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SUMARIO • SUMMARY • RESUMO

INVESTIGACIONES

Editorial

From the Editorial Board of the MLS Health and Nutritional Research journal, we continue to strengthen the transfer of scientific knowledge in the field of health, nutrition and food. We encourage you to continue sending us your articles in order to contribute to the advancement of knowledge.

The first article deals with "Chrononutrition: effect of time of intake on nutrient metabolism".
Nowadays, metabolic disorders are one of the most common conditions worldwide. This is why the study of the influence of the time of intake on the metabolism of a nutrient is of great importance for the development and application of new treatments for these diseases.

The following article discusses the "Impact of branched-chain amino acid (BCAA) intake on Type 2 Diabetes Mellitus. Elevated circulating levels of branched-chain amino acids (BCAA) have been described as a strong predictor of type 2 diabetes mellitus (DM2). The main objective is to evaluate whether a diet rich in these amino acids poses a risk for the development of DM2.

From the field of community nutrition "The feeding of university students and their learning during confinement by Covid -19, a look from the theories of learning: ecology of human development, constructivist and sociocultural". Food is a transversal axis for learning and academic achievement. The COVID-19 confinement, makes it necessary to generate new strategies that allow us to know this relationship between nutrition and academic performance, with the intention of improving the achievement of university students.
Related to "Effect of low-carbohydrate diet on body composition of individuals practicing strength-trained bodybuilding.". The low-carbohydrate diet has been studied, as it has shown significant results in the benefit of weight reduction, since it is composed mostly of proteins and natural fats with low inflammatory potential, also helping to reduce and combat fluid retention. This diet combined with strength training may help with muscle growth and reduce body fat.

The following study is in the field of clinical nutrition " e-health no acompanhamento de enfermagem a longo prazo de pacientes submetidos a cirurgia bariátrica - prevalência dos fatores de risco metabólico.". To analyze the effect of bariatric surgery, physical activity and weight regain on the long-term prevalence of metabolic risk factors using telemedicine.
Finally, "Omega-3 polyunsaturated fatty acid supplementation versus a Mediterranean diet as a treatment for non-alcoholic fatty liver disease". Non-alcoholic fatty liver disease (NAFLD) is becoming increasingly prevalent and is the leading liver disease worldwide. The aim is to

compare new dietary-nutritional strategies, such as the Mediterranean diet and omega-3 polyunsaturated fatty acids, to determine which is more effective as a treatment for this disease.

Editor-in-Chief
Dr. Iñaki Elío Pascual

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Conde, S. (2022). Crononutrición: efecto de la hora de la ingesta en el metabolismo de los nutrientes. *MLS Health & Nutrition Research*, 1(2), 104-122

CRONONUTRICIÓN: EFECTO DE LA HORA DE LA INGESTA EN EL METABOLISMO DE LOS NUTRIENTES.

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Resumen. Las alteraciones metabólicas suponen hoy en día una de las afecciones más padecidas en todo el mundo. Es por ello que la indagación en el estudio sobre la influencia de la hora de la ingesta en el metabolismo de un nutriente, es de gran importancia para el desarrollo y aplicación de nuevos tratamientos en lo que a estas enfermedades respecta. Mediante esta revisión bibliográfica, a través de la búsqueda bibliográfica profunda en diferentes bases de datos, se han obtenido diversos archivos, documentos, artículos y estudios que han servido para el análisis, desarrollo y ejecución del vigente artículo. La molécula de la glucosa presenta niveles más persistentes en la tarde versus la mañana, debido a la disminución de la actividad de la insulina con el avance del día. La mayoría de los lípidos presentan sus niveles más altos en la tarde. En cuanto a las proteínas se necesita más estudio para su conocimiento en este aspecto. Se requiere de más investigación para poder obtener una conclusión más exacta. Aun así, se puede concluir en que la hora de la ingesta es un factor que afecta en la ritmicidad de los procesos metabólicos, interfiriendo y alterando la actividad y respuesta de los nutrientes.

Palabras clave: cronobiología, metabolismo, nutrientes, timing u hora de la ingesta, alteraciones fisiológicas.

Abstract: Nowadays the metabolic variations are one of the most suffered illnesses in the world. Therefore, the investigation of the study about the influence of intake time in the metabolism of a nutrient, it is gaining importance for the development and applications on new treatments as far as these diseases are concerned. This bibliographic review, through an in-depth bibliographic search in different databases, has allowed us to obtain several files, documents, articles and researches that have been used for the analysis, development and execution of the current article. The glucose molecule has more persistent levels in the afternoon versus the morning, due to the decreased insulin activity throughout the day. Most lipids show their highest levels in the afternoon. Regarding proteins, more study is needed for their knowledge in this appearance. More research is required to obtain a better conclusion. Even so, it can be concluded that the time of intake is a factor that affects the rhythmicity of metabolic processes, interfering and modifying the activity and response of nutrients.

Key words: chronobiology, metabolism, nutrients, timing, physiological variations.

Introduction

We are at a time in history in which metabolic disorders of obesity and diabetes crown the list of diseases most suffered within the human collective. The number of affected people is around 1 billion worldwide (1).

Recent research on the human genome has discovered a possible treatment that can substitute and/or complement current therapies for these alterations. Which, for different reasons (economic, lack of resources, scope, etc.), are not 100% effective. We are talking about Chronobiology, a new science that studies the rhythmicity of physiological processes (2-5).

The main factor of these alterations is the process of eating. The results of which are usually given in terms of what and how much we eat. However, new studies differ in this, highlighting the existence of another factor that could participate or be the cause of this. This new factor would be determined by the time of nutrient intake (6,7).

This is supported by the possible correlation between the metabolic health of the human body and the time at which a particular macronutrient is ingested, regardless of the total amount of total calories or the food as a whole. For example, glucose tolerance is highest in the morning, gradually deteriorating as the day progresses into the evening. This aspect suggests that not only will a response be generated depending on the type of food or amount of it that we consume, but also the time of day in which we do it will be a factor that will influence this physiological response in terms of the availability of the nutrient or nutrients (1,6,8).

All these response processes are the responsibility of the study of chronobiology, which is important for the understanding of their mechanism of action. In this way, circadian rhythms regulate all these processes through a synchronization mediated by the known clock genes or circadian clocks. It is composed by a hierarchical gear headed by the central clock located in the suprachiasmatic nucleus (SCN) of the brain, which dominates and controls the peripheral clocks located in other organs such as the liver, muscles, or adipose tissue. While the NSQ is primarily mediated by environmental factor such as light and darkness, the rest of the peripheral clocks are mediated by several factors, of which food is one of the most important. In other words, the what, the how much, but, above all, the when, are decisive when it comes to avoiding disruptions with the NSQ and thus maintaining homeostasis and avoiding metabolic alterations (1,3,8-10).

With all this, it is possible to speculate on the relationship between circadian rhythms and metabolic function. In such a way that an alteration in each of them entails reciprocal repercussions. An important role in this is played by the binomial: type or class of macronutrient and time of day when it is ingested. Therefore, the understanding of the metabolic physiology schedule would serve as a gateway to behavioral interventions in lifestyle and/or therapies to treat metabolic diseases (1,9).

Method

For the elaboration of this article, a systematic review of the existing scientific literature was carried out through a bibliographic search, following a defined strategy. Through the use of different online databases, terms related to the topic, filters (year, type of publication, relevance, author/s, etc.), a wide selection of documents was compiled, identifying and choosing those with useful information and data for its development. The main sources and databases used were those related to the field of health that provided high quality information and scientific evidence, and gave rise to the contrast of ideas. Of a total of 35 articles used, the main database with the greatest contribution was Pubmed, with a total of 31 articles. In contrast, DOAJ and Google Scholar only contributed a total of 3 articles each, as well as Cochrane Library and LILACS only provided 1 article each. Temporal publication ranges were established in or after 2010. The most used terms were: *Chronobiology, Chronobiology and metabolism, Chronotype, nutrients, Circadian physiology, Circadian system architecture, Transcriptional architecture as circadian system, Central and peripheral clocks, Meal timing health effect, Glucose postprandial response morning evening, Diurnal glucose and fat levels, Diurnal protein levels, Plasma triglycerides and glucose, diabetes, Nutrients levels circadian clock health.*

Results

Chronobiology in nutrition: chrononutrition

Throughout history, living beings have been forced to adapt to a cyclical and changing world. This has originated the presence of an adaptive rhythmicity in the physiology of organisms with 24-hour periods marked mainly by daily light-dark cycles but also by other factors such as food (1, 4, 11, 12).

This rhythmicity is capable of synchronizing, coordinating, and regulating physiological processes (neuronal, endocrine, metabolic, behavioral, etc.) in the face of fluctuations or variations in time caused by external and internal factors. Adaptation produced thanks to the presence of genes, known as clock genes or biological clocks, which allow the body to anticipate any event that influences any of these processes. This mechanistic and regulatory system is the field of study of chronobiology. This science was first described in 1729 but was not recognized until the twentieth century through the contributions of the Nobel Prize winners Jeffrey Hall, Michael Rosbash, and Michael Young through their research on fruit flies (4, 13, 14).

From the hand of chronobiology comes chrononutrition. An emerging discipline subject to it but from a food point of view. This focuses on the study of the relationship between circadian rhythms and the metabolic process of food. The clock genes involved in these aspects are located in the main organs involved in metabolism, namely the liver, pancreas, adipose tissue, and muscle (4, 15).

Architecture of the circadian system

The light-dark binomial generates cycles or approximate rhythms ("circa") of 24h ("diem") in coordination with the clocks to provide the internal, temporal homeostasis of the organism with the outside. This mechanism is generated from a feedback loop of gene expression in the phases of cellular transcription and translation ordered by the central clock. This mechanism will be discussed later (1,16,11).

The central or master biological clock is the one that predominates over the rest of the clocks. It is located in the anterior part of the hypothalamus, specifically in the interior of the NSQ. Its function lies in the generation, regulation, and maintenance of all circadian rhythms based on orders transmitted to the other clocks, the "peripheral clocks" or "oscillators," located in the other tissues, thus allowing synchronization between the two. While the central clock is determined by the action exerted on it by the environmental factor of light and darkness, the peripheral clocks are driven not only by the orders of the central clock but also by external factors such as food or fasting (Figure 1) (3,8,9).

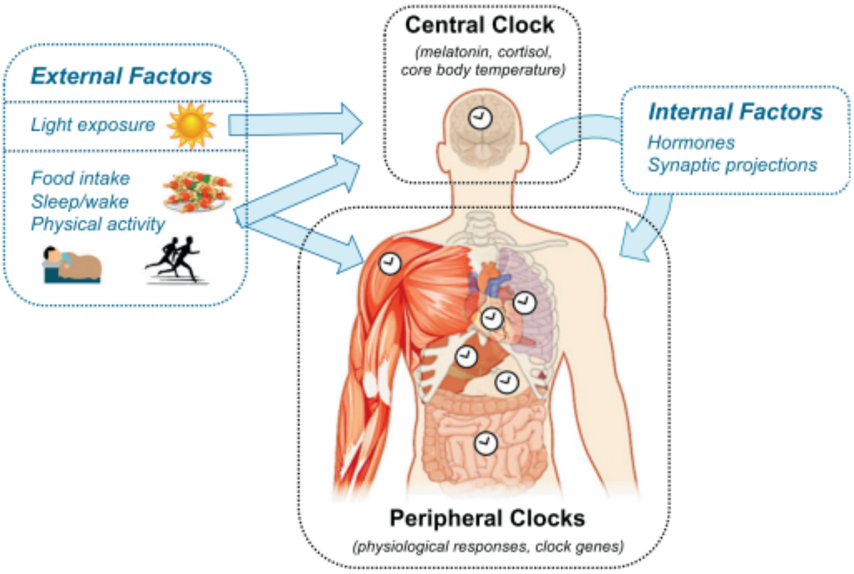

Figure 1. Architecture of the circadian system. Central and peripheral clock mediated by external and internal factors (3).

Note: Taken from Poggiogalle et al., (2018).

Circadian rhythms

Circadian rhythms are sequenced 24-hour cycles that coordinate all physiological and behavioral processes of an organism by synchronizing the central and peripheral clocks in response to environmental signals. These signals are known as *Zeitgebers*, with sunlight having the greatest effect in mammals, followed by others such as temperature, feeding/fasting, activity/rest, social cues, etc. (9, 10, 15-17).

