MLS – HEALTH & NUTRITION RESEARCH (MLSHNR)
http://mlsjournals.com/Health&nutritionrsearch-Journal
ISSN: 2603-5820
(2024) MLS-Health & Nutrition Research, 3(2), 166-183. doi.org/10.60134/mlshn.v3n1.2908

Macronutrient intake distribution according to circadian rhythms to enhance weight loss in overweight and obese individualss

Distribución de la ingesta de macronutrientes según los ritmos circadianos para potenciar la pérdida de peso en individuos con sobrepeso y obesidad

Lara Lozano Carrasco
European University of the Atlantic, Spain (lara.lozano@alumnos.uneatlantico.es)
(http://orcid.org/0009-0009-1028-9729)

Manuscript information:

Received/Recibido:11/06/24
Reviewed/Revisado: 02/07/24
Accepted/Aceptado: 04/11/24

Key words:
Chrononutrition, obesity, weightloss, macronutrients and circadian rhytms

ABSTRACT

(The progression of obesity has emerged as a global health issue in recent years. In response, new nutritional approaches, such as synchronizing macronutrient intake with circadian rhytms, have been explored as potentially effective strategies for improving body composition and promoting weight loss. The aim of this study is to determine the best times of day to consume each macronutrient to optimize weight loss. To achieve this, an exhaustive bibliographic review was carried out, selecting and analyzing a total of 14 articles published in the last five years from the Pubmed database, along with using the Google search engine for official pages. The results suggest that the nutritional composition of meals and their consumption timing during the day are effective dietary strategies for weight loss. Although further research is needed for more precisely define the optimal times for the intake of each macronutrient, it can be concluded that consuming macronutrients at specific time of the day may be an effective nutritional strategy to improve body composition and promote weight loss in individuals with overweight and obesity.

Palabras clave:
Crononutrición, obesidad, pérdida de peso, macronutrientes y ritmos circadianos.

RESUMEN

La progresión de la obesidad ha resaltado como un problema de salud global en los últimos años. En respuesta, se han explorado nuevos enfoques nutricionales, como la sincronización de la ingesta de macronutrientes con los ritmos circadianos, que podrían ser estrategias efectivas para mejorar la composición corporal y promover la pérdida de peso. El objetivo de este estudio es determinar los mejores momentos del día para consumir cada macronutriente con el fin de optimizar la pérdida de peso. Para ellos, se realizó una revisión bibliográfica exhaustiva, seleccionando y analizando un total de 14 artículos publicados de los últimos cinco años en la base de datos de PubMed. Además del uso del buscador de Google para páginas oficiales. Los resultados sugieren que tanto la composición nutricional de las comidas como el momento de su

consumo durante el día son estrategias dietéticas efectivas para la pérdida de peso. Aunque se requieren más investigaciones para definir con mayor precisión los momentos óptimos para la ingesta de cada macronutriente, sin embargo, se puede concluir que consumir macronutrientes en momentos específicos del día puede ser una estrategia nutricional efectiva para mejorar la composición corporal y promover la pérdida de peso en individuos con sobrepeso y obesidad.

Introduction

Obesity, defined as the abnormal or excessive accumulation of fat, is a global public health problem caused by multiple factors (1–3).Despite efforts focused on traditional risks such as excessive energy intake and lack of physical activity, obesity rates have increased in recent decades (1,2,4)recently, new factors such as the nutritional composition of meals and circadian misalignment have been identified that may contribute to the development of obesity (5,6).

Circadian rhythms, present in mammals, adapt to environmental changes on a 24-hour cycle and are essential for metabolic well-being(7–9).Recent studies suggest that energy regulation is linked to the circadian clock, and that the timing and composition of intake may influence obesity. Although the evidence is uncertain, understanding circadian clocks and their relationship to meal timing and composition may be an effective dietary approach to improving the quality of life for people with obesity (5,10).

General Objective: Define the best intake stages for each macronutrient according to circadian rhythms to drive weight loss.

Obesity

Obesity is a chronic disease characterized by an excessive accumulation of fat, which causes low-grade inflammation and can lead to cardiovascular disease, diabetes, musculoskeletal disorders and cancer (7,8). This inflammation, called lipoinflammation, associated with an increase in inflammatory factors and tissue infiltration, which perpetuates obesity and decreases satiety capacity (11). Fat accumulation causes hypertrophy and hyperplasia of adipocytes, leading to insulin resistance and dysfunctional tissue (9,10,12).

In Spain, in 2023, the prevalence of overweight in adults was 55.8% and of obesity 18.7% (4). Obesity is conditioned by multiple factors such as susceptibility in childhood and adolescence, a positive energy balance, genetic and socioeconomic factors, endocrine diseases, hypothalamic alterations, drugs and the chronodisruption of circadian rhythms (1,13,14).

Chrononutrition

The human circadian system generates and synchronizes circadian rhythms with the environment through a network of peripheral oscillators, with its regulatory center in the suprachiasmatic nucleus (SCN) of the hypothalamus (7–9). Light is the main synchronizer of the CNS, transmitting information through retinal ganglion cells and using the hormone melatonin to regulate the biological clock through membrane receptors, especially MTNR1B in the islets of the pancreas and retina (15–20).

In addition to light, other factors such as fasting/eating cycles, activity/rest, and temperature can also influence circadian regulation (8,9,21). At the molecular level, the ´´CLOCK´´ clock genes control the expression of circadian rhythms through transcriptional feedback mechanisms and transductions, forming complexes that inhibit their own synthesis in approximately 24-hour cycles (12,19,22).

