Received: 12 September 2024 | Revised: 16 December 2024 | Accepted: 19 December 2024

DOI: 10.1002/oby.24235

PERSPECTIVE

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

Mitigating muscle loss during weight loss: can nutritional ketosis make a difference? A call for more research

Shaminie J. Athinarayanan[1] | **Jeff S. Volek**[2]

[1]Virta Health, Denver, Colorado, USA

[2]Department of Human Sciences, The Ohio State University, Columbus, Ohio, USA

Correspondence
Shaminie J. Athinarayanan, Virta Health, 3513 Brighton Blvd., Denver, CO 80216, USA.
Email: shaminie@virtahealth.com

Abstract

Weight loss (WL) has an important role in managing obesity and type 2 diabetes, but preserving lean body mass (LBM) during WL is essential for maintaining muscle function and metabolic health. Significant WL with incretin mimetic-based therapies, similar to bariatric surgery, raises concerns regarding disproportionate LBM loss, which may lead to physical frailty. Recent analyses have suggested that high adherence to a ketogenic diet may mitigate LBM loss while improving physical function, even with substantial WL. However, more research is needed to understand the mechanisms behind LBM preservation in nutritional ketosis and the role of other lifestyle interventions. Future studies of pharmacological, surgical, and lifestyle-driven WL interventions should also assess LBM, physical function, and frailty. Research in this area is essential for developing strategies that optimize patient outcomes, especially for those who are considering their options for the treatment of obesity.

INTRODUCTION

Weight loss (WL) is associated with improved management of type 2 diabetes and obesity. However, preserving lean body mass (LBM) during significant WL mitigates the decline in physical strength and metabolic rate that can accompany substantial WL, leading to better long-term outcomes. However, it is expected that the reduction of some excess muscle mass during WL, especially in those with obesity, is considered beneficial and might not directly correlate with a decrease in physical function or muscle strength [1]. Typically, for every kilogram of WL, ~75% comes from fat mass and 25% from lean mass, reflecting a 3:1 ratio [2]. However, the significant WL associated with incretin mimetic-based antiobesity medications, similar to the results seen with bariatric surgery, has recently raised concerns regarding excess loss of lean tissue, accounting for 25% to 40% of total WL, as well as negative effects on physical function and the risk of treatment-induced physical "frailty" [3]. This highlights the importance of future WL research focusing not only on body composition but also on physical function and mobility. The impact of incretin mimetics on LBM has also sparked interest in developing adjunctive therapies to counteract the reduction in LBM and skeletal muscle mass, such as therapies targeting activin receptors or the myostatin pathway [4]. Although these pharmaceutical approaches are potentially promising, the essential role of lifestyle interventions should not be overlooked.

NUTRITIONAL KETOSIS AND LBM

A recent post hoc analysis of data that were previously published [5] suggests that achieving and maintaining nutritional ketosis, which is associated with greater WL, may help preserve lean mass. The analysis assessed changes in lower extremity lean mass (LELM) across different ketosis trajectory classes, finding that participants with higher ketosis experienced greater WL but had a lower proportion of LELM loss relative to total WL compared with those with lower adherence (Table 1) [6]. These findings are consistent with multiple studies that have demonstrated protein sparing effects of ketones [7, 8].

In order to further explore the impact of ketosis on total body lean mass and physical functioning, a subset of participants from the original study was examined (unpublished data). Full body composition data were not available for all participants due to insufficient scanning area of dual-energy x-ray absorptiometry to image the entire body of some large participants [5]. The subset of participants had complete body composition data and data on changes in physical functioning that were assessed using the following two subscales of the knee injury and osteoarthritis outcome score (KOOS): activities of daily living (ADL); and sports and recreation (Sports.Rec) [9]. Changes in weight and body composition were primarily observed at 1 year, with maintenance from 1 to 2 years. The analysis included 101 participants, 65 with type 2 diabetes and 36 with prediabetes. Over 1 year, participants experienced an average WL of 11.6% and a 5.2% LBM loss, accounting for 25% of the total WL, which aligns with the expected 3:1 ratio of fat mass to LBM loss. These participants also showed a 4.8% and 10.4% increase in KOOS ADL and Sports.Rec scores, respectively, suggesting that the decrease in total body mass and lean mass was accompanied by improvements in physical function.