This rhythmic succession of actions in living beings makes it possible for it to anticipate any Zeitgeber or change in the environment (food/metabolism or hunter/prey interaction, DNA damage, etc.), thus preparing its organism to make decisions at the cellular and behavioral level in order to be as effective as possible, maintain homeostasis with the surrounding environment, and survive (10,15,16).

Each individual presents a predisposition or preference for a type of active or rest cycle, this is known as chronotype or circadian preference. In this sense, we find morning or early chronotypes, more active during the first hours of the day, intermediate and evening or late, more active towards the last hours of the day (8,10).

Biological clocks or clock genes: a hierarchical system

Biological clocks or clock genes are endogenous timers present in most cells, responsible for genetically encoding the expression of proteins through a self-regulated feedback loop of transcription and translation, generating an internal time in them of 24 hours, with or without the presence of external signals. In other words, they are those whose function resides in the genetic codification and production of circadian rhythms (16,18).

There are two types of clocks: central and peripheral. Together, they form a network of connections creating a unique, organized, and sophisticated hierarchical system (Figure 2) (9,16).

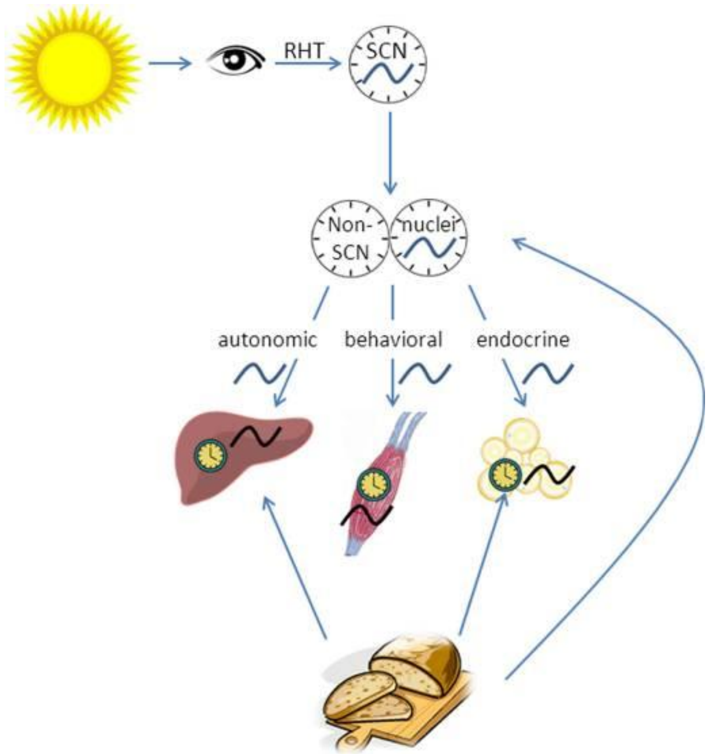

Figure 2. Clock output from the central clock to the peripheral clocks entrained by the light and power Zeitgebers (9). (RHT; Retinohypothalamic tract, SCN; Suprachiasmatic nucleus, Non-SCN; non SCN brain cloks).

Note: Taken from Oosterman et al., (2015).

Central or "master" clock: suprachiasmatic nucleus

The central or "master" clock is located inside each neuron that makes up the NSQ. Its function is similar to that of an endogenous pacemaker, creating, sustaining, and regulating first order circadian rhythms towards peripheral clocks of the rest of the tissues as a response to the information collected from the outside in response to the light-dark stimulus (9,16,17).

In this sense, light is captured by the receptors present in the retina and projected in the NSQ through the retinohypothalamic tract (RHT), producing the secretion of neurotransmitters that activate certain substances that stimulate the receptors of the neurons present in the NSQ, ending in the regulation of the genes that encode for the proteins related to these circadian mechanisms. This signal, transformed into information, is sent to the rest of the peripheral clocks by means of behavioral, autonomic, neuronal, and endocrine pathways, so that they can be activated or deactivated (9,15,16,19).

Peripheral clocks: tissue organization

They are semi-independent clocks present in most cells of the rest of the tissues of the main organs involved in vital functions (liver, pancreas, intestine, stomach, heart, lungs, muscle, etc.) (Figure 1). A priori, they reestablish their phases of gene expression by means of the signals ordered by the NSQ. The aim of the NSQ with the peripheral clocks lies in their coordination, activating or inhibiting them. However, their expression can also be restored by other external signals such as fasting or feeding. Therefore, it can be pointed out that this control does not occur strictly in most cases, but in some cases, it presents certain autonomy as in the case of the liver (1,9,16,20).

Molecular mechanism of the circadian clock

The clock mechanism in mammals functions through the joint action of two intertwined feedback loops of the molecular phase of transcription-translation (TTFL), thus generating 24-hour gene oscillations. For this feedback to function, the action and dominance of a series of proteins acting on the TTFL and the corresponding genes is required (1,11,16,18).

On the one hand, there are the CLOCK and BMAL-1 proteins, subunits of the basic heterodimeric transcription factor Helix-loop-helix (bHLH) Per-Arnt-Sim (PAS), which act as activators (positive product) and are regulated by the period Per (Per1, Per2, and Per3) and cryptochrome Cry (Cry1 and Cry2) genes. On the other hand, PER and CRY proteins, which act as repressors (negative product). And finally, kinases (CKIα, CKIδ, and CKIε) and phosphatases (PP1, PP5), which regulate the localization and stability of the previous proteins (3,9,16).

Briefly, the mechanism consists of the following: the activator proteins, CLOCK and BMAL-1; they dimerize forming the CLOCK:BMAL-1 complex (active during the day), which binds to regulatory sequences known as EBox (5′-CACGTG-3 ') to activate the transcription (in the afternoon) of the three Per genes and the two Cry genes. (7,18). In the evening, PER and CRY proteins heterodimerize in the cytoplasm and translocate to the nucleus to interact with the CLOCK:BMAL-1 complex. Once the degradation of PER and CRY by the action of ubiquitins has begun, the action of the CLOCK:BMAL-1 complex is gradually reduced until it disappears, and the cycle begins again with the characteristic periodicity of 24 hours (Figure 4) (3,5,9,16,18) (3,5,9,16,18).

On the other hand, there are metabolic transcription factors that regulate the transcription of cellular clock mechanism elements through competition for the RORE binding site. These are known as REV-ERBα and RORα. REV-ERBα is an adipogenesis-regulated factor that inhibits BMal-1 by binding to RORE. And RORα, a factor also involved in lipid homeostasis which, in contrast to the former, activates BMAl-1 upon binding to RORE (Figure 4) (5,9).

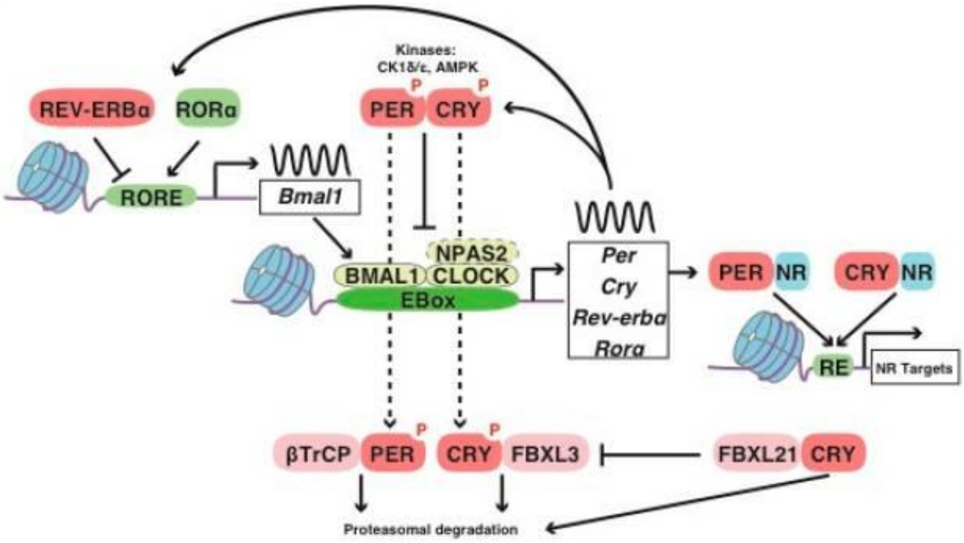

Figure 4. Network of the molecular mechanism of the circadian clock (5).

Note: Taken from Maury et al (2019).

Metabolic pathways, major metabolites, and their integration with the circadian clock

Nutrient metabolism works through two main pathways: the anabolic, which acts in the presence of food, and the catabolic, which acts in its absence. Since the body's energy needs vary according to the degree and type of activity and the time of day, both pathways take turns without actively participating at the same time thanks to circadian synchronization (22,23).

In order to maintain energy homeostasis and thus a functional and effective metabolism, circadian clocks must maintain a reciprocal synchronization with the liver, its metabolic pathways, and metabolites. In this way, processes necessary for this are enabled and occur. For example, the storage of nutrients during feeding phases in order to be able to use these stored energy reserves later during fasting phases (1,15).

In addition to the evidence of the presence of clocks in the metabolism, several studies show that mere disruptions in the metabolic cycles of different metabolites, such as off-time intake or high intakes of a particular nutrient at a particular time of day can damage the activity of the NSQ and thus the overall synchronization causing metabolic disturbances. This is known as circadian misalignment. That said, it is important to take into consideration both the timing and the composition of the food (1,3,9).

Carbohydrates and circadian synchronization

Glucose, the main energy substrate for the organism, presents a series of variations in its plasma levels throughout the day, and it is of great importance to keep them within normal ranges. To ensure homeostasis and avoid circadian misalignment or desynchronization, with its possible health effects, clocks and metabolism are synchronized by working on glucose detection and signaling systems (insulin, glucagon, somatostatin, etc.) and their transformation processes (9,22).

Anabolic and circadian carbohydrate pathway

Within the anabolic glucose pathway, the main components that show a rhythmicity in their activity during feeding periods are the following. Firstly, the GLUT2 transporter and GCK show their highest peaks of action during meals. Secondly, insulin, through a signaling cascade, activates glycogenesis by inhibiting glycogen synthase kinase (GSK3) and releasing glycogen synthase (GS). GSK3 is characterized by the ability to act on some circadian system clocks causing alterations; for example, it affects the stability of REV-ERB. Thirdly, the O-GlcNac protein, which is involved in the degradation, or ubiquitination, of the clock components PER, CLOCK, and BMAL-1 (Figure 5) (1,24).

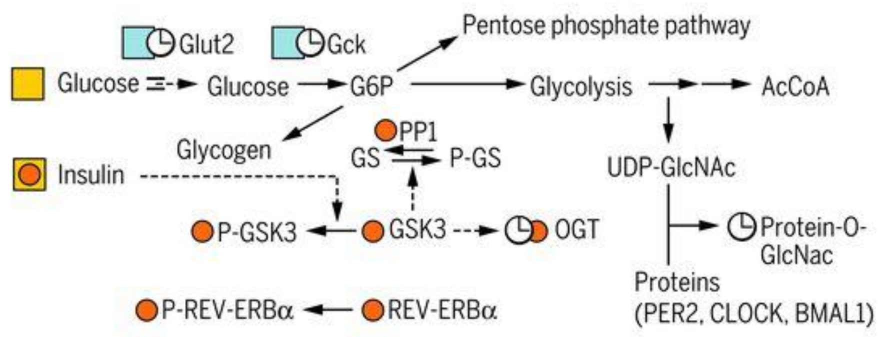

Figure 5. Cascade of glucose and insulin metabolic processing by circadian regulation (1).

Note: Taken from Satchidananda Panda (2016).

Catabolic and circadian carbohydrate pathway

Within the catabolic pathway, which is active during periods of fasting, the glucose metabolic pathway is also influenced by the circadian mechanism. Since the circadian system and metabolism mobilize glucose from the tissues to obtain energy, the circadian system and metabolism mobilize glucose from the tissues to obtain it. In this way, the NSQ signals the hormone glucagon, which binds to receptors (G protein and adenylate cyclase) that activate protein kinase A (PKA), finally promoting the degradation processes to obtain the product in question. This PKA phosphorylates activating the response towards cyclic AMP (CREB) to bind to CRE, activating the transcription steps of PER1 clock components and several glucogenic promoters. Finally, the role of CRY1 as a stabilizer against the effect of nutrient deficiency should be noted. It inhibits PKA when it acts negatively on G protein or adenylate cyclase. On the contrary, it is degraded by AMP-activated kinases once AMP reaches high concentrations induced by prolonged fasting (Figure 6) (1,25,26).