The connection between the circadian clock and metabolism is explained by the ability of clock genes to activate transcription factors that influence human metabolism (21,23). This mechanism varies among individuals according to factors such as age and chorotype, which determines sleep and activity patterns and can be influenced by gender, age and diet of the individual (23–25).

Carbohydrate Metabolism

Carbohydrates (CH) are essential biomolecules in human metabolism, mainly as a source of energy, with glucose being the most prominent molecule (26). Vital organs such as the heart, liver, kidneys and brain depend on glucose for their function (27,28). The body can produce glucose by gluconeogenesis in the absence of adequate intake and store it as glycogen in the liver and muscles for use during periods of high energy demand (18,26,27,29,30). Although part of the glucose is stored internally, a fraction remains in the blood, the concentration of which is strictly regulated to avoid hyperglycemia and hypoglycemia (26,31).

Glucose fluctuations, known as glycemic variability, depend on health and dietary factors (32–34). Glucose levels rise and fall within 1-2 hours after insulin administration (33–35). Although glycemic variability can cause harm if peaks are high and persistent, or troughs are slow, it is generally regulated by insulin and glucagon (23,32,34–36).

Glucagon promotes the release of glucose from the liver during fasting, while insulin facilitates the entry of glucose into cells after ingestion (37,38). In type 2 diabetes (DM2), insulin is not used efficiently, causing blood glucose accumulation and conversion to fat, especially in the abdomen and hips, contributing to obesity. Obesity in turn causes insulin resistance and can lead to DM2 if not corrected (36,39–41).

Glycemic variability varies throughout the day due to factors such as the timing and composition of meals, as well as melatonin levels (19,33,42). Melatonin, which increases at night, suppresses insulin release, decreases insulin sensitivity and is related to weight gain and hunger and satiety patterns (33,34,43,44). A study by Martorina et al. (33) found no significant difference in glycemic variability between people with DM2 supplemented with melatonin and those who produced melatonin endogenously, although there was a decrease in significance between the groups according to their chronotype (33).

The action of melatonin receptor (MTNR1B) (43) and the rs1080963 polymorphism, especially the G allele, are related to fasting glucose levels and melatonin expression in pancreatic islets (20,42–44). This allele is also associated with measures of adiposity and weight loss, Goni et al. (44). Studies suggest that high concentrations of melatonin negatively affect glucose tolerance. Garaulet et al. (43) found that carriers of the G allele were at increased risk of developing DM2, which may help to better understand the effects of melatonin on glucose metabolism, sleep disturbances, and breakfast glycemic response (33,34,43,44).

Lipid Metabolism

Fats are essential components in the human body, essential for the storage of energy, the synthesis of vitamins, hormones, bile salts and cell membranes, and the regulation of cell signaling (45–47). There are two metabolic processes for handling fats: lipid anabolism (lipogenesis) and lipid catabolism (lipolysis) (47). Lipogenesis, which occurs mainly in the liver and adipose tissue, involves the formation of complex lipids to store energy and form cell membranes (48–50). Lipolysis, enhanced during fasting or exercise, breaks down lipids to produce energy and metabolites (49–52). Specific enzymes regulate these processes to maintain energy balance. However, diseases affecting these enzymes can disrupt fat storage and cause cellular and tissue damage, especially in the brain, liver and bone marrow (49,52).

Fatty acids, the building blocks of lipids, are stored in adipocytes to form adipose tissue (AT), (5,11,53), which is classified into white (WAT), brown (BAT) and beige (BW) adipose tissue (54–59). The BAT, characterized by mitochondria with cytochromes, regulates body temperature and is found mainly in the central region of

the body, developing in the neonatal stage and transforming into WAT with time (56–61). The WAT is unilocular, composed of a large lipid droplet and some mitochondria, and is subdivided into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) (55,57,59,62). TAS is located under the skin, mainly in the trunk and middle area in men and in the hips and buttocks in women (62). HAT surrounds the internal organs in the abdominal cavity and is associated with serious health problems such as insulin resistance and cardiovascular disease (18,57,62).

Melatonin plays a key role in adipocyte regulation, influencing lipolysis and lipogenesis (48,51,63,64). Activates brown adipose tissue, participates in browning of white adipose tissue and regulates energy expenditure and intake (57,58,64). Initial research on hormones in adipose tissue revealed their importance in appetite and energy balance (65). De Luis et al. (66) observed that a high-fat diet affects the expression of endogenous rhythms such as leptin. Studying the expression of clock genes in human adipose tissue has helped to understand their influence on obesity (64,65). In addition, the variation of lipid profiles in individuals with DM2 (67,68) and the impact of breakfast on glycemic control were investigated. The studies by Oliveira et al. (67) and Chang et al. (68) suggest that breakfast composition influences energy balance, associated with the MTRN1B gene (20,66). Polymorphisms in this gene, such as the GC genotype, affect blood lipid concentrations, especially cholesterol, indicating that these polymorphisms may influence the metabolic response to diet and the regulation of adipose tissue (66,69).

Protein Metabolism

Proteins, made up of amino acids, have essential functions in the body, such as the formation of structures and the regulation of organs and tissues (70–72). Protein metabolism includes transamination (73), a process in the liver where an amino group is transferred from an amino acid to an alpha-keto acid, facilitated by transaminases and aminotransferases (72–74). This process aids in the elimination of the amino group, the creation of new amino acids and alpha-keto acids, and their elimination in the urea cycle (72,73,75). Although rarely used for energy, it can occur in cases of high protein intake or prolonged starvation. Normally, amino acids are used in biosynthetic pathways, but an excess can lead to lipid synthesis (72,76).

