

## EXERCISE-INDUCED N-LACTOYL-PHENYLALANINE AND ITS POTENTIAL ROLE IN APPETITE REGULATION AND OBESITY

**Dominika Raether**<sup>1</sup>  , **Adam Andrzejewski**<sup>1</sup> ,  
**Julia Wendt**<sup>1</sup> , **Aleksandra Markuszewska**<sup>2</sup> ,  
**Agnieszka Anna Bugała**<sup>3</sup> , **Olga Wcisłek**<sup>4</sup> ,  
**Urszula Chmielecka**<sup>5</sup> 

<sup>1</sup>F. Ceynowa Specialist Hospital in Wejherowo, Poland

<sup>2</sup>POLIMED Medical Center Ltd, Tczew, Poland

<sup>3</sup>Non-public Healthcare Facility No. 1 in Rumia, Poland

<sup>4</sup>F. Raszei Hospital in Poznan, Poland

<sup>5</sup>Regional Specialist Hospital in Wrocław, Poland



 [dominika.raether@gmail.com](mailto:dominika.raether@gmail.com)

### ABSTRACT

#### BACKGROUND

Obesity is a major global public health challenge associated with increased morbidity, reduced life expectancy, and substantial socioeconomic burden. Although lifestyle interventions, particularly dietary modification and physical activity, remain the cornerstone of obesity management, their underlying biological mediators are not fully understood. Recent research has identified exercise-induced metabolites, including N-lactoyl-phenylalanine (Lac-Phe), as potential contributors to metabolic adaptations related to appetite regulation and body weight control. Experimental findings have generated interest in Lac-Phe; however, its physiological relevance and clinical significance in humans remain uncertain.

#### AIMS

To critically synthesize and evaluate current experimental and clinical evidence on the biosynthesis, biological properties, mechanistic pathways, and exercise-related dynamics of Lac-Phe, with particular emphasis on its potential role in appetite regulation and body weight modulation in the context of obesity.

#### METHODS

A narrative review was conducted based on qualitative analysis of the literature. PubMed, Scopus, Web of Science, and Embase were searched for publications from 2015 to 2025 using combinations of the terms "Lac-Phe" or "N-lactoyl-phenylalanine" with obesity-related keywords. After removal of duplicates and screening for relevance, original experimental, clinical, and mechanistic studies were included for qualitative synthesis. Additional sources were used to provide physiological and clinical context.

#### RESULTS

Available evidence indicates that Lac-Phe is synthesized predominantly via CNDP2-dependent pathways and that circulating concentrations increase transiently after physical exercise, particularly following high-intensity activity. In animal models of diet-induced obesity, Lac-Phe administration reduced food intake without affecting lean animals, suggesting a context-dependent anorexigenic effect. In human studies, exercise-induced elevations of Lac-Phe were associated with reductions in subjective hunger ratings and, in some observational settings, with decreases in adipose tissue; however, consistent effects on

caloric intake have not been demonstrated. Mechanistic studies in preclinical models implicate central appetite-regulating pathways, including inhibition of hypothalamic AgRP neurons via KATP channels. At physiological concentrations, Lac-Phe appears metabolically neutral in animal models, whereas supraphysiological exposure in cellular systems has been associated with impaired insulin signaling and pro-inflammatory responses.

## CONCLUSIONS

Current evidence supports the interpretation of Lac-Phe as a marker and potential modulator of exercise-induced metabolic adaptations rather than as an independent therapeutic target for obesity. The translation of preclinical findings to clinically meaningful effects in humans remains limited. Further well-designed clinical studies are required to clarify the role of Lac-Phe in human appetite regulation, its long-term metabolic effects, and its relevance within comprehensive strategies for obesity management.