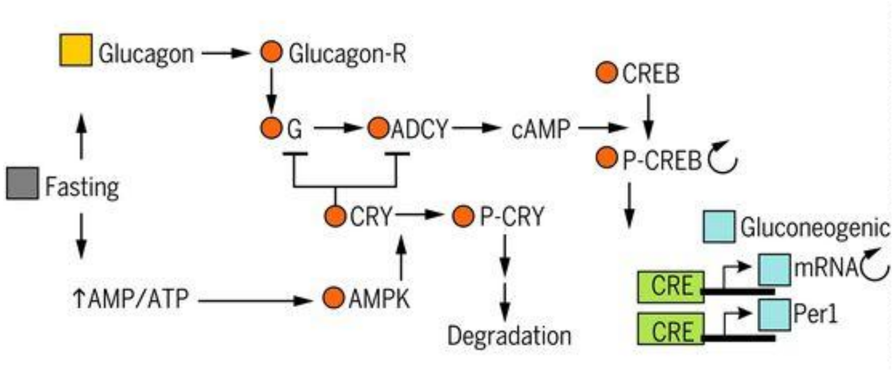

Figure 6. Clock coordination and power signals (1).

Note: Taken from Satchidananda Panda (2016).

Lipids and circadian synchronization

As in the glucose molecule, fatty acid metabolism also presents circadian rhythms in response to feeding or fasting states. Promoting in the former the activation of the anabolic pathways of lipogenesis and in the latter the catabolic pathway of β-oxidation (1,15).

Anabolic and circadian lipid pathway

The anabolic pathway of lipogenesis, activated by feeding begins with the exit of acetyl-CoA (AcCoA) from the mitochondria into the cytosol. Once there, it is carboxylated by the enzyme acetyl-CoA carboxylase (ACACA) to give rise to the product Malonyl-CoA. ATP citrate lyase (ACLY), the enzyme in charge of acetyl-CoA synthesis, shows its highest peak expression during this stage, thus showing daily rhythms. In addition, the entry of fatty acyl groups into the cell by carnitine palmitoyl transferase (CPT) 1 and 2 decreases catabolic activity. Once high levels of Malonyl-CoA are produced, a response that inactivates CPT is generated, thus ending lipogenesis (Figure 7) (1,27-30).

Catabolic and circadian lipid pathway

The catabolic pathway of β-oxidation, activated in the absence of food during periods of fasting, begins its activity by inducing AMPK to phosphorylate ACACA, thus interrupting the anabolic pathway. In contrast, as noted above, CPT1 and CPT2 decrease the rate of β-oxidation activity by introducing fatty acyl groups into the cell (Figure 7) (1).

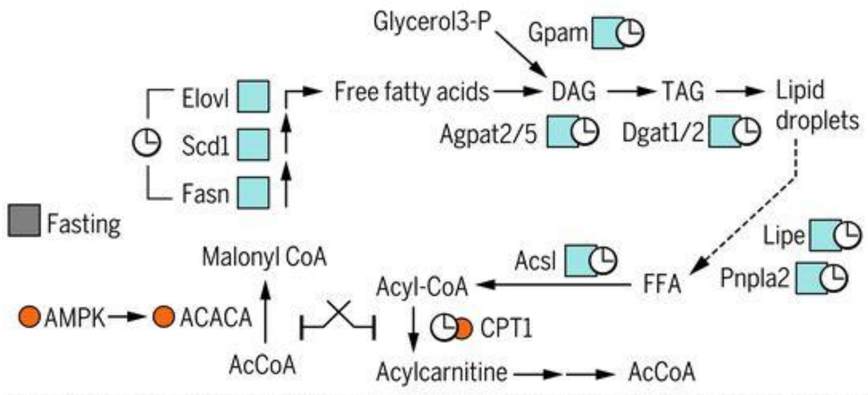

Figure 7. Cascade of the lipid metabolic process through circadian regulation (1).

Note: Taken from Satchidananda Panda (2016).

Proteins and circadian synchronization

In the same way as the previous metabolites, protein metabolism presents rhythms in response to feeding and fasting processes with the activation of its main pathways. In this case, the anabolic pathway is activated to synthesize and store proteins, and the catabolic pathway for gluconeogenesis, formation of active molecules or release of ammonia for the formation of urea (1,28).

Anabolic and circadian protein pathway

After the feeding phase, the insulin kinase receptor (AKT) activates the mTOR-S6 protein translation pathway. In turn, AKT and another protein-coding enzyme (S6K1), phosphorylate by recruiting BMAL-1 to promote translation. This rhythm is of utmost importance for the synthesis of some proteins vital for liver function such as albumin, proteins of the complement pathway, retinol binding protein or transthyretin (Figure 8) (1) (1).

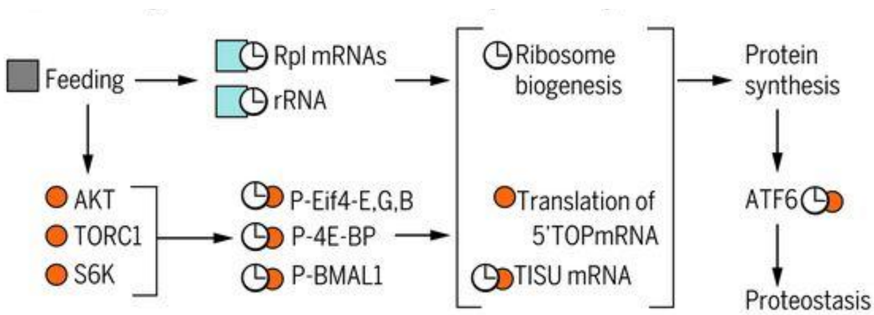

Figure 8. Cascade of the metabolic process of amino acids through circadian regulation (1).

Note: Taken from Satchidananda Panda (2016).

Catabolic and circadian protein pathway

During the fasting phase, circadian rhythms regulate and activate the KLF15 transcription factors present in hepatocytes and myocytes. These factors modulate the activity of the enzymes responsible for mobilizing amino acids from the muscle to the liver for subsequent utilization in gluconeogenesis and ammonia production for the urea cycle (1,31).

Nutrients and time of intake or timing, health implications

The time of the meal, also known by the term "fashionable *timing*" and its frequency, are two factors that notoriously influence the metabolic processes of the main energetic (glucose and lipids) and plastic (proteins) components of the organism, and consequently, on the synchronization that they maintain with the circadian system (5,6,32). In this way, these processes manifest throughout the day variations in the peak of expression of their activity being, in some cases, greater in the first hours and, in others, towards the last hours of the day. Therefore, the consumption of these components outside the stages corresponding to their greater tolerance can generate metabolic alterations, as well as circadian disruptions, leading to diseases such as dyslipidemia and/or diabetes (3,5,6,19,32).

Effects of Nutrients and Time on Health

Understanding the roles of nutrients at each hour of the day within the circadian system brings us closer to the development of quality health. For as mentioned above, the circadian regulation of these components involves the maintenance of many of the processes derived from metabolic physiology. Where simple and minimal misalignments can generate a long list of pathologies, such as glucose intolerance, insulin resistance, obesity, dyslipidemia, heart disease, chronic inflammation, liver disease, increased risk of cancer, and even muscle problems (1,3,6,15).

A bad carbohydrate intake plan leads to an imbalance of carbohydrates. This affects more acutely on people whose tolerance is weaker, as is the case of people with type 2 Diabetes Mellitus. It has been observed that a high nocturnal intake of carbohydrates in this group, and especially in people with obesity, produces severe hyperglycemia of long duration. This is also transferred to pre-diabetic people, causing them to become diabetic during these periods and suffer the same effects. All this is due to the deterioration in the tolerance of this nutrient because of a poor response of insulin activity during this period of the day. Therefore, its intake at night should be reduced, especially in diabetics and pre-diabetics (3,6,32-34,37).

Abusive intakes of fat, in the morning or midday stages, interfere with hepatic metabolism causing FFA to be increased in the blood. This leads to insulin resistance, resulting in the development of sustained hyperglycemia during the rest of the day. In the case of high fat intakes at night, this can generate an increase in unsaturated and pro-inflammatory fatty acids, mainly TRG, increasing the risk of developing diseases related to blood vascularity. Among these are arteriosclerosis, dyslipidemia, stroke, and heart disease (32-35,38).

In relation to protein intake, its poor practice can cause imbalances in the rhythms responsible for the regulation of the mediator of amino acid mobilization during fasting (KLF15). That said, a high protein meal at night is capable of causing metabolic alterations such as hypoglycemia, hyperammonemia, and even deterioration in the urea cycle (31,39).

Carbohydrates in timing

Most studies (6,21,22) point out that the maximum peaks of carbohydrate expression occur in the early hours of the morning, decreasing its tolerance with the passing of the day. This fact correlates, in some cases and in others not, with insulin secretion (3,5,6,32,33).

A study conducted in 2017 by Kessler et al. (32) evaluated these glycemic responses by subjecting healthy subjects to two types of diets separated in time. One group ingested a high carbohydrate (HC) meal in the morning and a high fat (HF) meal in the afternoon (HC/HG), and another group did so in the reverse order (HG/HF). After that, in subjects without impaired glucose tolerance, they observed that HC intakes in the morning produced blood glucose levels with a higher peak expression compared to the afternoon. In addition, after the afternoon intakes the levels persisted for longer periods of time as opposed to the morning where they declined at a faster rate. Simultaneously, the same happened with insulin levels. In which the response, sensitivity and secretion were lower in the later phases of the day.

Another study conducted in 2019 by Jamshed et al. (33) analyzed the effects of time-restricted feeding (TRF) with 3 meals (breakfast, snack, and dinner) spread over 6 hours versus 3 meals spread over 12 hours (control group). With respect to the first group, it was observed that, although glucose levels remained constant without any variation during the period of intakes, there was a decrease during the resting phase. In the second group (control group), their results showed that there was not much difference between the acrophases of the different meals. They noted slightly higher glucose activity in the active phase in the morning than in the resting phase in the afternoon, as was the case with insulin. In spite of this, they pointed out that at breakfast the time of disappearance of the glucose peak was shorter and faster than at the rest of the meals.

For another study developed in 2017 by Versteeg et al. (34) examined the influence of light on blood glucose in diabetic and healthy subjects, simulating the phases of activity (morning) and rest (evening) using different light intensities (bright light and dim light). As a result, they did not observe much variation in glucose levels in healthy subjects in both light levels. Specifically, neither fasting nor postprandial glucose and insulin levels were different in bright and dim light. In contrast to the previous studies, diabetics showed an increase in glucose levels in bright versus dim light but little variation in the case of insulin. Thus, they concluded that ambient light in the active phase can modify glucose levels in diabetic subjects.

Another study conducted in 2018 by Takahashi et al. (6) examined the effect of timing (morning vs. afternoon) of meal on postprandial glucose metabolism in healthy subjects. They were given a meal in the morning (9:00 h) after 10 hours of fasting and a meal in the afternoon (17:00 h) after 4 hours of fasting. In both times, hardly any differences were observed. The only difference was that insulin levels were higher in the morning than in the evening. While glycemic levels (Figure 13 A) were higher at night than in the morning.

Lipids in timing

As for the metabolic rhythms presented by lipids, almost in the same way as glucose, their peak of expression in most types is higher during the morning, but in this case, prolonging until midday (3,35).

For the study conducted in 2017 by Kessler et al. (32), based on the intake of two types of diets (HC/HF) distributed at different times of the day, it concluded that the HF diet did not show large differences in the levels of free fatty acids between the different times of intake. However, a slight increase in free fatty acids was observed throughout the day in subjects with glucose intolerance. Specifically, their peak remained more pronounced during the afternoon stage. This generated an insulin resistance that further decreased glucose tolerance as the day went on.

Likewise, in the study conducted in 2019 by Jamshed et al. (33), where the effects of TRF were analyzed by ingesting 3 meals spread over different time intervals, it was observed that in both cases lipid concentrations, in general, were more prominent during the day than at night, namely total cholesterol, LDL, HDL, and FFA. Triglycerides (TRG) were the only exception that was elevated during the night.