Protein, stored mainly in skeletal muscle, is essential for protein replenishment, (77) is essential for protein replenishment (76) and plays a crucial role in mobility, metabolic homeostasis and thermogenesis (78). In addition, skeletal muscle secretes myokines that regulate metabolic and lipid functions (79–82). Disorders in protein synthesis and degradation can cause muscle atrophy and sarcopenia, associated with weakness, fatigue and decreased quality of life (78). Sarcopenia, associated with aging, chronic diseases such as cancer and obesity, is associated with falls, fractures and mortality (82–86). Sarcopenic obesity, linked to an increased risk of type 2 diabetes, results from fat accumulation in muscle, which disrupts insulin signaling, impairs insulin sensitivity, and promotes weight gain (80–87).

Sarcopenic obesity and circadian rhythms are closely related and have a significant impact on metabolic and muscle health (80–82). Dysregulation of circadian rhythms, often due to modern lifestyles, may contribute to the development of sarcopenic obesity by affecting the secretion of key hormones such as melatonin, cortisol and growth hormone (66,88,89). Melatonin, in addition to regulating sleep-wake cycles, has antioxidant and anti-inflammatory effects that protect muscle mass. The melatonin receptor MTNR1B is involved in the regulation of glucose and body weight. Studies such as De Luis et al. (90) suggest that a high protein intake, especially

at breakfast, may improve the synchronization of circadian rhythms and have beneficial effects on body composition and metabolic health (90,91). According to Douglas et al. (89) skipping breakfast or consuming foods of low nutritional value can negatively affect appetite control and increase caloric intake, which can impact nighttime glycemic response and overall metabolic health (24,92,93).

Method

Pubmed

The following filters were established: 5 years old and ´´ free full text´´. The following keywords were used:

(Carbohydrates [MeSH Terms] AND morning intake [MeSH Terms]: We found 3 randomized controlled articles, all 3 were used.

(Carbohydrates [MeSH Terms] AND circadian rhythms [MeSH Terms]: Five articles were found, 3 were read for the TFG, 2 were literature reviews that were excluded.

(Lipids [MeSH Terms] AND circadian rhytms [MeSH Terms]: A total of 6 articles were found, of which only 1 was used, since 5 met the inclusion criteria.

(Lipid [MeSH Terms] AND thermogenesis [MeSH Tems]: Giving 2 results and using only 1, since the other was a literature review.

(Lipid [MeSH Terms] AND evening [MeSH Terms]: It yielded 5 results, of which only 2 were used, the other 3 being literature reviews.

(Protein [MeSH Terms] AND obesity [MeSH Terms]: Three results were found, of which all three were used.

(Protein intake [MeSH Terms] AND muscle [MeSH Terms]: We found 2 outcomes and used the 2 randomized controlled trials.

Google Scholar

This search engine proved to be very useful to access full texts, articles or official websites, where the filter was applied to articles between 2019 and 2024.

Macronutrients distribution and obesity: 17300 results, using a total of 7 because of their relevance and because they met the inclusion criteria.

Morning carbohydrates: 1800 results, using a total of 5 that met the inclusion criteria.

Glycolysis and circadian rhythms: 12200 results, using a total of 4 relevant and meeting the inclusion criteria.

Protein intake and weight loss: 10200 results, with only 1 relevant patient meeting the inclusion criteria.

Results

For the reasons given above, chrononutrition may be of interest as a treatment for overweight and obese individuals. The studies that deal with this association are shown in **Table 1.**

Table 1. Table on the association between macronutrients, circadian rhythms and weight loss. Own elaboration.

Reference	Type of study, sample size and characteristics Target	Study groups	Results
Garaulet et al(43)	Randomized controlled trial 845 participants	Conditions: -EE (early dinner) -LE (late dinner)	Higher average melatonin values in LE compared to EE. 3.5 times more. No significant differences between age, sex, adiposity, bedtime and dinnertime. Glucose concentrations were highest in GG, followed by GC and CC. Melatonin levels modulated insulin secretion in all genotype groups. If insulin concentrations decreased, only CG decreased insulin secretion under LE conditions.
Oliveira et al (67)	Randomized controlled trial 82 subjects with DM2 ≥1 year	G1: 41 with a low CH and high fat diet G2: 41 with a diet low in fat and rich in CH	Changes from initial calorie intake Body weight and BMI changes Glycemic changes between the first and last 14 days of intervention.
Sinturiel et al (69)	Cohort study 6 participants Men with and without obesity.	DN: thin DM: Diabetes and obesity	Significant differences in lipid profiles between lean men and men with DM2. Greater variation, especially at wake-up time (6:30-8:00)

			Differences between men and women with DM2. Alteration of SAT lipids in DM2 associated with changes in gene expression related to lipid metabolism and significant variation throughout the day.
Dalgaard et al (93)	Randomized controlled trial 30 young women	Two breakfasts - High in protein (PRO) - High in CH (CHO) -Control day (CON)	There are no differences in the amount of food ingested after test breakfasts. Similar glucose marker levels on all experimental days. After consumption of breakfast CHO and PRO, glucose and insulin levels increased more than after CHO. Lower glucose in PRO than with CHO. No difference between insulin levels between PRO and CHO.
Cunha et al (92)	Randomized controlled trial 14-night workers	HP-MCHO diet (high protein) LP-HCHO diet (low protein)	No significant differences in nutritional characteristics were shown between the two study protocols. The HP-MCHO condition observed lower post-meal glucose values. Both HP-MCHO and LP-HCHO breakfasts elicited similar metabolic responses in terms of glucose, insulin, triglycerides and HOMA-IR.