Keywords: Lac-Phe, N-lactoyl-phenylalanine, obesity, appetite regulation, physical activity

## INTRODUCTION

According to the World Health Organization, obesity is one of the major global public health challenges and in 2022 affected more than 890 million people worldwide [2]. In developed countries such as Poland, the prevalence of obesity is higher and reaches approximately 25 percent of the adult population [7]. Excess body weight can lead to a wide range of complications, beginning with the musculoskeletal system, where it represents a significant modifiable risk factor for knee osteoarthritis [4], and extending to impaired reproductive function due to hormonal imbalance, resulting in adverse pregnancy outcomes and an increased risk of infertility [3]. Ultimately, obesity reduces life expectancy by approximately six point seven years in individuals aged forty years [1]. To maintain a healthy body weight, individuals may restrict energy intake or increase levels of physical activity [5,6,8,9]. Following the approval by the European Medicines Agency of the first GLP-1 receptor agonist, liraglutide, on 23 March 2015, some patients with obesity and overweight gained access to pharmacological treatment aimed at reducing caloric intake [10,33,34]. According to data from Fair Health, prescriptions of GLP-1 receptor agonists among adults with obesity and overweight in the United States increased by 586.7 percent between 2019 and 2024 [28]. In the context of growing demand, researchers continue to search for alternatives to GLP-1 receptor agonists.

Physical activity is known to enhance the metabolism of energy substrates and is associated with reductions in body weight [16]. In recent years, it has been shown that physical exercise is accompanied by increased concentrations of several metabolites, including the recently identified N-lactoyl-phenylalanine [11,12]. Lac-Phe is formed through the condensation of lactate and phenylalanine [13], and its plasma levels rise under conditions associated with increased concentrations of lactate or phenylalanine, including intensive physical exercise [13,14,15,23,27]. Experimental and observational studies suggest a possible association between Lac-Phe and appetite regulation, although the nature and clinical relevance of these effects remain under debate [17,18,21,22].

## AIM

The aim of this narrative review is to systematize and critically analyze available experimental and clinical data on N-lactoyl-phenylalanine, with an assessment of its biological origin, mechanisms of action, relationship with physical exercise, and its potential role in the regulation of appetite and body weight in obesity.

To achieve this aim, the following research objectives were formulated.

1. To analyze data on the biosynthesis of Lac-Phe and the role of the CNDP2 enzyme in different tissues.
2. To summarize the results of preclinical studies evaluating the effects of Lac-Phe on food intake and metabolic parameters.
3. To review available human studies on the dynamics of Lac-Phe in response to physical exercise and its association with subjective and objective measures of appetite and adipose tissue.
4. To analyze the described central and peripheral mechanisms of action of Lac-Phe.
5. To critically assess the limitations of the existing evidence base and the translational barriers between preclinical models and clinical application.

## METHODS

A narrative review design was applied to synthesize evidence on N-lactoyl-phenylalanine (Lac-Phe) in relation to exercise, appetite regulation, and obesity. Literature searches were conducted in PubMed, Scopus, Web of Science, and Embase and covered publications from January 2015 to December 2025.

The search strategy used the following query: ("Lac-Phe" OR "N-lactoyl-phenylalanine") AND ("obesity" OR "adiposity" OR "overweight" OR "excess body weight" OR "excess body fat" OR "elevated body mass index" OR "elevated BMI").

The initial search identified 125 records. After removal of 43 duplicate entries, 82 unique records remained for title and abstract screening. Seventy publications were excluded because they were not directly related to Lac-Phe, represented review-only articles or commentaries, were preprints without peer review, or did not report original experimental or observational data.

Full texts of 12 eligible original studies were assessed in detail and constituted the core analytical set of this review. These studies included animal experiments, human exercise interventions, cellular models, and mechanistic investigations directly addressing Lac-Phe synthesis, regulation, or appetite- and metabolism-related effects. Findings from these studies formed the basis of the Results section.

In addition to these 12 core studies, further peer-reviewed publications were included to provide epidemiological, physiological, metabolic, and pharmacological context. These additional sources were primarily used in the Introduction and Discussion sections. After removal of one duplicate reference, the final reference list comprised 41 unique publications.

Due to substantial heterogeneity in study design, experimental models, populations, and outcome measures, quantitative synthesis and meta-analysis were not appropriate. All included studies were therefore analyzed qualitatively, with emphasis on study design, biological model, type of evidence, main findings, and reported limitations. No formal risk-of-bias assessment was performed, consistent with the narrative and mechanistic scope of the review.