Regarding the study developed in 2017 by Versteeg et al. (34) in which the influence of light on blood glucose was examined in diabetic and healthy subjects, reflecting the phases of activity and rest, it was noted that in healthy subjects exposure to bright light increased fasting and postprandial concentrations of TRG but not that of FFA. In subjects with type 2 diabetes, TRG levels were also increased by bright light exposure, although in this case even more so. For FFA, there was no significant difference in the observed variations.

Moving away from these studies, which coincided in the analysis of glucose and lipids, we are faced with other investigations related to lipid metabolism. One of them elaborated in 2018 by Poggiogalle et al. (3) points out that HDL and LDL molecules show their highest levels around midday ranges. Being able to establish 13:00 h as the average of these ranges. Another study carried out in 2015 by Sennels et al. (36) highlights that the rhythms of TRG and diglycerides vary, showing peaks in the afternoon around 15:00 h and in the evening from 17:45-20:00 h.

Proteins in timing

About the relationship between the time of intake and the rhythms of protein activity, the study conducted in 2018 by Takahashi et al. (6), which examined the effect of postprandial metabolic changes between morning and evening meal in healthy subjects, found that some amino acids such as leucine, lysine, histidine, tryptophan, arginine, asparagine, glutamic acid, glyceridic acid, or aspartic acid, among others, described higher levels during the morning.

In another study conducted in 2012 by Jeyaraj et al. (31), where the circadian regulation of the protein transcription factor KLF15 (mediator of fasting amino acid mobilization) was analyzed in mice, concluded that a diet rich in protein severely altered metabolism by affecting this factor, presenting especially blood levels of total amino acids, branched-chain amino acids (BCAAS), and urea more prominent at night.

Conclusions

Studies such as Takahashi, Kessler, or Jamshed (6,32,33) establish that the intake of carbohydrates during the first hours of the day reflects maximum peaks of blood glucose expression compared to lower levels produced in the final hours of the day. This in turn is accompanied by a faster rate of decline from the peak. In addition, these glucose responses are reflected in insulin activity. Insulin levels are lower at night than in the morning. This confirms a decrease in glucose tolerance as the day progresses in relation to the low insulin activity towards the end of the day. However, in people who are glucose intolerant (possible diabetics), glucose and insulin levels are even more increased at these times of the day despite following the same pattern as in healthy subjects. In contrast to the above, another study by Verteeg R et al. (34) notes that in both cases there are no differences between glucose and insulin levels in healthy subjects. Again, only alterations and discrepancies appear among subjects with diabetes, but in this case, glucose levels are even higher in the presence of daylight. All in all, it is emphasized that nocturnal carbohydrate intake exacerbates glucose levels over time, producing severe and long-lasting hyperglycemia in diabetes, prediabetes, and obesity due to the detriment of insulin action (3,6,32).

Regarding lipid intake, studies such as that of Poggiogalle, Verteeg, or Sennels (3,34,36) state that free fatty acids are the lipid molecules that present a greater affinity in their activity in the last hours of the day. On the other hand, the study developed by Jamshed et al. (33) indicates that free fatty acids present a better tolerance, due to a more efficient activity, during the first hours of the day. On the other hand, the studies carried out by Poggiogalle, Jamshed, and Sennels (3,33,36) point out that the TRG molecule presents a greater activity, again, in the final stages of the day. In contrast to these, the study by Verteeg et al. (34) contradicts this, arguing that this occurs in the early stages. In reference to the daily activity of total cholesterol, HDL and LDL, Jamshed et al. (33) are the only ones who include these values in their assessment. They point out their greater tolerance towards hours close to the morning and midday. In reference to people with glucose intolerance or predisposition to it, the study carried out by Kessler et al. (32) points out that an intake rich in fats in the morning increases FFA levels, maintaining them over time for several hours. And whose highest peaks are generated in the evening as opposed to healthy subjects. This correlates with the development of insulin resistance and thus decreased glucose tolerance, ultimately leading to nocturnal hyperglycemia. In addition, the study by Verteeg et al. (34) further supports this, indicating that high nocturnal GRT levels are further increased in this population group. Despite the inequality of results, all these studies yield to the same fact. And it is that the poor hourly intake of lipids is related to the increase of the probability for the development of arteriosclerosis and, with it, the drift to acute conditions such as cerebrovascular accident, heart attack, and cardiopathies (32-35).

In relation to the time of protein intake and its effect/influence on its activity, only two studies were found with conflicting results. On the one hand, Takahashi et al. (6) establish that the maximum levels of certain postprandial amino acids (leucine, lysine, histidine, tryptophan, etc.) are produced in the morning (6). While, on the other hand, Jeyaraj et al. (31) differ in this, highlighting that the rich protein intake generates alterations in the transcription factor KLF15 inducing an increase of plasma amino acids worsening in nocturnal stages. This generates an increase in the levels of total amino acids, BCAAS and urea. At the same time, increasing the risk of the appearance of metabolic alterations such as hypoglycemia, hyperammonemia, and even deterioration in the urea synthesis cycle (31,39).

All these contrasts of results between studies can be seen in the figure below (Figure 17) (3,6,31,32,33,34,35,36):

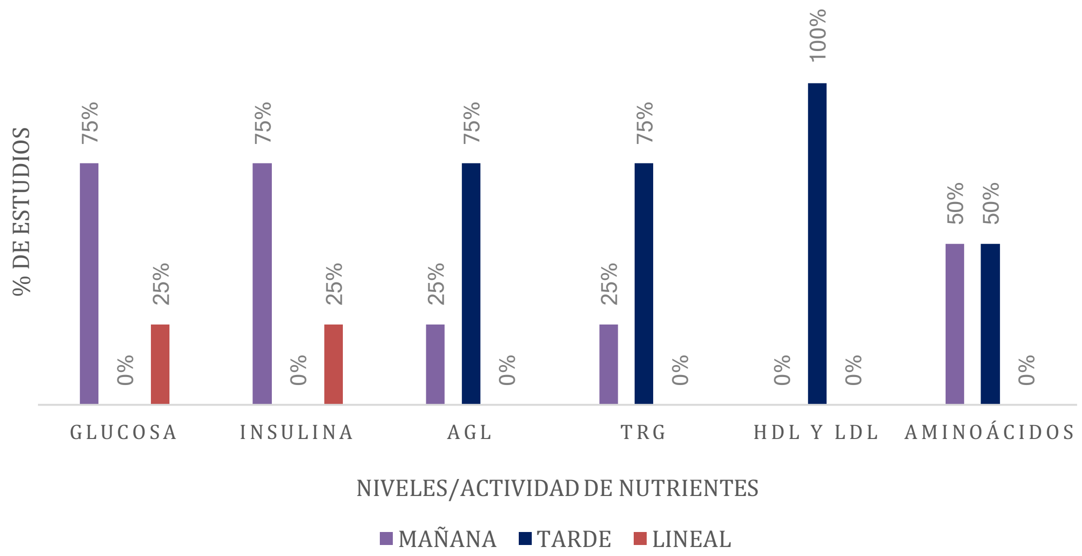

Figure 17. Nutrient activity at different times of the day according to different studies.

However, as can be seen, the studies cited throughout this review present conflicting results that limit the development of clear and reliable conclusions regarding the knowledge on the relationship between the time of intake and its effect on the metabolism of the main nutrients. Divergences attributed to one or more factors but mainly to the design of each study. Since each one presents different inclusion and exclusion criteria, different time periods (most of them short term, something unfavorable for obtaining consistent data), different intervention methods (in some cases, the diets were not well defined or adapted to each subject, or there was an absence of nutritional advice), as well as the methods and instruments used in data collection and analysis.

With all this, we conclude that the time of intake is a determinant on the activity and response of the main nutrients, as it exerts an effect on the synchronization that metabolic processes maintain with the circadian system. Most of the results agree that the maximum rhythms of glucose expression, and therefore of activity, occur during the first hours of the day. The tolerance, due to the decrease in insulin activity, is abandoned as the day progresses. As for lipid intake, its rhythms of expression are more prominent in nocturnal stages, declining in the morning. Regarding the rhythms of protein/amino acid expression, there are no conclusive data due to the lack of data for their study. All these results seem to be logical since the first hours of the day are related to the most active phase of the organism. In spite of this, the objective of this research must be studied in greater depth in order to have more exact and reliable information, which can be transferred and applied for the knowledge of the maintenance, improvement, and/or prevention of the health of the human being.

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IMPACT OF BRANCHED-CHAIN AMINO ACID (BCAA) INTAKE ON TYPE 2 DIABETES MELLITUS

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Summary: Elevated circulating levels of branched-chain amino acids (BCAA) have been described as a strong predictor of type 2 diabetes mellitus (DM2). The main objective is to assess whether a diet rich in these amino acids poses a risk for the development of DM2. Material and methods: This bibliographic review was based on scientific articles selected from different databases. A total of 23 articles were studied in depth. Results and discussion: A higher intake of BCAAs has shown a positive association with DM2, mainly if it comes from foods of animal origin. Also, their selective restriction improves the pathophysiology of DM2 without compromising the intake of other essential nutrients. On the contrary, supplementation with BCAAs has no negative health repercussions. Conclusion: BCAA intake does appear to be associated with an increased risk of DM2; however, this association cannot be studied in isolation, but must be considered part of a complex interaction of dietary components, in which the nutritional quality of the food plays an important role.

Key words: Diabetes Mellitus type 2, insulin resistance, branched chain amino acids, BCAA, dietary intake, supplementation.

IMPACTO DEL CONSUMO DE AMINOÁCIDOS DE CADENA RAMIFICADA (BCAA) EN LA DIABETES MELLITUS TIPO 2

Resumen: Niveles circulantes elevados de aminoácidos de cadena ramificada (BCAA) han sido descritos como un fuerte factor predictor de la diabetes mellitus tipo 2 (DM2). El principal objetivo es evaluar si una dieta rica en estos aminoácidos supone un riesgo para el desarrollo de DM2. Material y métodos: Esta revisión bibliográfica se ha sustentado en artículos científicos seleccionados de diferentes bases de datos.

Un total de 23 artículos fueron estudiados en profundidad. Resultados y discusión: Una mayor ingesta de BCAA ha presentado una asociación positiva con la DM2, principalmente si esta proviene de alimentos de origen animal. Asimismo, su restricción selectiva mejora la fisiopatología de la DM2 sin comprometer la ingesta de otros nutrientes esenciales. Al contrario, la suplementación con BCAA no presenta repercusiones negativas para la salud. Conclusión: La ingesta de BCAA si parece estar asociada a un mayor riesgo de padecer DM2; pero esta asociación no puede estudiarse de forma aislada, sino que debe considerarse parte de una interacción compleja de componentes dietéticos, en la cual, la calidad nutricional de los alimentos adquiere un importante papel.

Palabras clave: Diabetes Mellitus tipo 2, resistencia a la insulina, aminoácidos de cadena ramificada, BCAA, ingesta dietética, suplementación.

Introduction

Diabetes Mellitus (DM) refers to the group of metabolic diseases characterized by alterations in the secretion or action of insulin, inducing one of the most characteristic signs of the disease, hyperglycemia. DM can be classified into four general categories: type 1 diabetes mellitus (DM1), type 2 diabetes mellitus (DM2), gestational diabetes (GD) and diabetes secondary to other comorbidities (1).

Among the different types of DM, as confirmed by various societies (2-4), DM2 is the most common of all, accounting for approximately 90-95% of all cases of diabetes. The pathophysiology of this disease is characterized by the presence of insulin resistance (IR) and deficient insulin secretion. In this case, symptoms usually begin slowly and at a lower intensity than in other types of diabetes, consequently, the diagnosis tends to be made late, once complications have already arisen; all this makes early diagnosis a great clinical challenge (5-7).

Currently the diagnostic techniques used are based on a fasting blood glucose test, a glucose tolerance test or an analysis of glycosylated hemoglobin (HbA1c) (1,6,8), these techniques are useful for identifying the disease once pathophysiological changes in blood glucose homeostasis have already occurred; and, therefore, it would be interesting to detect new markers that serve as early indicators of the disease. For this reason, biomedical research based on metabolomics has intensified in recent years to discover new biomarkers that facilitate the early diagnosis of DM2; among those studied, branched-chain amino acids (BCAA) stand out (9-11).

