistent with the ability of GH to stimulate lipolysis in isolated adipocytes (6) and promote fat metabolism in vivo (3, 18, 22).

The effect of exogenous GH on fat metabolism in denning bears was profound enough to promote the development of a ketoacidosis demonstrated by a reduction in serum levels of bicarbonate and an increase in the “anion gap,” reflecting an increase in levels of unmeasured anions, including β-hydroxybutyrate. These effects were all reversed after withdrawal of GH treatment. GH has occasionally been associated with ketoacidosis in clinical settings, including acromegaly (17, 44), and in obese subjects provided high-dose GH treatment during an extended fast (8). Although GH is thought to play an important role in the adaptation to fasting, where increased lipolysis and fatty acid metabolism may be important for protecting protein stores (21, 28), this study highlights the potential risk of GH treatment during catabolic states, including nutritional deprivation or severe illness (35).

The mechanisms responsible for seasonal changes in the activity of the GH-IGF-I axis in the bear remain to be determined. Previous studies indicate that hypothalamic-pituitary control of thyroid and gonadal function is altered during winter denning in bears. Serum levels of testosterone decrease in male bears in autumn, remain low in early denning, and increase later before bears emerge from the den (11, 29), similar to the pattern we observed for changes in IGF-I levels. Subsequent studies showed that levels of gonadotropins are decreased, and the ability of gonadotropin-releasing hormone to stimulate gonadotropin secretion is impaired in fall and early denning and then recovers (14), indicating that seasonal changes in testosterone levels reflect changes in hypothalamic-pituitary function. Similarly, thyroid hormone levels also are decreased during denning, and testing with thyrotropin-releasing hormone indicates that this reflects changes in hypothalamic function (2). Webster et al. (43) have reported that photoperiod contributes to seasonal regulation of GH secretion and IGF-I levels in reindeer. It is interesting to speculate that seasonal changes in day length may also contribute to alterations in GH secretion in black bears in autumn and early denning, when IGF-I levels decline, and in later denning, when IGF-I levels increase.

Reactivation of pituitary function, including the GH-IGF-I axis, during late denning may help to prepare the bear for emergence from the den in multiple ways. Donahue et al. (7) have suggested that increased GH-IGF-I activity may promote bone remodeling and formation in bears at the end.
disclosed. Interestingly, the rise in IGF-I levels we observed closely parallels the increase in metabolic rate and body temperature in late denning reported by Toien et al. (38). Recent findings in laboratory animals (32) suggest the interesting possibility that alterations in the GH-IGF-I axis may contribute to seasonal changes in metabolism and thermoregulation in the bear. In summary, we found that activity of the GH-IGF-I axis is seasonally regulated (decreased in autumn and early denning and restored in later denning) in the black bear living in the wild or in captivity. Seasonal changes in IGF-I levels do not reflect changes in food intake but may be regulated by other factors, including day length. Physiologically, we speculate that decreased GH activity during autumn, when bears are hyperphagic, may help bears store large amounts of body fat required to survive prolonged starvation during denning. Reduced GH activity during early denning may help to conserve fat stores, the only source of energy and water available during prolonged denning. Later, increased GH activity may help to mobilize remaining fat stores, which may be important for protein-sparing effects of GH, and help prepare the bear for active living outside the den. Together, the results of these studies provide new insight into the regulation of the GH-IGF-I axis in the black bear and suggest how modulation of the GH-IGF axis may contribute to the integrated regulation of metabolism in the American black bear, a “metabolic marvel.”

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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