## RESULTS

N-lactoyl-phenylalanine (Lac-Phe) is produced mainly by epithelial cells and macrophages by condensation of lactate and phenylalanine. Carnosine Depeptidase 2 (CNDP2) has been identified as the main enzyme catalyzing this reaction, as CNDP2-knockout macrophages produce more than 75% less Lac-Phe [18]. Production of this molecule correlates with lactate levels. To assess whether the rise in lactate concentration during exercise is associated with an increase in Lac-Phe levels, metabolomic profiling was performed on mouse blood plasma collected after treadmill running to depletion. This analysis showed that Lac-Phe concentrations peaked immediately after activity. In the next step, human blood plasma was examined for exercise-induced changes in Lac-Phe, and Lac-Phe was identified as the third-most-significant exercise-induced metabolite in the dataset. The most pronounced effect was observed after the sprint, with elevated N-lactoyl-phenylalanine levels persisting up to 3 hours after the training session [18].

These findings were further supported in human cells by researchers from the Department of Life Sciences and Health, Oslo Metropolitan University (OsloMet), Norway, and collaborating institutions. The researchers isolated human skeletal muscle cells, applied electrical pulse stimulation (EPS) as an *in vitro* model of exercise for 24 hours, and then assessed the extracellular vesicles (EVs) and microvesicles (MVs) released by the cells. Among the proteins upregulated after stimulation was CNDP2 ( $p = 0.031$ ) [38].

Researchers from Vocational and Technical University of Construction, Dongyang, China and associated institutions performed a metabolomic crossover study including 14 obese college students. Participants were randomly assigned to one of three groups: moderate-intensity continuous exercise (MICE), MICE + blood flow restriction (BFR) and high-intensity interval training (HIIT). Among metabolites Lac-Phe was one of the most significantly upregulated post-exercise particles. Moreover, when MICT+BFR was compared with MICT, Lac-Phe was higher in the BFR condition. These findings confirmed exercise Lac-Phe upregulation in humans [37]. An increase of Lac-Phe level after exercise in humans was confirmed in other studies [12,41].

Based on the observation that CNDP2 mutations are associated with body mass index, Lac-Phe was hypothesized to function as an energy balance regulator. To test this hypothesis, Lac-Phe was administered to obese mice induced by diet. These mice showed a 50% reduction in food intake compared with the control group [18].

Due to the lack of data on the effects of Lac-Phe on hunger and food intake in humans, researchers from the School of Sports Science at Nantong University, China, conducted a study to address this question. In this experiment, they recruited 14 obese adults aged 18–24 years and allocated them to three groups. The first group performed MICE without BFR, the second group performed MICE with BFR, and the third group served as a non-exercising control. BFR reduces blood flow to working muscles, leading to local hypoxia and higher plasma lactic acid levels than during non-BFR exercise. The researchers confirmed that plasma lactate concentrations were highest in the BFR group and lowest in the control group. During the study, participants also completed visual analogue scale (VAS) subscales assessing appetite. The results were promising, as hunger levels immediately after exercise and one hour post-exercise were significantly lower in the MICE+BFR group. However, caloric intake measured one hour after training did not differ significantly between groups [25]. The authors suggested that this may be due to peak plasma Lac-Phe production occurring 30–60 minutes after exercise [18,25].

However, a prior study conducted by the Institute for Clinical Chemistry and Pathobiochemistry, Department for Diagnostic Laboratory Medicine, University Hospital Tübingen, Germany, and collaborating institutions provides a somewhat different perspective on the anti-obesity properties of Lac-Phe. In this experiment, 22 individuals underwent an eight-week intervention, exercising three times per week for one hour at 80%  $VO_{2peak}$ . Investigators collected blood samples before and after training to measure Lac-Phe levels. The researchers reported that Lac-Phe concentrations measured in blood plasma both before and after a training intervention correlated with reductions in subcutaneous adipose tissue. They also found that post-exercise Lac-Phe levels were correlated with reductions in visceral adipose tissue. Nevertheless, this study does not establish whether these associations are causal or specifically mediated by Lac-Phe rather than other exercise-induced factors [26].