BCAAs (valine, leucine and isoleucine) are a type of essential amino acids (EAA) of great metabolic relevance, which participate in processes ranging from protein synthesis to insulin secretion (12). Today, a great deal of research (9-11) has been devoted to studying the role of these amino acids in the body. Among the findings, elevated circulating levels of BCAAs stand out as a strong predictor of numerous diseases, including DM2. There is some uncertainty as to the origin of this increase and, therefore, the hypothesis arises as to whether their dietary intake could have some kind of influence, taking into account that the only source of these amino acids is through food. The current evidence concerning the link between dietary BCAAs and their circulating levels seems to be unclear (13-15).

The objective of the present literature review is to evaluate whether a diet rich in branched-chain amino acids (BCAA) poses a risk for the development of Type 2 Diabetes Mellitus; in turn, we also aim to identify whether a dietary restriction of BCAA could have a preventive effect on the development of DM2.

Method

A bibliographic search of scientific articles was carried out through different databases; during the period from January to April 2022. Studies in children, pregnant women, case reports and abstracts or letters to the editor were excluded, giving priority to human trials, review articles and meta-analyses.

The database that mainly supported this research was PubMed; the Cochrane Library and Google Scholar were used in a complementary manner. A keyword search strategy was applied, facilitating the identification of the research, among which "Type 2 Diabetes Mellitus", "insulin resistance", "branched chain amino acids", "BCAA", "dietary intake" and "supplementation" stand out.

Results

Dietetic-nutritional treatment of DM2

Nutritional therapy is a basic component in the approach to DM2; despite this, there is currently no clear consensus on the optimal proportion of macronutrients (carbohydrates, proteins and fats) to be maintained by people with DM2 in order to optimize glycemic control; this is why numerous researchers have become involved in the task of elucidating what type of dietary pattern may be the most appropriate for DM2 (6,16,17).

In a meta-analysis, conducted by Papamichou D. *et. al*. (18) compared the medium- to long-term effectiveness of different dietary patterns for the management of DM2. The authors conclude that the most effective dietary patterns for improving glycemic control and cardiovascular risk factors, taking adherence into account, are the vegetarian and Mediterranean diets. These results are also confirmed in another meta-analysis, Schwingshackl L. *et. al*. (19), which establishes that the dietary pattern based on a Mediterranean diet is the most effective in controlling the pathophysiology of DM2.

In another review, by Lewgood J. *et. al*. (20) conclude that the Mediterranean diet is ideal for the improvement of metabolic health and the adequate management of DM2 and that a plant-based diet (vegetarian or vegan diet) shows promise in the prevention of the disease. On the other hand, they also propose nutritional strategies that may be useful in the short term, such as caloric deficit and low-carbohydrate diets, although further research is required to confirm their effects in DM2 (Figure 1).

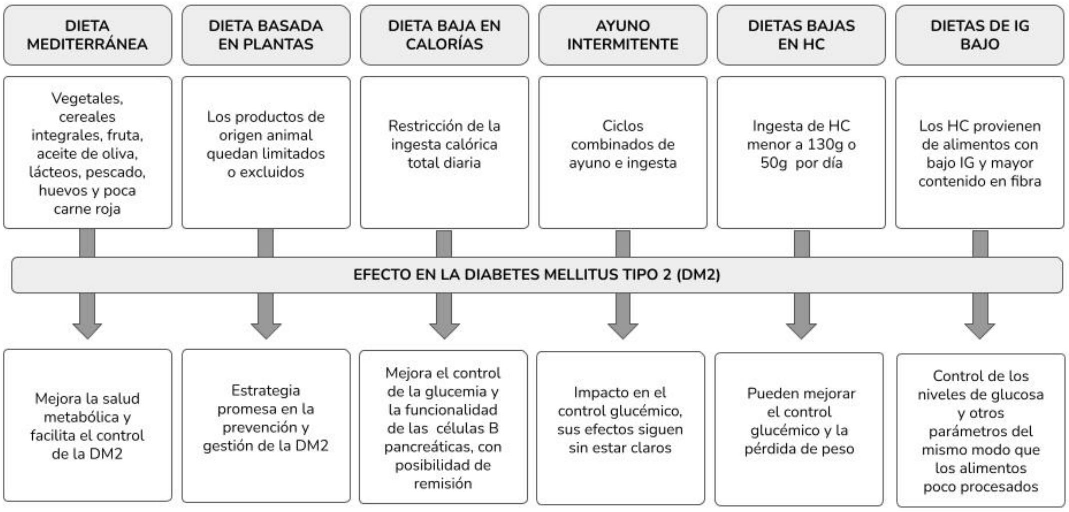


Figure 1. Dietary strategies and outcomes for the management of DM2. Source: Adapted from Lewgood J. *et al*. (2020) (20).

In spite of this, alternative dietary patterns are sometimes chosen, among which the use of the high-protein (HP) diet stands out, where protein intake accounts for approximately 30% of the total caloric content of the diet (21). No significant effects on the improvement of glycemic control have been demonstrated (21-24), in fact, a higher protein intake (mainly of animal origin) has been related to a higher prevalence of DM2 due to its involvement in glucose and insulin metabolism (24-26).

Branched-chain amino acid (BCAA) metabolism

BCAAs refer to leucine, isoleucine and valine (Leu:Ile:Val), understood as a single entity, which, as their name suggests, have a branched structure. They are a type of essential amino acids (EAA), i.e. our body is not able to synthesize them, so they must be supplied through the diet. Consequently, under homeostatic conditions, there must be a balance between intake and elimination (12,27,28).

Normal serum values for an adult are set in ranges of: 66-170 µmol/L for leucine, 42-100 µmol/L for isoleucine and 150-310 µmol/L for valine. This would mean an average of 590 µmol/L for total BCAA (29); taking into consideration that 80% of these values are determined by their intake and the remaining 20% are determined by the products of their metabolism (14).

The metabolism of BCAAs differs from other amino acids in that the liver is not the main metabolic destination, due to the absence of BCAA aminotransferases (BCAT). Instead, these are transaminated (transfer of an amino group from an amino acid to an α-keto acid) in other extrahepatic tissues, most notably skeletal muscle, due to its high BCAT activity (30-32). In this process, α-branched chain keto acids (BCKA) originate, which can already be taken up by the liver. At this point they can either go to the protein synthesis process or be oxidized to maintain the BCAA intake-loss balance (12,33).

Because BCAA metabolism occurs primarily in the mitochondria of peripheral tissue, proper mitochondrial functionality will have a significant impact on plasma BCAA levels (26).

For protein synthesis to occur, mainly in skeletal muscle, two essential factors are required: an anabolic signal and sufficient amounts of amino acids. In particular, BCAAs (especially leucine) act as promoters of this anabolic signal, which explains their growing interest as an ergogenic aid in sport (12). However, they do not act alone, but require other hormonal promoters, such as insulin, to trigger this process. This combination of hormonal and amino acid signals, in turn, coincides with the maximal activation of the mechanistic target of rapamycin (mTOR), the main regulator of cell growth and protein synthesis. Specifically, among the regulatory and signaling functions performed by BCAAs, their significant role in the activation of mTOR should be highlighted (12,31).

As developed above, if BCAAs are not reincorporated into the protein pool, they will be oxidized to maintain balance. This process involves oxidative decarboxylation mediated by the enzyme complex known as branched-chain α-ketoacid dehydrogenase (BCKDH), whose activity is elevated in the liver and decreased in the rest of the body (skeletal muscle, heart, kidney, adipose tissue and brain). The final products obtained in the process are acetyl-CoA and succinyl-CoA; these participate in the course of the Krebs cycle, whose purpose is to produce adenosine triphosphate (ATP), the energy nucleotide par excellence (30,31).

Following a logical sequence, this oxidation process will be enhanced after ingestion. However, there are other processes that can favor its increase, such as exercise or starvation (12,32). The following image (Figure 2) shows a schematic representation of all the processes mentioned above.

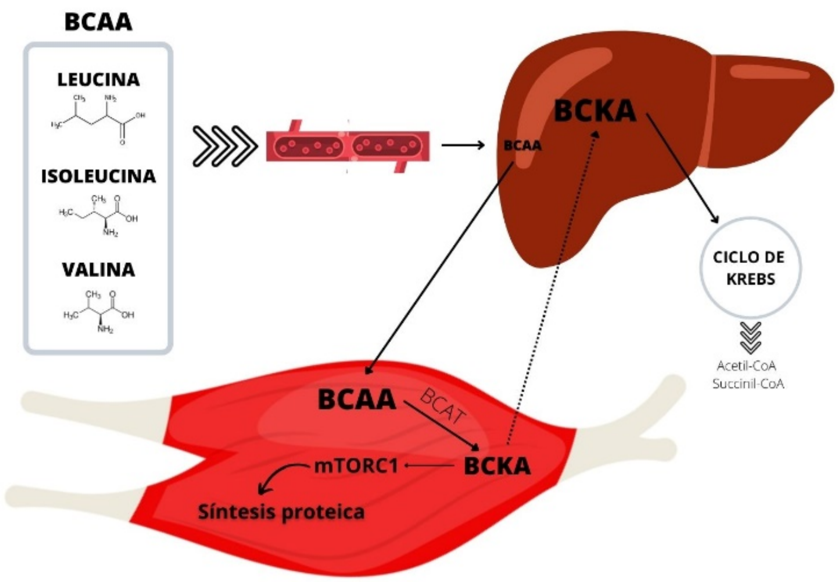


Figure 2. Metabolism of BCAAs, which, after entering the body through food, are used both to synthesize proteins and to be degraded in the Krebs cycle to obtain other secondary metabolites. *Source*: Own elaboration.

BCAA and Insulin Resistance (IR)

The first studies reporting alterations in circulating BCAA levels in patients with diabetes or insulin resistance date back to the 1960s (35,36). Since then, biomedical research devoted to the study of this phenomenon has intensified, although the origins of this increase in BCAA in the pathophysiology of DM2, especially its correlation with IR, are still under discussion (13,14).

The most relevant and common characteristic in the pathology of DM2 is IR; a condition in which the cells stop responding adequately to this hormone, requiring increasing amounts to produce the same effect. This situation, maintained over time, promotes hyperglycemia, the main clinical symptom of DM2 (1,37). It has become clear that there is a stage prior to IR in which there is dysregulated hyperinsulinemia. In this situation, elevated insulin levels are maintained without causing hypoglycemia, which causes a desensitization of the insulin receptor response (IRS-1) and, consequently, IR occurs (38-40).

Although the correlation between BCAAs and IR has been mentioned many times (12,30,32,33,35,41,42), the underlying mechanisms linking them are not fully understood at present.

On the one hand, the hypothesis that increased BCAA acts as a promoter of IR is supported. This theory is mainly based on the situation of hyperactivation of mTOR (specifically, mTORC-1) caused by the increase in BCAA. This hyperactivation causes an increase in insulin receptor degradation (IRS-1) and a decrease in insulin sensitizing hormone (FGF21) interfering with insulin signaling (30,32-34,41,43). In turn, insulin signaling is also altered by inflammation and oxidative stress, triggered by the storage of lipids in muscles caused by BCAAs and their metabolites (32,34,42,44).

1. Conversely, there is also the theory that it is, in the first instance, the IR that induces the increase in BCAAs. Some of the mechanisms that cause its increase can be summarized as: a situation of systemic hyperinsulinemia due to IR, the presence of genetic markers that induce IR (42) and, finally, it is proposed that the first trigger for its increase arises from the presence of IR at the cerebral level (31).

A recent review by White P.J. *et. al.* (42) provides a comprehensive view of the BCAA-RI association, in which all the mechanisms mentioned above are included. The authors propose that, in the early stages of DM2, in which IR is already present, elevations in BCAA levels occur. These elevations are mediated by the presence of predisposing genetic variants, high levels of adiposity (especially abdominal), alterations of its metabolism in the liver and alterations in the microbiota. BCAAs, once elevated, contribute to the development of disease phenotypes through lipid accumulation in muscle, hyperactivation of protein synthesis mechanisms (mTOR) or depletion of tryptophan levels leading to hyperphagia and behavioral changes.