First, four studies on carbohydrates and circadian rhythm were reviewed (33,34,43,44), three of which were clinical trials suggesting an association between glycemic response variability and interaction with melatonin, especially at night (33,43,44), especially at night. However, (34) the effects in relation to melatonin secretion were not directly examined, but the consequences of the intake of different macronutrients on rest was studied. (33), in a randomized clinical trial, found no significant difference in the glycemic variability of individuals with DM2 and melatonin, which could be due to the lack of specific meals in their study. On the other hand, (43) showed a correlation between late dinners and glucose tolerance, similar results to those of (34) who showed that glucose consumption before bedtime increased insulin sensitivity and worsened sleep (34,43). In addition, no significant relationship was found between genotype, BMI, and sex with glycemic response, although significant variations by ethnicity were observed in the studies of (34) and (44). Secondly, fat metabolism and

chrononutrition were addressed, where (68) and (67) contradictory results were obtained on the effects of melatonin on adipose tissue (67,68), suggested that a low-carbohydrate diet at breakfast had a significant impact with respect to an isocaloric diet, while (67) found a non-significant glycemic variability between the diets (67,68). The differences may be due to the design of the studies, the sample and the duration: the study of (68) lasted three months and was conducted in Canada, whereas the study of (67) lasted only one day and included participants from Canada and Australia. (de Luis et al., 2020) also observed variations in blood lipid concentrations, especially in individuals with the CC genotype of the MTNR1B polymorphism, with significant changes in the morning, coinciding with the findings of (69). Third, results on protein metabolism and circadian rhythms were discussed. Studies such as that of (93) and (89) showed that there were no significant differences in the sensation of hunger and satiety between protein and isocaloric diets, although women who consumed more protein at breakfast had a lower need to eat during the day. Both studies observed non-significant differences in the hormonal response of ghrelin, CCK and GLP-1, as well as a decrease in leptin levels (92,93). Despite these findings, no information was obtained on the effect in men, in DM2 and long term studies, such as the one in (92), possibly due to differences in the study subjects, (24) took into account the chronotype of the individuals, suggesting that nighttime food consumption is associated with higher BMI and higher fat percentage.

Discussion and Conclusions

The results suggest that both the nutritional composition of meals and the timing of meal consumption during the day are effective dietary strategies for weight loss. Although more research is needed to define more precisely the optimal times for the intake of each macronutrient, it can be concluded that consuming macronutrients at specific times of the day can be an effective nutritional strategy to improve body composition and promote weight loss in overweight and obese individuals.

Once the articles have been read, some limitations could be taken into account for the development of future research, the following points are proposed:

To improve the quality and relevance of studies in metabolic health and body composition, it is essential to implement several important changes in research methodology.

First, it is essential to broaden the diversity of the samples to include a more equitable representation of different demographic groups, ages, genders and ethnicities. This diversification will allow a deeper understanding of the effects of biological and sociocultural variables on the results, ensuring that the conclusions are more generalizable and applicable to a broader population.

In addition, it is crucial to incorporate a greater number of long-term studies. These studies are necessary to evaluate the sustained effects over time of interventions on metabolic health and body composition. The collection of data over time will provide valuable information on the efficacy and durability of interventions, allowing the development of more effective strategies for the management and prevention of metabolic problems.

Another important aspect to consider is the inclusion of a greater number of women in the interventions. It is vital to explore the metabolic variations that exist between women and men, such as the influences of menstruation on metabolism.

Understanding these differences will allow the design of more personalized and effective interventions for both genders.

It is also necessary to evaluate the influence of the time of year on the studies. Time changes, such as summer and winter time, can alter the circadian rhythm, especially affecting breakfast and dinner times. Analyzing how these seasonal changes influence outcomes will allow interventions to be adjusted to be more precise and effective, taking into account variations in people's biological rhythms.

Conflict of Interest

I declare that the work submitted for publication in the journal mls health & nutrition research is original and has not been and is not currently under evaluation in any journal or conference. Likewise, I am responsible for the content of the same and I agree that my name appears as the author. Finally, I declare that I have no conflict of interest in those activities that could introduce bias in the results of the work.

References

1. Sobrepeso y obesidad - Causas y factores de riesgo | NHLBI, NIH [Internet]. 2022 [citado 21 de marzo de 2024]. Retrieved from: https://www.nhlbi.nih.gov/es/salud/sobrepeso-y-obesidad/causas
2. Kaufer-Horwitz M, Pérez Hernández JF, Kaufer-Horwitz M, Pérez Hernández JF. La obesidad: aspectos fisiopatológicos y clínicos. Inter disciplina. abril de 2022;10(26):147-75. Retrieved from: https://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S2448-57052022000100147
3. Obesidad y sobrepeso [Internet]. [citado 15 de febrero de 2024]. Retrieved from: https://www.who.int/es/news-room/fact-sheets/detail/obesity-and-overweight
4. World Obesity Federation [Internet]. [citado 17 de mayo de 2024]. World Obesity Atlas 2022. Retrieved from: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022
5. San-Cristobal R, Navas-Carretero S, Martínez-González MÁ, Ordovas JM, Martínez JA. Contribution of macronutrients to obesity: implications for precision nutrition. Nat Rev Endocrinol. junio de 2020;16(6):305-20. Retrieved from : https://pubmed.ncbi.nlm.nih.gov/32235875/
6. Vujović N, Piron MJ, Qian J, Chellappa SL, Nedeltcheva A, Barr D, et al. Late isocaloric eating increases hunger, decreases energy expenditure, and modifies metabolic pathways in adults with overweight and obesity. Cell Metab. 4 de octubre de 2022;34(10):1486-1498.e7. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36198293/
7. Trastornos del ritmo circadiano - ¿Qué son los trastornos del ritmo circadiano? | NHLBI, NIH [Internet]. 2022 [citado 16 de abril de 2024]. Retrieved from: https://www.nhlbi.nih.gov/es/salud/trastornos-del-ritmo-circadiano