The exact central mechanism underlying the anorexigenic action of Lac-Phe in mice was unclear until recent studies. Researchers from Baylor College of Medicine and collaborating institutions published in *Nature Metabolism* and investigated two types of hypothalamic neurons: AgRP, which promotes hunger, and TRH, which promotes satiety. Lac-Phe acts on KATP channels in AgRP cells. Activation of these channels leads to hyperpolarization of the neuron. Inhibition of AgRP neurons activates TRH neurons, reducing hunger and promoting satiety. The authors proposed an interesting hypothesis regarding the possible relevance of Lac-Phe's anorexigenic effects, especially during sprint exercise, when its concentration is highest. They suggested that running may signal exposure to a hazardous environment and a higher likelihood of needing to run again in the

near future. Thus, high post-exercise levels of Lac-Phe may transiently suppress hunger, thereby delaying eating, which could interfere with a subsequent sprint [20].

Another way to increase Lac-Phe concentrations, other than direct administration or exercise, is to enhance CNDP2 expression. Some compounds with this specific effect have already been identified. Researchers from the Department of Molecular Biology and Genetics at Tokat Gaziosmanpasa University in Tokat, Turkey, investigated the influence of fatty acids on CNDP2 expression in mice. They found that conjugated linoleic acids (CLA), particularly t10-c12 CLA, increased CNDP2 transcript levels in mouse fat tissue. A similar effect was observed in human colon cancer cells. Researchers also found that CNDP2 levels rise in rats' adipose tissue due to a caloric restriction diet. However, this finding needs further research [24]. In a study conducted by the Department of Endocrinology at Peking Union Medical College Hospital and affiliated institutions, researchers evaluated another molecule that may promote Lac-Phe synthesis: hydroxysafflor yellow A (HSYA), derived from safflower. They assessed the effects of intragastric HSYA administration in diet-induced obese (DIO) mice fed a high-fat diet (HFD). Mice in the HFD-HSYA group maintained a lower body weight, reaching 83.96% of the HFD group's weight by week 10 ( $p < 0.05$ ), and showed reduced weight gain (3.0 vs -1.4 g in HFD and non-HFD mice, respectively;  $p < 0.05$ ). Next, cecal contents were analyzed to identify metabolite differences between groups. One of the most prominent changes was a 7.51-fold increase in Lac-Phe (reported as the third most abundant metabolite) in HFD-HSYA versus HFD mice. This effect was sustained in mice treated with antibiotics, suggesting that HSYA-induced Lac-Phe production is independent of the gut microbiota. Immunohistochemical analysis of the small intestine showed increased CNDP2 expression in the HFD-HSYA group ( $p < 0.05$ ). Notably, serum Lac-Phe levels did not increase, implying a distinct, potentially intestine-mediated anorexigenic mechanism. This was supported by reduced intestinal GIP levels in HFD-HSYA mice [36].

An important observation from mouse studies is the apparent metabolic neutrality of Lac-Phe compared to the control group. Administration of Lac-Phe did not alter locomotor activity, water intake, or circulating lactate, and appetite-regulating hormone levels were likewise unaffected. Also, oxygen consumption, respiratory exchange ratio and carbon dioxide production stayed unchanged, indicating that overall energy expenditure did not increase. Likewise, kaolin consumption remained the same, suggesting that Lac-Phe does not induce nausea or visceral malaise. What is most interesting is that in lean mice, Lac-Phe did not reduce food intake, even at a threefold higher dose, so it is unlikely to pose a risk of malnutrition or anorexia [18].

However, researchers from the Biomedical Research Center, QU Health, Qatar University, and collaborating institutions reported that supraphysiological Lac-Phe exposure may have adverse metabolic effects in cell models, including C2C12 (mouse skeletal muscle cells) and HepG2 cells (human hepatocyte-like liver cell line). Lac-Phe impaired insulin-stimulated phosphorylation of key proteins in the insulin signaling pathway, particularly in C2C12 myotubes, increased the secretion of pro-inflammatory cytokines (notably TNF- $\alpha$  and IL-6) in C2C12 cells, and reduced oxygen consumption in HepG2 cells [39].