Finally, most studies (12,30-33,43) conclude that the BCAA-RI ratio arises from an impaired BCAA catabolic pathway, leading to its accumulation in blood. In fact, it has been suggested to use BCAA signaling and metabolism pathways as therapeutic targets for the treatment of IR (43).

Intestinal Microbiota and BCAA

Interestingly, the intestinal microbiota also plays an important role in the pathological increase of circulating BCAA levels. The intestinal microbiota forms a complex ecosystem in the gastrointestinal tract, which is constituted by different microorganisms (bacteria, archaea, viruses, fungi, protozoa...) (45-48).

Like the diet, the microbiota is a substantial source of these nutrients. In fact, a difference has been reported between the microorganisms present in the microbiota of patients with DM2 and those of healthy individuals, which show a greater biosynthesis of BCAAs and repression of their degradation (45,49). Therefore, targeting the metabolism of BCAA produced in the microbiota through dietary intervention could show promise in the prevention and treatment of DM2 (49).

Dietary intake of BCAA and DM2

BCAA's are in a 2:1:1 ratio (Leu:Ile:Val), i.e. for every 4g of BCAA's, 2g of leucine, 1g of isoleucine and 1g of valine are included. Thus, it has been established that the average daily requirements for healthy adults are 40, 20 and 20 mg/kg body weight/day, respectively, for a total of 80 mg/kg body weight/day (50).

Given the close link between circulating BCAAs and DM2, a diet rich in these amino acids could be a risk factor for the development of the pathology, and consequently, their selective restriction could be part of a good strategy to restore metabolic health (13,14,51,52).

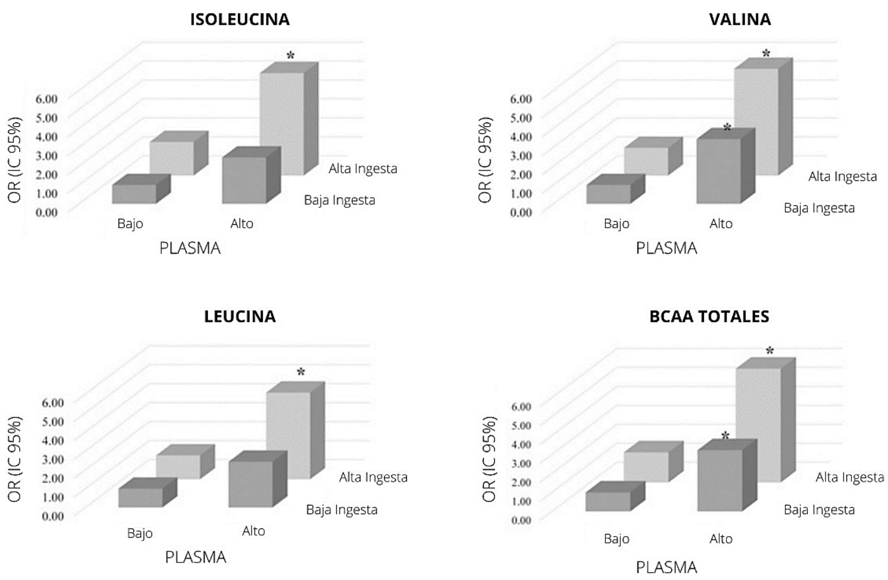
Discussion

On the one hand, observational studies (longitudinal, cross-sectional, cohort and case-control studies) (26,52,15,53,14,54-57) aimed to clarify whether a higher BCAA intake was related to an increased risk of DM2; for this purpose, validated frequency of consumption questionnaires (FFQ) were used to estimate total BCAA intake. Their plasma levels were evaluated through a blood test performed under fasting conditions and the estimation of diabetes risk was measured through the HOMA-IR index. These had a variable durability between six weeks and three years.

Combining all the information gathered in the different investigations, it has been shown that the dietary pattern plays an important role in the amount of BCAA ingested and their circulating levels. On the one hand, it was found that BCAA intake comes mainly from meat, more specifically from red meat and derivatives (26,52,57); this reflects the high consumption of this type of product in the population compared to other protein sources, especially compared to proteins of vegetable origin (legumes, soy...); a dietary pattern which has been associated on numerous occasions with a higher prevalence of diseases and with an intensification of hyperinsulinemia prior to IR (39).

Wang W. *et. al*. (53) argued that high BCAA intake only had negative repercussions in those with a genetic susceptibility to DM2; a statement that is also mentioned in a recent meta-analysis by Supruniuk E. *et. al*. (34). It is hypothesized that those at risk for DM2 have a reduced mitochondrial capacity to catabolize BCAAs, manifesting in an increase in circulating BCAAs. Therefore, under this condition, if BCAA intake is high, it will likewise increase the mitochondrial oxidation load, eventually saturating its system and causing catabolism dysfunction, as well as poor insulin action. On the contrary, in those individuals with an adequate mitochondrial capacity to catabolize BCAAs, these amino acids may have beneficial effects on health, especially muscle protein synthesis (34,53). Similarly, in the research carried out by Tobias D.K. *et. al.* (54) did not obtain a significant trend in the interaction of intake and serum BCAA concentrations when these were at normal values; but they did in those with high plasma concentrations (Figure 3).

Figure 3. Joint representation between circulating levels of BCAAs (low versus



high) and dietary intake of BCAAs (low versus high). *Source*: Adapted from Tobias D.K. *et. al*. (2018) (54).

In this same context, we must take into account the important role played by the catabolic process of BCAAs in their circulating levels, beyond the fact that intake may also have a modest effect. Therefore, elevated circulating BCAA values could reflect an early alteration in protein metabolism, a situation that is worsened if a high BCAA intake is maintained (59).

Meta-analyses and reviews (34,58-60) established a positive association between higher dietary BCAA intake and DM2, with the exception of a meta-analysis conducted by Vieira E.E.S. *et. al*. (13), which claimed to obtain inconsistent results in relation to BCAA intake and DM2 since it did not confirm an impairment of IR; but, in the same way, it supports the metabolic damage that an unhealthy diet presents, producing alterations in BCAA metabolism. It should be noted that this study included only 3 observational studies. All of them explain the importance of taking into account the global computation of dietary behavior and the intervention of environmental factors in the study population in order to establish a correct interpretation of the impact of BCAA intake on metabolic health.

When studying the impact of a BCAA supplementation protocol, randomized clinical trials (61-63) found no negative effects on glucose metabolism or IR. A meta-analysis performed by Okekunle A.P. *et. al.* (60), which compared the impact of oral BCAA supplementation versus dietary intake in relation to DM2, showed that supplementation had no significant impact on circulating BCAA levels, whereas a higher intake of dietary BCAA was associated with a higher risk of DM2.

On the other hand, the intervention studies (51,64-70) assessed the variations in circulating BCAA and in the parameters indicative of DM2 presented by a reduction in BCAA consumption. The trials had a variable duration between one week and two years and their main objective was to clarify whether this selective restriction could reduce circulating BCAA levels and, consequently, improve DM2 analytical values (serum glucose, HOMA-IR...). In all interventions, BCAA intake was provided through dietary intake and both plasma levels and glycemia were measured through a blood test performed under fasting conditions. Likewise, the estimation of diabetes risk was measured through the HOMA-IR index.

In general terms, after the interventions, favorable results were shown in the reduction of plasma BCAA levels, implying a lower incidence of DM2; with the exception of a study carried out by Prodhan U.K. *et. al*. (68) in which no significant changes in plasma BCAA levels were observed, although this was only limited to assessing the impact of the consumption of dairy products, without assessing overall intake. Importantly, these restrictions did not compromise the intake of other essential nutrients (69).

The intervention carried out by Ruiz Canela M. *et. al*. (67) suggest that a dietary pattern based on the Mediterranean diet could mitigate the adverse effects of elevated plasma BCAA on the development of DM2 and, in turn, contribute to its reduction. The impact of a dietary pattern of transition to a vegan diet, in which fish was included as the only animal protein source, was also discussed. In this research conducted by Elshorbagy A. *et. al*. (56) showed a rapid and sustained decrease in plasma BCAA concentrations; leucine decreased on average by 13.5%, isoleucine by 11% and, finally, valine showed a greater decrease at 19.5%.

Asghari G. *et al*. (14) and Fontana L. *et. al*. (51) did not obtain a significant association in insulin levels or pancreatic β-cell functionality when restricting dietary intake of BCAA; but they did obtain an improvement in IR by increasing insulin-sensitizing hormone (FGF21) levels and a considerable decrease in fasting blood glucose. These results have also been reported in other trials (64,66,67,69) and could indicate a certain reversibility of this physiological situation.

Because obesity is considered one of the main risk factors for DM2, it is interesting to observe what happens to BCAA levels in these patients and how they respond to dietary modifications in these patients. On the one hand, a positive association has been found between the BMI value and circulating BCAA (55,71); in fact, it is proposed that elevated levels of these amino acids, at the same time, can be used as markers of cardiovascular disease (58,72,73); likewise, elevated serum BCAA concentrations in obese individuals are reversed with weight loss, until adequate values are reached (71). It is true that, in this context, the scientific evidence is inconsistent

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Conclusions

Despite the essential nature of BCAAs, an excessive accumulation of BCAAs or their metabolites in the blood has been correlated with different pathological conditions, among which the IR characteristic of DM2 stands out. The origin of this increase is still unknown; the main hypotheses point in two directions: a high dietary intake of BCAAs or a dysfunction in their catabolism.

A higher intake of BCAAs has shown a positive association with DM2, especially if it comes from animal products; also, their selective restriction contributes to reduce serum levels and improve metabolic health, without compromising the intake of other essential nutrients. In contrast, BCAA supplementation protocols do not have negative health effects.

This contradiction shows that the effects of BCAAs on metabolic health related to DM2 cannot be studied in isolation; rather, they must be considered as part of a complex interaction of dietary components, in which the nutritional quality of the food is of great importance.

These results, once again, demonstrate the important role that nutrition plays in health and disease, and how certain dietary patterns can seriously worsen our health. However, more research is needed to fully study the impact of BCAA intake on health.

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UNIVERSITARIOS Y SU RENDIMIENTO ACÁDEMICO DURANTE EL CONFINAMIENTO POR COVID -19, UNA MIRADA DESDE LAS TEORÍAS DEL APRENDIZAJE: ECOLOGÍA DEL DESARROLLO HUMANO, CONSTRUCTIVISTA Y SOCIOCULTURAL

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Resumen. INTRODUCCIÓN. La alimentación es un eje transversal para el aprendizaje y aprovechamiento académico. El confinamiento COVID-19, obliga a generar nuevas estrategias que permitan conocer esta relación de la alimentación y rendimiento académico, con la intención de mejorar el aprovechamiento de estudiantes universitarios. OBJETIVO. Aportar algunas consideraciones que permitan conocer la relación entre hábitos de vida saludable, aprendizaje y rendimiento escolar en universitarios. MÉTODO. Este trabajo corresponde a un diseño documental. Se relatan estudios sobre conducta alimentaria, hábitos de vida saludable y su relación en el rendimiento escolar y procesos de aprendizaje en estudiantes universitarios. CONCLUSIÓN. Los estudios encontrados demuestran que los patrones alimentarios así como los niveles de actividad física, horario de sueño entre otros en estudiantes universitarios se han modificado durante el confinamiento COVID-19, además, los niveles de actividad física han disminuido. Con relación, al aprovechamiento escolar se percibe por debajo del esperado. Se puede concluir que es tarea de los nutriólogos incidir en la educación alimentaria de la ciudadanía, para lograr habitos de vida saludable que repercutan en el rendimiento académico de estudiantes universitarios

Palabras clave: conducta alimentaria, hábitos de vida saludable, universitarios, confinamiento COVID-19.

ALIMENTATION OF UNDERGRADUATES AND THEIR LEARNING PROCESS WHILE COVID-19 LOCKDOWN; A NEW OUTLOOK LEARNING THEORIES: HUMAN DEVELOPMENT ECOLOGY, CONSTRUCTIVIST AND SOCIOCULTURAL

Abstract INTRODUCTION. Nutrition is a transversal axis for learning and academic achievement. The COVID-19 confinement forces us to generate new strategies that allow us to know this relationship between nutrition and academic performance, with the intention of improving the achievement of university students. OBJECTIVE. To provide some considerations that allow us to know the relationship between healthy life habits, learning and academic performance in university students. METHOD. This work corresponds to a documentary design. Studies on eating behavior, healthy life habits and their relationship with school performance and learning processes in university students reported. CONCLUSIONS. The studies found show that eating patterns in university students have been modified during COVID-19 confinement, and that physical activity levels have decreased. In another sense, school achievement perceived to be lower than expected and with socioeconomic gaps that have repercussions on university students' learning. In addition, nutritionists should be responsible and designated by the countries to generate this reeducation and modification in school curricula for the promotion of healthy lifestyle habits.