8. Fisiología, ritmo circadiano - StatPearls - NCBI Bookshelf [Internet]. [citado 16 de abril de 2024]. Retrieved from: https://www.ncbi.nlm.nih.gov/books/NBK519507/
9. Kessler K, Pivovarova-Ramich O. Meal Timing, Aging, and Metabolic Health. International Journal of Molecular Sciences. enero de 2019;20(8):1911. Retrieved from: https://www.mdpi.com/1422-0067/20/8/1911
10. Chamorro R, Farias R, Peirano P, Chamorro R, Farias R, Peirano P. Circadian rhythms, eating patterns, and sleep: A focus on obesity. Revista chilena de nutrición. septiembre de 2018;45(3):285-92. Retrieved from: https://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0717-75182018000400285
11. González-Jurado JA, Suárez-Carmona W, López S, Sánchez-Oliver AJ. Changes in Lipoinflammation Markers in People with Obesity after a Concurrent Training Program: A Comparison between Men and Women. Int J Environ Res Public Health. septiembre de 2020;17(17):6168. Retrieved from : https://pubmed.ncbi.nlm.nih.gov/32854366/
12. Cox KH, Takahashi JS. Circadian Clock Genes and the Transcriptional Architecture of the Clock Mechanism. J Mol Endocrinol. noviembre de 2019;63(4):R93-102. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6872945/
13. Hammarstedt A, Gogg S, Hedjazifar S, Nerstedt A, Smith U. Impaired Adipogenesis and Dysfunctional Adipose Tissue in Human Hypertrophic Obesity. Physiol Rev. 1 de octubre de 2018;98(4):1911-41. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30067159/
14. Moreno-Cortés ML, Meza-Alvarado JE, García-Mena J, Hernández-Rodríguez A. Chronodisruption and Gut Microbiota: Triggering Glycemic Imbalance in People with Type 2 Diabetes. Nutrients. 23 de febrero de 2024;16(5):616. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38474745/
15. Triguero DLL. Ritmo circadiano sueño-vigilia: sutilidad, salud y enfermedad - Neuroexeltis España [Internet]. 2022 [citado 22 de abril de 2024]. Retrieved from: https://neuroexeltis.es/editorial/ritmo-circadiano-sueno-vigilia/
16. Blume C, Garbazza C, Spitschan M. Effects of light on human circadian rhythms, sleep and mood. Somnologie (Berl). 2019;23(3):147-56. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31534436/
17. Lax P, Ortuño-Lizarán I, Maneu V, Vidal-Sanz M, Cuenca N. Photosensitive Melanopsin-Containing Retinal Ganglion Cells in Health and Disease: Implications for Circadian Rhythms. International Journal of Molecular Sciences. enero de 2019;20(13):3164. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31261700/
18. Peng F, Li X, Xiao F, Zhao R, Sun Z. Circadian clock, diurnal glucose metabolic rhythm, and dawn phenomenon. Trends Neurosci. junio de 2022;45(6):471-82. Retrieved from : https://pubmed.ncbi.nlm.nih.gov/35466006/
19. Speksnijder EM, Bisschop PH, Siegelaar SE, Stenvers DJ, Kalsbeek A. Circadian desynchrony and glucose metabolism. Journal of Pineal Research. 2024;76(4):e12956. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38695262/
20. Efectos de la melatonina en el metabolismo de la glucosa - Noticias médicas - IntraMed [Internet]. [citado 31 de mayo de 2024]. Retrieved from: https://www.intramed.net/contenidover.asp?contenidoid=96854
21. Zlacká J, Zeman M. Glycolysis under Circadian Control. International Journal of Molecular Sciences. enero de 2021;22(24):13666. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8703893/