On the other hand, researchers from the Department of Pain Management, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (China), and collaborating institutions investigated mice with spinal cord injury (SCI). Examination of the lesion site revealed marked lipid droplet accumulation after SCI. One group of mice performed wheel running for 30 minutes daily, which reduced lipid droplet accumulation and decreased the expression of pro-inflammatory markers, including CD86. A similar beneficial pattern was observed when SCI mice were administered Lac-Phe instead of undergoing exercise [40].

Table 1 compiles experimental, observational and methodological studies on Lac Phe across cell, animal and human models summarizing study design, biological effects, metabolic and appetite related outcomes and conditions associated with Lac Phe elevation.

Table 1. Articles about Lac-Phe with summed up main features and findings.

Title of Article	Type of Study on Lac-Phe	Study Model	Main Effects	Conditions Leading to Increased Lac-Phe	Data Limitations	Reference
N-Lactoyl-Phenylalanine modulates lipid metabolism in microglia/macrophage via the AMPK-PGC1 $\alpha$ -PPAR $\gamma$ pathway to promote recovery in mice with spinal cord injury	Interventional (therapeutic role in neuroinflammation and tissue repair)	Mouse model of spinal cord injury (SCI)	Lac-Phe increases lipid metabolism in microglia/macrophages, activates AMPK-PGC1 $\alpha$ -PPAR $\gamma$ pathway shifting polarization to anti-inflammatory M2 phenotype.	Administration of Lac-Phe post-injury; exercise as a metabolic byproduct.	Limited to mouse model; no human data; small sample size; lacks long-term follow-up on recovery.	40
Deciphering Blood Flow Restriction Training to Aid Lipid Lowering in Obese	Observational (metabolomics analysis of exercise effects)	Human crossover experiment with obese	MICT+BFR shows superior lipid-lowering effects via upregulation	Blood flow restriction (BFR) combined with	Small sample size (n=14); no long-term outcomes;	37

College Students through Untargeted Metabolomics		college students (MICT, MICT+BFR, HIIT)	of metabolites like Lac-Phe, xanthine, succinate, lactate, citrate, urocanic acid, and myristic acid; involves citric acid cycle and amino acid metabolism pathways.	moderate-intensity continuous training (MICT)	limited to obese young adults.	
An exercise-inducible metabolite that suppresses feeding and obesity	Interventional and observational (metabolomics and gain/loss-of-function)	Mice (diet-induced obese and lean), human exercise cohorts, horse metabolomics	Lac-Phe suppresses feeding, reduces body weight and adiposity, improves glucose homeostasis in obese mice; synthesized by CNDP2 from lactate and phenylalanine.	Intense exercise (e.g., treadmill running in mice, sprinting in humans);	Primarily mouse-based; human data limited to acute exercise; no long-term human intervention	18
Rapid indirect detection of N-lactoyl-phenylalanine using dual DNA biosensors based on solution-gated graphene field-effect transistor	Methodological (biosensor development for detection)	In vitro cell culture (RAW264.7 macrophages) and biosensor testing	Developed biosensor for indirect Lac-Phe detection via L-lactate and L-phenylalanine; high linearity and accuracy (91-99%); potential for exercise evaluation.	Exercise-induced production in CNDP2+ cells (e.g., macrophages); not directly studied but implied via L-lactate/L-phenylalanine levels.	In vitro only; no in vivo validation; model based on assumptions of Lac-Phe synthesis; limited to RAW264.7 cells.	42
The effect of blood flow restriction exercise on N-lactoylphenylalanine and appetite regulation in obese adults: a cross-design study	Interventional (exercise effects on appetite)	Human cross-design with obese adults (MICE, MICE+BFR)	BFR increases Lac-Phe and lactate, reduces hunger and ghrelin, increases GLP-1; involves citric acid cycle and amino acid metabolism; no significant calorie intake change.	Blood flow restriction (BFR) with moderate-intensity exercise (60% VO2max); acute bouts post-standardized meal.	Small sample size (n=14); short-term (acute effects only); no control for diet variability; limited to young obese adults.	25
Distinct microRNA and protein profiles of extracellular vesicles secreted from myotubes from morbidly obese donors with type 2 diabetes in response to electrical pulse stimulation	Observational (proteomics and miRNA profiling)	Human myotubes from morbidly obese T2D donors; electrical pulse stimulation (EPS) as exercise model	EPS changes EV cargo: 15 exosome miRNAs (e.g., miR-1233-5p upregulated) and proteins (e.g., CNDP2 increased); Lac-Phe linked to appetite regulation via CNDP2.	Electrical pulse stimulation (EPS) mimicking exercise	In vitro myotube model only; small donor sample (n=6); no in vivo confirmation; data from morbidly obese T2D donors may not generalize.	38
N-Lactoyl amino acids as metabolic biomarkers differentiating low and high exercise	Observational (metabolomics of exercise response)	Human intervention with overweight/obese	Low exercise responders have higher Lac-Phe and N-lactoyl amino acids;	Low exercise response ( $\Delta 6$ -MWD=27m); aerobic exercise	Small intervention cohort (n=43); validation	41