Key words: eating behavior, healthy lifestyle habits, college students, COVID-19 confinement.

Introduction

In December 2019 in the city of Wuhan, China, in the province of Hubei, medical authorities classified several cases of pneumonia of unknown etiological origin. This alerted health authorities worldwide, warning about the possible spread of this microorganism of unknown origin and with a remarkably aggressive symptomatology, causing the death of those infected. Due to the need of knowledge about the outbreak of this microorganism, some investigations were oriented, generated that they were undertaken, so they managed to have more knowledge and therefore a new classification; new Coronavirus, which, if not properly treated, was the cause of severe acute respiratory syndrome. This is how they managed to identify the Coronavirus 2 (SARS CoV-2), causal agent of the new respiratory disease, COVID-19 (1, 2, 3).

In March 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic. Some countries decided to follow health recommendations, such as confinement and social distancing (4).

Since then, and until now, joint efforts have been generated that contribute to the decrease in the incidence rate and spread of the various variants of COVID-19. This had an impact on several productive sectors of the countries, including the education sector (5). These efforts and, specifically, the confinement had an important impact on education and eating habits in students of all educational levels. Psychological factors are related to overweight or obesity, according to a study conducted on university students (6).

Confinement as a preventive measure brought not only reassurance that COVID-19 would not spread, but it also reduced the perceived anxiety about the development of SARS-COV2 in its new variants over time (7).

It is considered that confinement can result in a decrease in physical activity, an increase in unhealthy eating patterns, for example, consumption of saturated fats and ultra-processed foods (pastries, cookies, packaged bread, desserts), thus generating unhealthy lifestyle habits that put at risk the quality of life of individuals and also a possible development of Chronic Non-Communicable Diseases (NCDs) (8).

It is known that NCDs have a close relationship with eating patterns and behaviors in adults, free and conscious in the choice of food they decide to eat. Some NCDs are type II diabetes mellitus, hypertension, dyslipidemia, overweight and obesity, protein-energy malnutrition, folate or iron-dependent anemias. These diseases are related to unhealthy eating patterns, adopted by the community, and it is known that there is a significant deterioration in people living with them, when they are not controlled or attended by the medical-nutritional team. It is for this reason that the implementation of an adequate nutrition and health orientation should be considered (9).

According to the National Health and Nutrition Survey, 2018 (5) (ENSANUT, 2018) applied to 126.5 million Mexican people, there was a combined prevalence of obesity of 75.2% in adults over 20 years old, in addition, 19.5% of the sample presented high levels in triglycerides and serum cholesterol, while 6.7% of Mexicans reported knowing their diagnosis about diabetes mellitus type II, while 12 % of Mexicans claimed to live with arterial hypertension. There is an increase and, in the same sense, a greater concern for the development of ENTCAN in the Mexican adult population over 20 years of age.

The data obtained from the ENSANUT show that Mexico belongs to one of the countries with a high rate for the development of NCDs. There is also concern about the development of these diseases, it also requires adequate guidance for the acquisition of healthy lifestyle habits (HLHs) that provide attitudes and skills for the improvement of dietary patterns and habits. On the other hand, the system leaves disease prevention in the background (10). Regarding healthy lifestyle habits, the following was reported: 63.8% of Mexicans stated that they consumed alcohol, 29% consumed tobacco. In another sense, only 29% of Mexican respondents performed less than 150 minutes of physical activity at the time of the survey during the day. This is the minimum recommended amount of physical activity per week, according to the WHO. High alcohol consumption, combined with low levels of physical activity, could be relevant factors in the early development of ENTCAN in the Mexican population over 20 years of age (11).

Regarding eating habits in the frequencies of food consumption, applied to Mexicans older than 20 years, at the time of the survey, the following was observed in consumption of healthy foods: it was highlighted a low consumption of fruits and vegetables (49.7% and 44.9%), respectively, in addition, a high consumption of sugary drinks (85.8%), (5). A low consumption of fruits and vegetables can cause an increase in metabolic fats, resulting in heart problems, in addition, due to the proliferation of firmicutes and bacteroidetes (constituents of the intestinal microbiota), a development of chronic gastrointestinal problems (12).

In another sense, it is known that the consumption of excessive sugar, contained in sugar-sweetened beverages (fruit juices, processed juices, processed flavored waters) and carbonated, sugar-sweetened beverages (soft drinks with syrups), are precursors in the early development of ETCAN. However, despite various public policies [increase in Value Added Tax (VAT)] to decrease the consumption of these liquids in the Mexican population, significant changes have been seen in the decline of consumption. Leaving the consumption of drinking water in the background (13).

It is good to consider the following, the development of HLHs depends on strategies planned punctually by governments, state, and federal; however, sometimes Mexico is far from them. In addition, it is necessary to bet on the training of professionals in preventive health, in addition, in the designation of this attention to the collectivities, with the intention of generating a correct orientation habit. Mexican nutritionists are the professionals to guide the task of guiding in preventive health and HLHs management.

The confinement by COVID-19 brought with it an important psychological impact on people all over the world (14), investigations carried out in Western countries: (Australia, Canada, China, Hong Kong, etc.). Composed by the review of 25 scientific articles, they managed to highlight the following: it could be observed how people developed problems at a psychological level, affecting their mood derived from: uncertainty, little information, and fear of contagion by COVID-19, to mention a few (14).

In another sense, Romero-Díaz, and Matamoros (2020) conducted a study composed of 214 students in Nicaragua, where they evaluated, through the scale *"Satisfaction with life scale"* (SWLS), the satisfaction that the students perceived during the confinement. The descriptive data obtained in the psychological factor of the students considered the following (15): "to feel fear during the pandemic," evident data due to the little information that existed at the beginning and during the confinement derived from the COVID-19. This research allows us to recognize how, in general, the population and university students perceived greater uncertainty, depending on the lack of knowledge about the pandemic and the COVID-19 confinement.

Taking into account the above, it is necessary to know what is the impact and its possible relationships with eating behaviors and eating habits, in addition, if these are related (6) with school performance and learning of college students, focusing on the following educational theories: ecology of human development, constructivist, and sociocultural. These theories will help to look with a broad approach, in addition, in the understanding of the possible that they keep in the relationship of behavior and eating habits in college students.

Method

The present work was retrieved from a review of scientific articles, whose objective was to determine if the eating behaviors during the pandemic and confinement derived from COVID-19 have an impact on school performance and learning of university students. To do this, a search for scientific articles related to the topic was conducted. The search was composed of original articles and review articles, using the following search engines: "Google Academic," "Redalyc," and "Pubmed." The search for articles began in February 2022 and ended in March 2022.

To locate articles that will be related to eating behavior, school performance, and learning, the filter no older than five years was applied; the different search strategies were used: ("Learning" [MeSH] or "Learning" [in title and abstract]) and ("Eating behavior" [MeSH] or "Eating behavior" [in title and abstract] and "School performance" [MeSH] or "School performance" [in title and abstract] and "Healthy lifestyle habits" [MeSH] or "healthy lifestyle habits" [in title and abstract] or "learning styles" [in title and abstract] or "risky eating behaviors" [in title and abstract]).

Once the titles and summaries of the different articles were obtained, we discarded those articles that did not fit the topic; they would be carried out in preschoolers, schoolchildren, and adolescents or were very short interventions. In another sense, we discarded all those in which it was impossible to read beyond the title/summary.

Finally, a total of fifteen articles were selected and included in the review, six referring to eating behavior and COVID-19 confinement, four referring to healthy lifestyle habits in university students and COVID-19 confinement, and five referring to performance/learning in university students and COVID-19 confinement.

Results

Educational theories: ecology of human development, constructivist, and sociocultural

The ecological theory of human development, postulated by Bronferbrenner, 1987 (16), "*It comprises the scientific study of the progressive mutual accommodation between an active, developing human being and the changing properties of the immediate environments in which the developing person lives*" (p.729). It is possible to emphasize the importance of the surroundings and the environment on the development of the human beings; an adequate environment will bring benefits for the integral health of the people. Therefore, the care of the systems for the development of the human being: macrosystem, microsystem, and mesosystem, will have as an objective the acquisition of HLHs that contribute to a better quality of life (16).

In the same sense, nutrition is implicit in the development of these spheres, which will have an impact on adequate growth, for example, adults with smaller stature tend to suffer from food insecurity in their childhood. This forces us to question the need to adequately inform about the importance of the structure of these systems and their relationship with the HLHs for communities, with the intention that these are key to proper development at different stages of life (16).

The duality that exists between food scarcity and excess weight in the population worldwide is not fully understood (17). Considering the contributions of Stuckler and Nestle (2012), the system of food distribution in the population must be improved. It is clear that this distribution becomes a problem and this inequitable distribution dictated by the macrosystem will directly affect the microsystem, which will affect the possibility of acquiring healthy food and the possibility of having recreational times that contribute to a quality of life shaped by HLHs (17).

In the same vein, maldistribution during the COVID-19 pandemic may have had an impact on HLHs improvement; furthermore, this distribution was mostly limited by confinement and border closures between different countries, it could be attributed that such government mandates may have been the causes of lower HLHs attachment, Stuckler and Nestle (2012).

The constructivist theory. In an epistemological sense, constructivism considers that (18):

> *"The problem of the construction of knowledge is one of the most mysterious and enigmatic problems facing human beings... What men and women are essentially is the product of their ability to acquire knowledge that has enabled them to anticipate, explain, and control the workings of nature"* (pg. 354).

Emphasizing bases on the above, it can be perceived as food has an important role since this should be seen as a construction. This construction will give rise to a healthy or unhealthy eating pattern, linked to beliefs, attitude, and social aptitude towards the preparation, choice, etc.

Humans build from the learning and experiences lived during our lives. These constructions of knowledge can range from uses and customs, and some very particular ones such as hygiene habits, dietary habits, free time management, and incorporation of physical activity into their lives. These constructions will give rise to bodily practices, in this sense, these practices will sometimes dictate relevant scenarios in the life of the human being, the construction of a food pattern and HLHs. Seen from this approach, these turn out to be bodily practices that will allow to potentiate the quality of life of human beings. Therefore, it is possible to notice the need to evoke the HLHs construction during the confinement by COVID-19 since it could be observed how many people were victims of greater complications related to the NCDs, with which they lived previously (18).

Returning to Vygotsky and the development of his sociocultural theory (19), the following can be observed:

"Through coexistence, human beings tend to build knowledge that will allow them to have a better quality of life, together with the development of new learning, without leaving behind their previous experiences" (pg. 42).

Eating patterns are established during life from early childhood, are key in the growth and eating behavior that will be acquired as adults. The proper development of these patterns, established in the family, will be carried into practice for the rest of one's life. In contrast, during the pandemic, people were forced to improve their HLHs, and this change could be attributed to fear of getting sick or dying. Although there is an opportunity to change them, sometimes the context is not conducive to changing these HLHs.

An example in the establishment of unhealthy HLHs is "the use of lard by Mexican matrons in the 20th century to flavor food." It is clear that generations in the 21st century sometimes continue to carry these unhealthy practices with them, but some others question the possible impact on their health and seek alternatives that are beneficial in preventing the early development of NCDs (19).

The above allows us to understand the importance of building and developing or, sometimes, maintaining HLHs during the adult stage, with the intention of generating greater quality of life, and in the COVID-19 context, we sought the maintenance or improvement of health, improving HLHs, which were put in less practice before it and the impact on people's lives.

Bourdieu defines lifestyle as *"the routine actions product of a knowledge originated in social structures and reproduced through concrete acts and actors"* (1998). The impact of non-formal education oriented to the development of HLHs, within the family, such as, the culture in each kitchen, the belief system about healthy or unhealthy food, the ways of preparation, the preference in consumption of certain foods, and other culinary practices have been the product of collective knowledge and social structure and its adoption throughout life (culinary heritage); (16, 19).