22. Ashbrook LH, Krystal AD, Fu YH, Ptáček LJ. Genetics of the human circadian clock and sleep homeostat. Neuropsychopharmacol. enero de 2020;45(1):45-54. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31400754/
23. Shukla AP, Dickison M, Coughlin N, Karan A, Mauer E, Truong W, et al. The impact of food order on postprandial glycaemic excursions in prediabetes. Diabetes Obes Metab. febrero de 2019;21(2):377-81. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31400754/
24. Xiao Q, Garaulet M, Scheer FAJL. Meal timing and obesity; interactions with macronutrient intake and chronotype. Int J Obes (Lond). septiembre de 2019;43(9):1701-11. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30705391/
25. Vidmar AP, Jones RB, Wee CP, Berger PK, Plows JF, Claudia Rios RD, et al. Timing of food consumption in Hispanic adolescents with obesity. Pediatric Obesity. 2021;16(7):e12764. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33370849/
26. Examen de glucemia: MedlinePlus enciclopedia médica [Internet]. [citado 16 de abril de 2024]. Retrieved from: https://medlineplus.gov/spanish/ency/article/003482.htm
27. Enríquez Meza R. La glucosa en el cuerpo humano. Revista Institucional Tiempos Nuevos. 2020;25(27):43-53. Retrieved from: https://dialnet.unirioja.es/servlet/articulo?codigo=8993413
28. Glucosa en la sangre [Internet]. National Library of Medicine; [citado 17 de abril de 2024]. Retrieved from: https://medlineplus.gov/spanish/bloodglucose.html
29. Carbohidratos en la dieta [Internet]. National Library of Medicine; [citado 24 de marzo de 2024]. Retrieved from: https://medlineplus.gov/spanish/carbohydrates.html
30. Definición de gluconeogénesis - Diccionario de cáncer del NCI - NCI [Internet]. 2011 [citado 19 de mayo de 2024]. Retrieved from: https://www.cancer.gov/espanol/publicaciones/diccionarios/diccionario-cancer/def/gluconeogenesis
31. Mayo Clinic [Internet]. [citado 17 de abril de 2024]. Hiperglucemia en la diabetes-Hiperglucemia en la diabetes - Síntomas y causas. Retrieved from: https://www.mayoclinic.org/es/diseases-conditions/hyperglycemia/symptoms-causes/syc-20373631
32. Rico Fontalvo JE, Daza Arnedo R, Pájaro N, Leal Martínez V, Abuabara Franco E, Pérez Calvo C, et al. Variabilidad glicémica y su impacto cardiovascular y renal. Archivos de medicina. 2020;16(6):2. Retrieved from: https://www.itmedicalteam.pl/articles/variabilidad-gliceacutemica-y-su-impacto-cardiovascular-y-renal-103490.html
33. Martorina W, Tavares A. Glycemic Variability in Patients with Type 2 Diabetes Mellitus (T2DM): The Role of Melatonin in a Crossover, Double-Blind, Placebo-Controlled, Randomized Study. Nutrients. 10 de agosto de 2023;15(16):3523. Retrieved from : https://www.mdpi.com/2072-6643/15/16/3523
34. Tsereteli N, Vallat R, Fernandez-Tajes J, Delahanty LM, Ordovas JM, Drew DA, et al. Impact of insufficient sleep on dysregulated blood glucose control under standardised meal conditions. Diabetologia. 2022;65(2):356-65. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34845532/
35. Sun B, Luo Z, Zhou J. Comprehensive elaboration of glycemic variability in diabetic macrovascular and microvascular complications. Cardiovasc Diabetol. 7 de enero de 2021;20:9. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33413392/
36. Sbraccia P, D'Adamo M, Guglielmi V. Is type 2 diabetes an adiposity-based metabolic disease? From the origin of insulin resistance to the concept of dysfunctional adipose

tissue. Eat Weight Disord. diciembre de 2021;26(8):2429-41. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33555509/
37. Regulación de los niveles de glucosa en sangre - Labster [Internet]. [citado 16 de abril de 2024]. Retrieved from: https://theory.labster.com/es/regulation-blood-glucose/
38. Rahman MS, Hossain KS, Das S, Kundu S, Adegoke EO, Rahman MdA, et al. Role of Insulin in Health and Disease: An Update. Int J Mol Sci. 15 de junio de 2021;22(12):6403. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8232639/
39. Wondmkun YT. Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. Diabetes Metab Syndr Obes. 9 de octubre de 2020;13:3611-6. Disponible: https://pubmed.ncbi.nlm.nih.gov/33116712/
40. Leyva Montero M de los Á, Rodríguez Moldón Y, Rodríguez Duque R, Niño Escofet S, Leyva Montero M de los Á, Rodríguez Moldón Y, et al. Mecanismos moleculares de la secreción de insulina. Correo Científico Médico. junio de 2020;24(2):764-80. Retrieved from: https://revcocmed.sld.cu/index.php/cocmed/article/view/3547
41. Utzschneider KM, Johnson TN, Breymeyer KL, Bettcher L, Raftery D, Newton KM, et al. Small changes in glucose variability induced by low and high glycemic index diets are not associated with changes in β-cell function in adults with pre-diabetes,. J Diabetes Complications. agosto de 2020;34(8):107586. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32546421/
42. Mason IC, Qian J, Adler GK, Scheer FAJL. Impact of circadian disruption on glucose metabolism: implications for type 2 diabetes. Diabetologia. marzo de 2020;63(3):462-72. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31915891/
43. Garaulet M, Lopez-Minguez J, Dashti HS, Vetter C, Hernández-Martínez AM, Pérez-Ayala M, et al. Interplay of Dinner Timing and MTNR1B Type 2 Diabetes Risk Variant on Glucose Tolerance and Insulin Secretion: A Randomized Crossover Trial. Diabetes Care. 1 de marzo de 2022;45(3):512-9. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35015083/
44. Goni L, Sun D, Heianza Y, Wang T, Huang T, Martínez JA, et al. A circadian rhythm-related MTNR1B genetic variant modulates the effect of weight-loss diets on changes in adiposity and body composition: The POUNDS Lost trial. Eur J Nutr. junio de 2019;58(4):1381-9. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29516223/
45. Bioquímica, Lípidos - StatPearls - NCBI Bookshelf [Internet]. [citado 24 de marzo de 2024]. Retrieved from: https://www.ncbi.nlm.nih.gov/books/NBK525952/
46. issuu [Internet]. [citado 22 de mayo de 2024]. EL METABOLISMO LIPÍDICO Y SUS PATOLOGÍAS. Autores: David Cuevas Gómez, Cecilia Cueto Felgueroso Ojeda. Retrieved from: https://issuu.com/bioquimica.analisis.12.octubre/docs/clin12lab_2021_isbn/s/12273878
47. Chandel NS. Lipid Metabolism. Cold Spring Harb Perspect Biol. septiembre de 2021;13(9):a040576. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8411952/
48. Lipogénesis [Internet]. [citado 23 de mayo de 2024]. Retrieved from: https://www.quimica.es/enciclopedia/Lipog%C3%A9nesis.html
49. Metabolismo de lípidos: una descripción general | Temas ScienceDirect [Internet]. [citado 23 de mayo de 2024]. Retrieved from: https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/lipid-metabolism