response		women; validation in GTEx cohort	negatively correlates with slow-twitch muscle fibers; biomarkers for exercise efficacy.	intervention; negatively linked to CNDP2 expression in muscle.	cohort indirect (GTEx gene expression); no causal mechanisms tested; limited to females.	
N-Lactoyl Phenylalanine Disrupts Insulin Signaling, Induces Inflammation, and Impairs Mitochondrial Respiration in Cell Models	Interventional (cellular effects of Lac-Phe exposure)	In vitro cell models (HepG2 liver cells, C2C12 muscle cells); rat brain mitochondria/synaptosomes	Lac-Phe impairs insulin signaling (reduced phosphorylation), increases pro-inflammatory cytokines, impairs mitochondrial respiration; potential metabolic risks.	High-dose Lac-Phe exposure; exercise-inducible but studied as exogenous treatment.	In vitro only; high concentrations may not reflect physiological levels; no in vivo data; limited cell types.	39
Trans-10, cis-12 conjugated linoleic acid- and caloric restriction-mediated upregulation of CNDP2 expression in white adipose tissue in rodents, with implications in feeding and obesity	In silico (analysis of existing datasets)	Rodent models (mice/rats) from prior studies on t10-c12 CLA and caloric restriction	Upregulation of CNDP2 (Lac-Phe synthase) in adipose tissue; hypothesized to increase Lac-Phe, reduce feeding and obesity via high-fat diet context.	Treatment with t10-c12 CLA; caloric restriction; high-fat diet.	In silico based on re-analysis; no new experiments; assumptions on Lac-Phe levels; limited to rodents.	24
Exercise-Induced N-Lactoylphenylalanine Predicts Adipose Tissue Loss during Endurance Training in Overweight and Obese Humans	Interventional (exercise intervention with metabolomics)	Human endurance training in overweight/obese subjects (8-week program)	Higher post-exercise Lac-Phe predicts greater reduction in abdominal subcutaneous/visceral adipose tissue	Acute endurance exercise; higher levels post-intervention.	Small sample size (n=22); short intervention (8 weeks); no control group; limited to sedentary overweight/obese.	26
Lac-Phe induces hypophagia by inhibiting AgRP neurons in mice	Interventional (how injection of Lac-Phe reduce food intake)	Mouse model (lean and DIO) being administered Lac-Phe	Lac-Phe open KATP channels in hypothalamic AgRP neurons causing its hyperpolarisation and subsequent TRH neurons activation which promotes satiety.	Direct injection of Lac-Phe (50 mg/kg)	Mouse based primarily focused on males; Focus on AgRP and KATP neurons with shallow researches on different neural cells	20
Hydroxysafflor Yellow A Promotes Lac-Phe Synthesis to Suppress GIP and Ameliorate Obesity in DIO Mice	International (HSYA administration)	Mouse models (lean, DIO, with or without antibiotics treatment)	HSYA administration leads to intestinal Lac-Phe and CNDP2 elevation irrelevant to intestinal microbiota. There was no change in Lac-Phe serum concentration. Food intake reduction was connected with decrease in	Exercise and HSYA administration	Mouse based; No serum Lac-Phe elevation	36

Table 2 outlines the key mechanisms of Lac Phe synthesis and action focusing on CNDP2 mediated production, central appetite regulation and experimentally supported effects on food intake and metabolism.