TABLE 1 Changes in LELM and total LBM in participants following a well-formulated ketogenic diet.

	LELM changes		
Ketosis trajectory classes	**WL, %**	**LELM loss, %**	**LELM: WL, %**
SNK, $n = 17$	−21.0***	−7.0	4.7
MDNK, $n = 99$	−12.4***	−4.5	5.7
LNK, $n = 105$	−8.6***	−6.6*	12.5
UNK, $n = 27$	−10.7	−6.3	9.5
	LBM changes		
Early ketone adherence groups (unpublished data)	**Total mass loss, %**	**LBM loss, %**	**LBM: total mass loss, %**
High (≥1.0 mM), $n = 10$	−16.7**	−7.4	23.5
Moderate (0.5–0.99 mM), $n = 32$	−12.1***	−5.3	24.5
Low (<0.5 mM), $n = 59$	−10.3***	−5.0*	27.0

Note: LELM changes were assessed in the original cohort of 248 participants with type 2 diabetes from the initial study [5]. Total LBM changes were assessed in a subset of participants with type 2 diabetes and prediabetes ($n = 101$) from the original clinical trial who had full body composition data available. LELM: WL (%) refers to the percentage of LELM loss relative to total WL. WL for this parameter was calculated using weights collected at clinic visits during the assessment periods. LBM: total mass loss (%) refers to the percentage of total LBM loss relative to total mass loss. Total mass loss for this parameter was calculated based on total mass estimated from dual-energy x-ray absorptiometry measurements. Between-group differences and within-group changes in weight, LELM, total mass, and LBM were assessed using a linear mixed-effects model with age, gender, and race and ethnicity as covariates. Between-group differences in LELM: WL (%) and LBM: total mass loss (%) were assessed using a general linear model with age, gender, and race and ethnicity as covariates. *P* values were nonsignificant for cells without asterisks. There were no significant between-group differences in weight, LELM, total mass, LBM, LELM: WL (%), and LBM: total mass loss (%).
Abbreviations: LBM, lean body mass; LELM, lower extremity lean mass; LNK, low nutritional ketosis; MDNK, moderately decreasing nutritional ketosis; SNK, sustained nutritional ketosis; UNK, unsustained nutritional ketosis; WL, weight loss.
***$p < 0.001$.
**$p < 0.01$.
*$p < 0.05$ (all for within-group changes in weight, LELM, total mass, and LBM).

In order to determine whether our previously observed trend between ketosis adherence and LELM preservation carried over to this cohort ($n = 101$), we stratified participants into three groups based on early ketosis adherence, i.e., low, <0.5 mM; moderate, 0.5 to 0.99 mM; and high, ≥1.0 mM. The results showed that higher ketosis adherence was associated with greater WL compared with the moderate and lower ketosis adherence groups, whereas the proportion of LBM loss relative to total WL slightly decreased with increasing ketosis adherence (Figure 1A; Table 1). These changes were accompanied by increased physical functioning in all three groups, as indicated by improvements in KOOS ADL and Sports.Rec scores (Figure 1B).

These preliminary findings suggest that increased adherence to ketosis may mitigate LBM loss while simultaneously improving physical function, even with a greater degree of WL. Despite the early stage of these data and the limitations of the analysis, such as a limited sample size, lack of a control group, and the fact that the study was not specifically powered for body composition analysis, these intriguing results warrant further investigation, especially given their corroboration with other published studies. For example, several studies using a hypocaloric carbohydrate restriction diet have reported preservation of LBM with greater fat loss [10, 11] for up to 1 year [12]. Another study in normal-weight men reported an increase in lean mass following a 6-week carbohydrate restriction intervention [13]. Hypothetical mechanisms by which ketosis may preserve LBM include direct effects on the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway [14] or decreased leucine oxidation, which increases the availability of essential branched-chain amino acids [15]. Therefore, more research is needed to explore how lifestyle modifications and specific nutritional strategies, such as a ketogenic diet, could be used adjunctively to prevent lean mass loss in individuals treated with highly potent incretin mimetics.