50. Enfermedades de almacenamiento de lípidos | NINDS Español [Internet]. [citado 23 de mayo de 2024]. Retrieved from: https://espanol.ninds.nih.gov/es/trastornos/forma-larga/enfermedades-de-almacenamiento-de-lipidos
51. Lipolisis [Internet]. [citado 23 de mayo de 2024]. Retrieved from: https://www.quimica.es/enciclopedia/Lipolisis.html
52. Natesan V, Kim SJ. Lipid Metabolism, Disorders and Therapeutic Drugs – Review. Biomol Ther (Seoul). 1 de noviembre de 2021;29(6):596-604. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34697272/
53. Russo S, Kwiatkowski M, Govorukhina N, Bischoff R, Melgert BN. Meta-Inflammation and Metabolic Reprogramming of Macrophages in Diabetes and Obesity: The Importance of Metabolites. Front Immunol. 2021;12:746151. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34804028/
54. Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S, Stewart AJ, et al. Leptin and Obesity: Role and Clinical Implication. Front Endocrinol (Lausanne). 18 de mayo de 2021;12:585887. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34084149/
55. White Adipose Tissue - an overview | ScienceDirect Topics [Internet]. [citado 23 de mayo de 2024]. Retrieved from: https://www.sciencedirect.com/topics/medicine-and-dentistry/white-adipose-tissue
56. Tejido adiposo beige: descripción general | Temas ScienceDirect [Internet]. [citado 23 de mayo de 2024]. Retrieved from: https://www.sciencedirect.com/topics/medicine-and-dentistry/beige-adipose-tissue
57. Cheng L, Wang J, Dai H, Duan Y, An Y, Shi L, et al. Brown and beige adipose tissue: a novel therapeutic strategy for obesity and type 2 diabetes mellitus. Adipocyte. 10(1):48-65. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33403891/
58. Liu X, Zhang Z, Song Y, Xie H, Dong M. An update on brown adipose tissue and obesity intervention: Function, regulation and therapeutic implications. Front Endocrinol (Lausanne). 11 de enero de 2023;13:1065263. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36714578/
59. Palacios-Marin I, Serra D, Jimenez-Chillarón J, Herrero L, Todorčević M. Adipose Tissue Dynamics: Cellular and Lipid Turnover in Health and Disease. Nutrients. 14 de septiembre de 2023;15(18):3968. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37764752/
60. Jung SM, Sanchez-Gurmaches J, Guertin DA. Brown Adipose Tissue Development and Metabolism. Handb Exp Pharmacol. 2019;251:3-36. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30203328/
61. Bienboire-Frosini C, Wang D, Marcet-Rius M, Villanueva-García D, Gazzano A, Domínguez-Oliva A, et al. The Role of Brown Adipose Tissue and Energy Metabolism in Mammalian Thermoregulation during the Perinatal Period. Animals (Basel). 1 de julio de 2023;13(13):2173. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37443971/
62. Mittal B. Subcutaneous adipose tissue & visceral adipose tissue. Indian J Med Res. mayo de 2019;149(5):571-3. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31417024/
63. Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA, et al. Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications. Int J Mol Sci. 13 de mayo de 2019;20(9):2358. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31085992/

64. Halpern B, Mancini MC, Bueno C, Barcelos IP, de Melo ME, Lima MS, et al. Melatonin Increases Brown Adipose Tissue Volume and Activity in Patients With Melatonin Deficiency: A Proof-of-Concept Study. Diabetes. 14 de febrero de 2019;68(5):947-52. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30765337/
65. Protective Effects of Melatonin against Obesity-Induced by Leptin Resistance - PubMed [Internet]. [citado 31 de mayo de 2024]. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34563600/
66. de Luis DA, Izaola O, Primo D, Aller R. Efecto del polimorfismo rs10830963 MTNR1B y la composición de grasa de la dieta en la resistencia a la insulina tras la pérdida de peso durante 3 meses. Endocrinol Diabetes Nutr. 1 de enero de 2020;67(1):43-52. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30765337/
67. Oliveira BF, Chang CR, Oetsch K, Falkenhain K, Crampton K, Stork M, et al. Impact of a Low-Carbohydrate Compared with Low-Fat Breakfast on Blood Glucose Control in Type 2 Diabetes: A Randomized Trial. The American Journal of Clinical Nutrition. 1 de julio de 2023;118(1):209-17. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37257563/
68. Chang CR, Francois ME, Little JP. Restricting carbohydrates at breakfast is sufficient to reduce 24-hour exposure to postprandial hyperglycemia and improve glycemic variability. Am J Clin Nutr. mayo de 2019;109(5):1302-9. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30968140/
69. Sinturel F, Chera S, Brulhart-Meynet MC, Montoya JP, Stenvers DJ, Bisschop PH, et al. Circadian organization of lipid landscape is perturbed in type 2 diabetic patients. Cell Rep Med. 27 de noviembre de 2023;4(12):101299. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38016481/
70. Protein [Internet]. [citado 24 de marzo de 2024]. Retrieved from: https://www.genome.gov/genetics-glossary/Protein
71. What are proteins and what do they do?: MedlinePlus Genetics [Internet]. [citado 24 de marzo de 2024]. Retrieved from: https://medlineplus.gov/genetics/understanding/howgeneswork/protein/
72. https://www.cun.es [Internet]. [citado 25 de mayo de 2024]. Proteínas en la dieta. Nutrición y salud. Clínica Universidad Navarra. Retrieved from: https://www.cun.es/chequeos-salud/vida-sana/nutricion/proteinas
73. https://www.cun.es [Internet]. [citado 24 de mayo de 2024]. ¿Qué es Transaminación? Diccionario Médico - Clínica U. Navarra. Retrieved from: https://www.cun.es/diccionario-medico/terminos/transaminacion
74. https://www.cun.es [Internet]. [citado 25 de mayo de 2024]. Aminotransferasa. Diccionario médico. Clínica Universidad de Navarra. Retrieved from: https://www.cun.es/diccionario-medico/terminos/aminotransferasa
75. Anomalía hereditaria del ciclo de la urea: MedlinePlus enciclopedia médica [Internet]. [citado 25 de mayo de 2024]. Retrieved from: https://medlineplus.gov/spanish/ency/article/000372.htm
76. Rose AJ. Amino Acid Nutrition and Metabolism in Health and Disease. Nutrients. 1 de noviembre de 2019;11(11):2623. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31683948/
77. Brooks SV, Guzman SD, Ruiz LP. Chapter 1 - Skeletal muscle structure, physiology, and function. En: Younger DS, editor. Handbook of Clinical Neurology [Internet]. Elsevier; 2023 [citado 25 de mayo de 2024]. p. 3-16. (Motor System Disorders, Part I: Normal Physiology and Function and Neuromuscular Disorders; vol. 195). Retrieved from: https://www.sciencedirect.com/science/article/pii/B9780323988186000133