*Table 2. Mechanisms related to Lac-Phe production, function and effect on appetite.*

Mechanism	Description	Type of Evidence	Reference
CNDP2 Enzyme	CNDP2 (cytosolic nonspecific dipeptidase 2) catalyzes the synthesis of Lac-Phe condensing lactate (Lac) and phenylalanine (Phe) in CNDP2-positive cells (e.g., macrophages, monocytes, stromal cells). Knockout of CNDP2 reduces Lac-Phe levels by >75%. Upregulation of CNDP2 (e.g., by t10-c12 CLA or HSYA) may increase Lac-Phe production, contributing to anti-obesity effects. In EVs from myotubes, CNDP2 protein increases with EPS.	Experimental: CNDP2-KO studies in cells/mice; proteomics/microarray in myotube EVs; Mice after HSYA or t10-c12 CLA administration	18, 24, 36, 38
Neuronal Targets (AgRP and TRH)	Lac-Phe acts centrally in the brain to suppress appetite, potentially targeting AgRP (agouti-related peptide) neurons in the hypothalamus, which promote hunger, and TRH (thyrotropin-releasing hormone) neurons, involved in energy homeostasis.	Experimental: Brain administration studies showing reduced food intake	20
Effects on Appetite	Lac-Phe suppresses appetite and food intake (e.g., ~50% reduction in obese mice), leading to weight loss, reduced adiposity, and improved glucose homeostasis. In humans, higher post-exercise Lac-Phe correlates with reduced hunger.	Experimental: Direct Lac-Phe or HSYA administration in obese mice; BFR exercise in obese humans showing reduced hunger/VAS scores.	18, 20, 25, 36

## DISCUSSION

Lac-Phe is a recently identified metabolite that has demonstrated anorexigenic effects in animal models, whereas its role in appetite regulation in humans remains uncertain. In a small clinical study involving 14 adults with obesity, no significant association was observed between post exercise Lac-Phe concentrations and subsequent energy intake, despite transient reductions in subjective hunger ratings [25]. These findings underline the limited translatability of current animal data and indicate the need for adequately powered clinical studies to clarify whether Lac-Phe exerts any clinically relevant effects on eating behavior in humans [18,25].

In humans, available evidence suggests that Lac-Phe is more consistently associated with exercise related metabolic responses than with direct regulation of food intake. Studies comparing continuous moderate exercise and continuous vigorous exercise demonstrated a pronounced and transient increase in circulating Lac-Phe following vigorous exercise, while concentrations remained relatively stable after moderate activity [30]. This pattern indicates that Lac-Phe production primarily reflects metabolic stress and lactate related signaling induced by high intensity exercise, rather than acting as a direct mediator of appetite suppression.

Mechanistically, Lac-Phe belongs to a broader group of phenylalanine derived metabolites generated through CNDP2 dependent pathways. Related compounds such as N-beta-hydroxybutyryl phenylalanine have also been shown to influence feeding behavior in experimental models, likely reflecting integrated metabolic signaling linked to ketogenesis and energy availability rather than isolated appetite suppressing mechanisms [19]. In this context, Lac-Phe should be viewed as part of a coordinated network of exercise induced metabolites, rather than as a standalone regulatory factor.

Experimental studies have identified central and peripheral pathways potentially involved in Lac-Phe signaling, including modulation of hypothalamic AgRP neuronal activity. However, these mechanistic insights are largely derived from animal models and cellular systems, and their relevance for human physiology remains uncertain. At present, there is no direct evidence linking these pathways to sustained changes in energy intake or body weight in humans.