OTHER LIFESTYLE CONSIDERATIONS

Although nutritional strategies are important, combining them with lifestyle changes such as regular physical activity and a structured exercise regimen can significantly enhance their benefits, particularly for preserving lean mass. Research primarily conducted over shorter durations indicates that pairing a ketogenic diet with resistance training or interval-based exercise supports LBM while promoting fat loss, decreasing visceral adiposity, and improving insulin sensitivity and

Obesity A Research Journal THE OBESITY SOCIETY WILEY

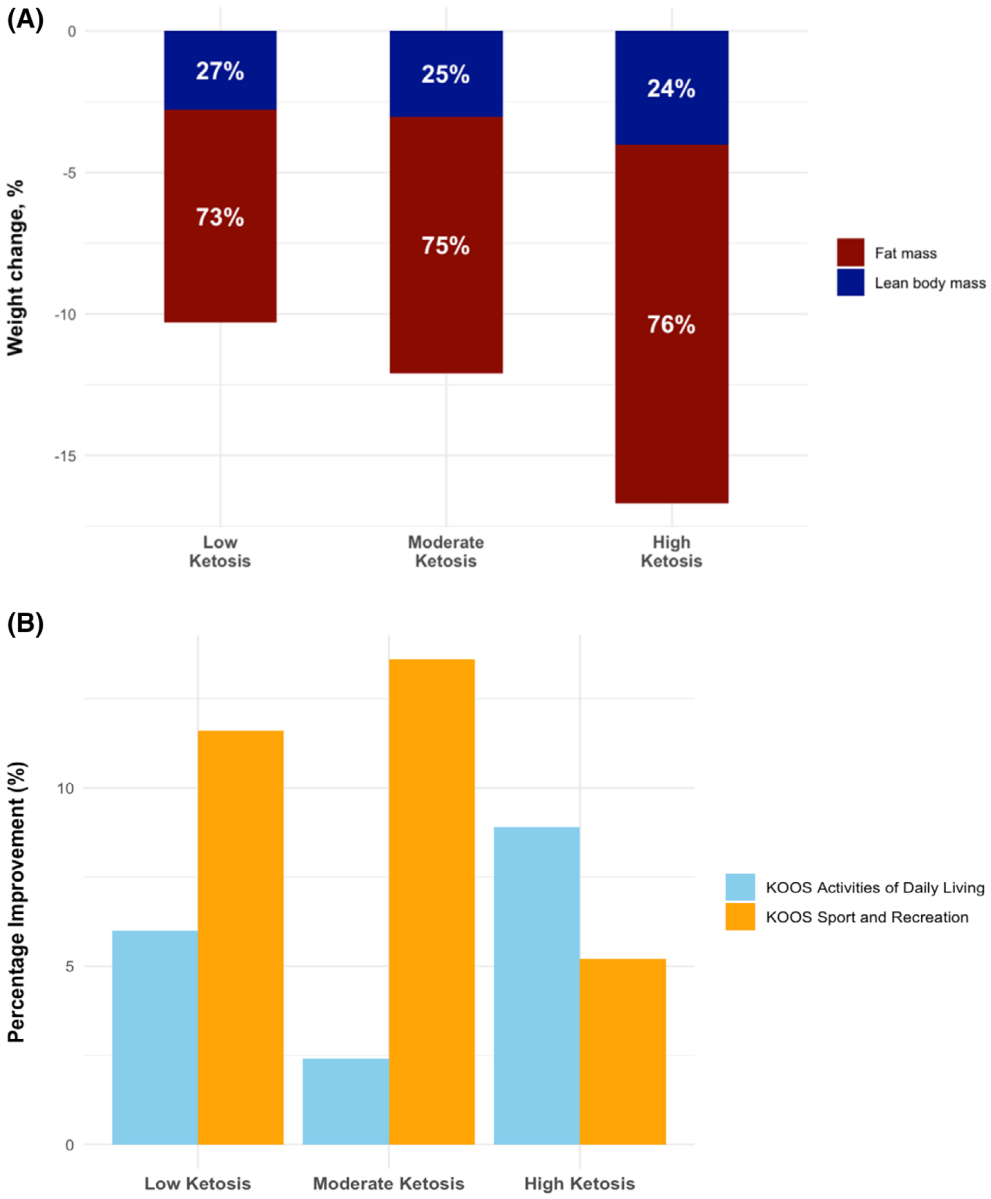

FIGURE 1 (A) Effect of WL from ketogenic diet, stratified by early ketosis adherence (low ketosis, <0.5 mM; moderate ketosis, 0.5–0.99 mM; and high ketosis, ≥1.0 mM), on body composition. (B) Effect of WL from ketogenic diet stratified by early ketosis adherence on KOOS activities of daily living and KOOS sports and recreation. KOOS, knee injury and osteoarthritis outcomes score; WL, weight loss. [Color figure can be viewed at wileyonlinelibrary.com]

overall metabolic health [16, 17]. This comprehensive approach to body composition management maximizes fat loss while maintaining muscle mass and function. Additionally, ensuring adequate, but not excessive, protein intake (i.e., 1.2–1.5 g/kg reference weight) from high-quality sources that are rich in essential amino acids such as leucine can further mitigate the loss of LBM [14]. For those who struggle to increase endogenous ketone levels through carbohydrate restriction, exogenous ketone supplementation may be a valuable option [18]. This strategy can help induce ketonemia, hypothetically supporting both LBM preservation and overall metabolic health during WL.

CONCLUSION

There is a critical need for research examining the interaction between specific nutritional interventions and glucagon-like peptide-1 (GLP-1) therapy to better understand the role of various lifestyle interventions in preserving lean mass. Future studies should focus not only on the effects on lean mass but also include assessments of physical function and frailty, particularly through objective measures such as the handgrip strength test and sit-to-stand test. Additionally, these studies should incorporate advanced body composition methods such

as magnetic resonance imaging to overcome the limitations of dual-energy x-ray absorptiometry, as well as explore emerging approaches such as Visual Body Composition [19] to evaluate their reliability and potential for use in patient care.

CONFLICT OF INTEREST STATEMENT

Shaminie J. Athinarayanan is an employee and shareholder of Virta Health. Jeff S. Volek is a cofounder and shareholder of Virta Health.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author with a reasonable proposal. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Shaminie J. Athinarayanan https://orcid.org/0000-0001-5427-6748