78. Yin L, Li N, Jia W, Wang N, Liang M, Yang X, et al. Skeletal muscle atrophy: From mechanisms to treatments. Pharmacological Research. 1 de octubre de 2021;172:105807. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34389456/
79. Gomarasca M, Banfi G, Lombardi G. Myokines: The endocrine coupling of skeletal muscle and bone. Adv Clin Chem. 2020;94:155-218. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31952571/
80. Purnamasari D, Tetrasiwi EN, Kartiko GJ, Astrella C, Husam K, Laksmi PW. Sarcopenia and Chronic Complications of Type 2 Diabetes Mellitus. Rev Diabet Stud. 30 de septiembre de 2022;18(3):157-65. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36309772/
81. Chen H, Huang X, Dong M, Wen S, Zhou L, Yuan X. The Association Between Sarcopenia and Diabetes: From Pathophysiology Mechanism to Therapeutic Strategy. Diabetes Metab Syndr Obes. 30 de mayo de 2023;16:1541-54. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37275941/
82. Mesinovic J, Zengin A, De Courten B, Ebeling PR, Scott D. Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. Diabetes Metab Syndr Obes. 8 de julio de 2019;12:1057-72. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31372016/
83. Tournadre A, Vial G, Capel F, Soubrier M, Boirie Y. Sarcopenia. Joint Bone Spine. 1 de mayo de 2019;86(3):309-14. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30098424/
84. Supriya R, Singh KP, Gao Y, Gu Y, Baker JS. Effect of Exercise on Secondary Sarcopenia: A Comprehensive Literature Review. Biology (Basel). 30 de diciembre de 2021;11(1):51. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35053049/
85. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, et al. Definition and Diagnostic Criteria for Sarcopenic Obesity: ESPEN and EASO Consensus Statement. Obes Facts. 23 de febrero de 2022;15(3):321-35. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35196654/
86. Axelrod CL, Dantas WS, Kirwan JP. Sarcopenic obesity: emerging mechanisms and therapeutic potential. Metabolism. 1 de septiembre de 2023;146:155639. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37380015/
87. Ciudin A, Simó-Servat A, Palmas F, Barahona MJ. Sarcopenic obesity: A new challenge in the clinical practice. Endocrinol Diabetes Nutr. 1 de diciembre de 2020;67(10):672-81. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32565081/
88. Morrison M, Halson SL, Weakley J, Hawley JA. Sleep, circadian biology and skeletal muscle interactions: Implications for metabolic health. Sleep Medicine Reviews. 1 de diciembre de 2022;66:101700. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36272396/
89. Douglas SM, Byers AW, Leidy HJ. Habitual Breakfast Patterns Do Not Influence Appetite and Satiety Responses in Normal vs. High-Protein Breakfasts in Overweight Adolescent Girls. Nutrients. 29 de mayo de 2019;11(6):1223. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6628162/
90. de Luis DA, Izaola O, Primo D, Aller R. Efecto del polimorfismo rs10830963 MTNR1B y la composición de grasa de la dieta en la resistencia a la insulina tras la pérdida de peso durante 3 meses. Endocrinol Diabetes Nutr. 1 de enero de 2020;67(1):43-52. Retrieved from: https://www.elsevier.es/es-revista-endocrinologia-diabetes-nutricion-13-articulo-efecto-del-polimorfismo-rs10830963-mtnr1b-S253001641930062X
91. de Luis DA, Izaola O, Primo D, Aller R. A circadian rhythm-related MTNR1B genetic variant (rs10830963) modulate body weight change and insulin resistance after

9 months of a high protein/low carbohydrate vs a standard hypocaloric diet. J Diabetes Complications. abril de 2020;34(4):107534. Retrieved from: https://europepmc.org/article/med/32057567

92. Cunha NB, Silva CM, Mota MC, Lima CA, Teixeira KRC, Cunha TM, et al. A High-Protein Meal during a Night Shift Does Not Improve Postprandial Metabolic Response the Following Breakfast: A Randomized Crossover Study with Night Workers. Nutrients. julio de 2020;12(7):2071. Retrieved from: https://www.mdpi.com/2072-6643/12/7/2071
93. Dalgaard LB, Kruse DZ, Norup K, Andersen BV, Hansen M. A dairy-based protein-rich breakfast enhances satiety and cognitive concentration before lunch in young females with overweight to obesity: A randomized controlled cross-over study. J Dairy Sci. 20 de diciembre de 2023;S0022-0302(23)02014-3. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38135050/