Importantly, the beneficial effects of physical activity on body composition and metabolic health are well established and do not depend on any single metabolite. Regular physical activity, particularly aerobic exercise, reduces visceral adipose tissue, improves cardiometabolic risk profiles, and is associated with reduced all-cause, cardiovascular, and cancer related mortality [29,31,32,35]. Within this established framework, Lac-Phe is best interpreted as a potential marker or modulator of exercise

induced metabolic adaptations rather than as an independent therapeutic agent.

## LIMITATIONS OF THE STUDY

The evidence base reviewed in this article has several fundamental limitations that directly arise from the analyzed sources. Randomized evidence is limited to small-scale human trials and lacks large, placebo-controlled studies, restricting statistical power and assessment of long-term outcomes [25,26,37]. The majority of data derive from animal models and observational human studies with varying designs, inclusion criteria, and endpoints, increasing risks of bias and complicating comparisons [12,18,20,24,36,38-41]. Mechanistic conclusions rely on cellular and imaging surrogates without direct links to clinical endpoints [20,39,40]. The absence of comparative studies with other exercise mimetics or appetite suppressants limits positioning Lac-Phe in therapeutic contexts.

## CONCLUSIONS

The analysis of experimental, clinical, and cellular studies indicates that N-lactoyl-phenylalanine is a metabolite whose synthesis is predominantly mediated by the enzyme CNDP2 in epithelial cells and macrophages and is closely linked to lactate levels, particularly under conditions of physical activity. Metabolomic studies in both animals and humans consistently demonstrate increased Lac-Phe concentrations following exercise, with the most pronounced elevations observed after high-intensity activity and persistence of elevated levels for several hours. These findings are supported by in vitro models, including electrical pulse stimulation of human skeletal muscle cells, which show upregulation of CNDP2 expression and related metabolites.

Preclinical evidence suggests that administration of Lac-Phe to mice with diet-induced obesity results in reduced food intake without affecting lean animals, indicating a context-dependent anorexigenic effect. In human studies, exercise is associated with reductions in subjective hunger ratings, whereas consistent and statistically significant changes in caloric intake have not been reliably demonstrated. Observational data link higher Lac-Phe levels with reductions in adipose tissue; however, the available evidence does not allow causal relationships to be established and does not exclude the contribution of other exercise-related factors.

From a safety perspective, Lac-Phe at physiological concentrations appears to exhibit a neutral metabolic profile in animal studies, without effects on energy expenditure, locomotor activity, hormonal parameters, or signs of visceral discomfort. In contrast, cellular models indicate potential adverse effects under supraphysiological exposure, including impairment of insulin signaling and enhanced inflammatory responses. Additional beneficial effects of Lac-Phe have been reported in models of spinal cord injury, where reductions in lipid accumulation and inflammation were observed, although the clinical relevance of these findings remains uncertain.

Mechanistic data point to the involvement of central appetite-regulating pathways, particularly inhibition of hypothalamic AgRP neurons via KATP channels; however, these mechanisms have been confirmed mainly in preclinical models. Alternative approaches to increasing Lac-Phe synthesis, including the influence of specific nutrients and phytochemical compounds on CNDP2 expression, are of interest from a metabolic standpoint but currently lack evidence of clinical applicability.

Overall, the existing body of evidence supports viewing Lac-Phe as a marker and potential modulator of exercise-related metabolic adaptations rather than as an independent therapeutic agent for obesity treatment. Future research should focus on clarifying its role in human appetite regulation, assessing long-term effects, and determining its clinical relevance within comprehensive non-pharmacological and pharmacological strategies for body weight management.

## DISCLOSURE

### AUTHORS' CONTRIBUTIONS

Conceptualization and methodology: Dominika Raether, Adam Andrzejewski

Literature review and data extraction: Dominika Raether, Adam Andrzejewski

Writing - original draft preparation: Dominika Raether, Adam Andrzejewski

Writing - review and editing: Dominika Raether, Adam Andrzejewski, Aleksandra Markuszewska, Julia Wendt, Agnieszka Anna Bugała, Urszula Chmielecka, Olga Wcisłek

All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

### CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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### USE OF AI

Artificial Intelligence had been used for the purpose of style and language correction.

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