REFERENCES

1. Choi SJ, Files DC, Zhang T, et al. Intramyocellular lipid and impaired myofiber contraction in normal weight and obese older adults. *J Gerontol A Biol Sci Med Sci*. 2016;71:557-564. doi:10.1093/gerona/glv169
2. Heymsfield SB, Gonzalez MCC, Shen W, Redman L, Thomas D. Weight loss composition is one-fourth fat-free mass: a critical review and critique of this widely cited rule. *Obes Rev*. 2014;15:310-321. doi:10.1111/obr.12143
3. Conte C, Hall KD, Klein S. Is weight loss-induced muscle mass loss clinically relevant? *JAMA*. 2024;332(1):9-10. doi:10.1001/jama.2024.6586
4. Rodgers BD, Ward CW. Myostatin/activin receptor ligands in muscle and the development status of attenuating drugs. *Endocr Rev*. 2022;43(2):329-365. doi:10.1210/endrev/bnab030
5. Athinarayanan SJ, Adams RN, Hallberg SJ, et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year non-randomized clinical trial. *Front Endocrinol (Lausanne)*. 2019;10:348. doi:10.3389/fendo.2019.00348
6. Athinarayanan SJ, Volk BM, Adams RN, et al. Effects of nutritional ketosis on weight loss and lean mass preservation in type 2 diabetes. ObesityWeek Poster 304. *Obesity (Silver Spring)*. 2024;32(suppl 1):176-177. doi:10.1002/oby.24195
7. Pawan GL, Semple SJ. Effect of 3-hydroxybutyrate in obese subjects on very-low-energy diets and during therapeutic starvation. *Lancet*. 1983;1(8314–5):15-17. doi:10.1016/s0140-6736(83)91560-x
8. Koutnik AP, Poff AM, Ward NP, et al. Ketone bodies attenuate wasting in models of atrophy. *J Cachexia Sarcopenia Muscle*. 2020;11(4):973-996. doi:10.1002/jcsm.12554
9. Lyman KS, Athinarayanan SJ, McKenzie AL, et al. Continuous care intervention with carbohydrate restriction improves physical function of the knees among patients with type 2 diabetes: a non-randomized study. *BMC Musculoskelet Disord*. 2022;23(1):297. doi:10.1186/s12891-022-05258-0
10. Benoit FL, Martin RL, Watten RH. Changes in body composition during weight reduction in obesity. Balance studies comparing effects of fasting and a ketogenic diet. *Ann Intern Med*. 1965;63(4):604-612. doi:10.7326/0003-4819-63-4-604
11. Willi SM, Oexmann MJ, Wright NM, Collop NA, Key LL Jr. The effects of a high-protein, low-fat, ketogenic diet on adolescents with morbid obesity: body composition, blood chemistries, and sleep abnormalities. *Pediatrics*. 1998;101(1 Pt 1):61-67. doi:10.1542/peds.101.1.61
12. Moreno B, Bellido D, Sajoux I, et al. Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. *Endocrine*. 2014;47(3):793-805. doi:10.1007/s12020-014-0192-3
13. Volek JS, Sharman MJ, Love DM, et al. Body composition and hormonal responses to a carbohydrate-restricted diet. *Metabolism*. 2002;51(7):864-870. doi:10.1053/meta.2002.32037
14. Volek JS, Kackley ML, Buga A. Nutritional considerations during major weight loss therapy: focus on optimal protein and a low-carbohydrate dietary pattern. *Curr Nutr Rep*. 2024;13(3):422-443. doi:10.1007/s13668-024-00548-6
15. Phinney SD, Bistrian BR, Wolfe RR, Blackburn GL. The human metabolic response to chronic ketosis without caloric restriction: physical and biochemical adaptation. *Metabolism*. 1983;32(8):757-768. doi:10.1016/0026-0495(83)90105-1
16. Crabtree CD, McSwiney FT, Beeler MK, et al. Extended ketogenic diet and physical training intervention in military personnel. *Mil Med*. 2019;184(9–10):e538-e547. doi:10.1093/milmed/usz046
17. Miller VJ, LaFountain RA, Barnhart E, et al. A ketogenic diet combined with exercise alters mitochondrial function in human skeletal muscle while improving metabolic health. *Am J Physiol Endocrinol Metab*. 2020;319(6):E995-E1007. doi:10.1152/ajpendo.00305.2020
18. Buga A, Kackley ML, Crabtree CD, et al. The effects of a 6-week controlled, hypocaloric ketogenic diet, with and without exogenous ketone salts, on body composition responses. *Front Nutr*. 2021;8:618520. doi:10.3389/fnut.2021.618520
19. Agarwal AA, Narayan A, Stanford FC. Body composition in anti-obesity medication trials-beyond scales. *JAMA Intern Med*. 2024;184(4):341-342. doi:10.1001/jamainternmed.2023.7733

How to cite this article: Athinarayanan SJ, Volek JS. Mitigating muscle loss during weight loss: can nutritional ketosis make a difference? A call for more research. *Obesity (Silver Spring)*. 2025;33(3):431-434. doi:10.1002/oby.24235