It is known in clinical nutrition that the stages of human development will demand specific nutritional requirements (kilocalories, macronutrients, micronutrients, water, and fiber); therefore, attention should be paid to the importance of building healthy eating patterns (Table 1), which will contribute to have a better quality of life and not only put into practice the improvement of healthy eating patterns in unfavorable contexts as COVID-19. In another sense, these patterns will conceive the eating behaviors of people. On the other hand, eating behaviors (Table 1) as well as patterns will contribute to the preservation of metabolic health and, therefore, the prevention of the development of NCDs through the practice of HLHs. It is worth mentioning that during the COVID-19 pandemic there may have been changes in eating behavior linked to the emotional state of individuals (9).

Table 1

Difference between eating behavior and eating pattern (20)

Food pattern	"Strong attachment to the products that make it up in the eating habits of the population, along with a marked territorial rootedness in time; it also represents a constant of traditions and a socially segmented consumption structure, an expression of national and regional culture."
Feeding behavior	"The set of actions that establish the relationship between human beings and food."

Note: Taken from: Torres-Torres, F. Changes in the dietary pattern in Mexico City. 2007; Oyarce-Merino K, Valladares-Vega M, Elizondo-Vega R, Obregón A. Eating behavior in children. 2016.

It is necessary for the nutrition professional to understand how the mentioned educational theories play an important role in human development; and how socio-cultural factors will endow the person with knowledge to make use of informed decisions, thereby building with conscious bases the choice on some foods healthier than on others that are less healthy. In addition, as such sociocultural context in the COVID-19 pandemic, it could have a negative impact on the practice of HLHs. In another sense, that the population have tools that allow to understand their food culture and allow to relearn or transform the HLHs, which do not favor the maintenance in the quality of life, will be determinants in the process of health-disease and, in the future, these could prevent them and provide them with tools that help to improve their quality of life and not be disadvantaged in contingency situations (19).

Eating behaviors in university students

Eating behavior is multifactorial, i.e., it includes psychological, biological, social/cultural and, sometimes, spiritual aspects. For Lazarevich, (2016), eating behavior in college students is key to the preservation of health, in the same sense, it is considered key to incorporate programs to generate spaces for physical activity and dietary guidance, as adjuvants in reducing stress and factors associated with the acquisition of unhealthy or risky eating behaviors. (21)

Findings related to eating behavior in Hispanic students (6) have shown that college students prefer to follow unhealthy HLHs, associated with COVID-19 confinement, binge eating, associated with emotions and food consumption, has been little studied. In a multicenter study of 829 participants, changes in body composition and eating behavior were observed. It is worth mentioning that the multicenter study was conducted in patients with eating disorders during COVID-19 confinement (22).

In review studies, it has been shown that there is a change in eating behavior associated with COVID-19 confinement, motivated by experiencing negative emotions (23). Eating behavior in students could be affected by stress overload (technostress) (24), although it is an existing topic of which little is said, it can be considered that students are affected by these feelings/emotions and the compensation with comfort foods: sweet, energy-dense foods with low nutritional intake during COVID-19 confinement (24).

This could be related to the change in the eating behavior of university students, in addition, this eating behavior may be conditioned to the technostress generated in virtual education spaces, little linked to behavioral changes, such as the eating pattern of university students (23, 24).

In a study conducted in Mexico (25), in 323 students, it was possible to locate two new components for a better understanding of eating behavior: food neophobia (fear of trying new foods) and food neophilia (daring to try new foods). This study was conducted during the COVID-19 pandemic, the data showed that women tend to be more fearful of including new foods in their diet, and they would not try foods they are unfamiliar with. These findings underscore the importance of further research to understand the *"dietary variety"* that dictates the laws of eating as a healthy behavior and to prevent the development of NCDs (15).

Healthy lifestyle habits in university students

When talking about healthy life habits, the following can be understood (16), *"group of attitudes and behaviors that people practice and develop consciously and voluntarily during the course of their lives"* (pg. 247), life habits have been altered in university students by the pandemic and the confinement derived from the COVID-19. In cross-sectional research, (Veramendi, NG. 2020) observed that the perception in university students "lifestyle," it was associated with a higher quality of life, in addition, when submitting to the analysis non-grouped data, the food practices were not entirely healthy, preferring ultra-processed foods (26).

It is necessary to return to the importance of access to food due to economic income in university students and how this could potentially affect a varied diet and consumption of foods rich in vitamin D (yogurt, cheese, etc.), animal proteins (beef, fish, seafood, pork, poultry), and fruits. In the Mexican context, these are foods that some households with low incomes have difficulty accessing. An investigation oriented to know the family income and the perception of university students shows how this influenced their emotional stability, derived from the concern of the economic income and its distribution (27). The above could reveal the difficulties and food insecurity in university students, which in turn could modify healthy life habits in them, depending on the economic income, in addition during COVID-19, different scenarios were experienced that were related to unemployment of citizens, having a lower income and, therefore, less access to nutritious food.

Regarding the HLHs that are related to their eating patterns, it was observed in investigations conducted in Latin America a poor adjustment to meal times, a high consumption of ultra-processed foods (cookies, pastries, packaged sweet bread), and a perception of weight different from the real one (real weight less than the perceived), (28). The quality of food in college students may be influenced by poor or no management of free time and procrastination dependent on their ontological stage; however, attention should be focused on the dissemination of information for decision making to generate greater HLHs.

In contrast, current research developed in Spain showed that during the confinement derived from COVID-19, regarding the change of food, habits had favorable repercussions (29); a higher consumption of healthy food was observed. Besides, there was a decrease in the consumption of unhealthy food.

In another sense, it observed an increase in food prepared at home. People acknowledged spending more than nine hours sitting and little physical activity during confinement. In addition, media publicity on the importance and relevance of nutrition and food guidance for the management of healthy HLHs, distributed by the WHO, positioned nutrition as a transversal axis in the improvement of HLHs, conscious choice of food, and home cooking practices.

In Peru, 875 adults (30), behavioral change around food was observed. Participants showed increased interest in eating healthy foods, and improved food preparation, both behavioral changes were encouraged by two important factors; the first was the belief that prevention of infection by COVID-19, and the second was associated with post-infection by COVID-19. It was believed that they would have a quick recovery and less symptomatology than people who did not follow healthy eating patterns. In addition, within the study was observed the consumption of food supplements, vitamins, and minerals that could help prevent infection or restore health, an attitude that was not noticed in previous studies. The consumption of supplements has not been of attention in Latin American countries.

In conclusion, it is possible to notice an increasing modification in HLHs, both positive and negative. Regarding those that do not seek to preserve health and avoid the development of ETCAN of the individual, they suggest as an indicator the necessary and immediate adequacy/instauration of programs that reinforce HLHs in university students, being the "terminal" education. It is necessary to reinforce the promotion of health for prevention and preservation of the quality of life (10).

Learning, school performance, and nutrition

University students perceive as a cofactor (31,32) the difficulties that have been found in the virtual educational environments, caused by the confinement derived from the COVID-19 through it. An education not centered on the student can be perceived, having repercussions on their learning and, therefore, on their school performance and, not less important, the acquisition of significant knowledge for life, and their next professional practice.

Villa et al. (2020), when conducting a cross-sectional study in 1612 university students at the beginning of the course and, consequently, an application in exam period to 872 university students. They observed that institutional communication was difficult; they did not feel comfortable in distance education, preferring face-to-face classes, and they also noted that there were unequal gaps with respect to access to virtual education (33).

Other studies, Muñoz, Lluch, (2020), and J. Clemente (2021) consider that educational inequalities in the new normality are multifactorial, affecting the acquisition and development of new learning (34). Maslow states that if the human being does not have basic aspects covered, it is difficult for him to advance to the next step that grants him self-realization. If food needs are not covered because they also depend on the economy, geographic location, etc., and are unfavorable, then academic performance can be negatively impacted (27, 31, 35).

However, Cotoonieto-Martínez, E. et al (2021); (36), invite us to reflect on the areas of opportunity, teacher training and openness to learning and the use of new technologies, oriented to the development of new skills for university students in the new normality. There are many external factors that must be considered in order to understand how students can develop learning and have optimal academic performance in the new normal.

In conclusion, research oriented to know school performance and eating habits, as well as HLHs, consider that low school performance is associated with various unhealthy eating practices: consumption of junk food, alcohol, tobacco, and drug use. In addition, university students who are overweight or obese tend to have lower academic performance. This should be a central axis in considering that nutrition has an impact on university students during the new normality caused by the pandemic and confinement derived from COVID-19 (36).

Conclusions

Considering the above data, it can be concluded that:

Eating patterns are influenced by several factors, in addition, these have an impact on unhealthy eating behaviors, and these are adopted from within the family and the lack of education and guidance in relevant food at different stages of life.

Food in Mexicans has been viewed with disinterest by the regulatory bodies of public health policies, so that inequality and inequity have generated a country that presents food insecurity, in the same sense. It is difficult for Mexicans to develop HLHs from early stages.

Programs that can be tailored to meet needs in the redirection of HLHs in college students, with the intention of helping them become adults less likely to develop ETCAN, are identified as a need.

Strategies to implement physical activity in the educational programs of university education in Mexico should emphasize the importance of the adoption of physical activity within the HLHs pantry.

The population should be informed about the proper use of dietary supplements. These recommendations should be based on scientific evidence to safeguard the safety and health of people.

The new normality forces to rethink how to develop relevant HLHs. The development of them will have an impact on the academic achievement of university students. In addition, it will decrease the repercussions that may exist at the mental level at different educational levels derived from stress; nutrition should be seen as the basis for the maintenance and prevention of these episodes. Due to the fact that mental health in university students is considered relevant, in addition, university students are considered a vulnerable group and of special attention (37). It has been observed in systematic review studies how university students perceive a decrease in their mental health caused by multiple factors. An inadequate attention to mental health could be associated to the teaching-learning processes besides affecting their academic performance and, in the same sense, their scholastic achievement. In another sense, eating behavior, as has been observed, sometimes depends on feelings and emotions, such as, worry; adding motives to the experience of emotional instability in university students.

Researchers in human nutrition are invited to generate new strategies that can relate to education and the development of adequate, realistic, and applicable HLHs in the Mexican population.

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EFEITO DA DIETA LOWCARB SOBRE A COMPOSIÇÃO CORPORAL DE INDIVÍDUOS PRATICANTES DE MUSCULAÇÃO COM TREINAMENTO DE FORÇA

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Resumo. Introdução: A dieta low-carb vem sendo estudada, pois têm mostrado resultados significativos no benefício da redução de peso, por ser composta maioritariamente por proteínas e gorduras naturais com baixo potencial inflamatório, ajudando também a reduzir e a combater a retenção de líquidos. Esta dieta associada a treino de força poderia auxiliar no crescimento muscular bem como na redução da gordura corporal. Objetivo**:** Este estudo teve como objetivo analisar o efeito de uma dieta low-carb na composição corporal de praticantes de musculação submetidos ao treino de força. Metodologia: A amostra foi composta por 24 indivíduos do sexo masculino, não atletas, com idade entre 19 a 34 anos, com experiência em treinamento. Os participantes foram divididos em dois grupos, onde em um grupo foi submetido ao treino de força com dieta normocalórica, normoproteica, normolipídica e normoglicidica e o segundo grupo submetido ao treino de força com dieta lowcarbhipoglicídica, hiperproteica, hiperlipídica, durante o período de quatro semanas. Resultados**:** Ao comparar a composição corporal do grupo com a intervenção low-carb com relação ao grupo controle, não foram observadas diferenças significativas com relação aos dados de percentual da gordura corporal, percentual de massa magra, índice de massa corporal. Conclusão**:** Dadas as evidências prévias sobre a estratégia dietética low-carb, sugere-se a realização de mais estudos nesta área para o levantamento de novos resultados e conclusões.

Palavras-chave: Composição corporal, dieta baixa em carboidrato, dieta low-carb, fortalecimento por levantamento de peso.

Effect of carbohydrate diet on body compositionofindividualspracticingbodybuildingwithstrengthtraining

Summary. Introduction: The low-carb diet has been studied, as it has shown significant results in the benefit of weigh treduction, as it iscomposed most lyofproteins and natural fats with low inflammatory potential, also help ingto reduce and combat fluid retention. This diet combined withs trength training could help with muscle growth as well as reducing body fat. Objective: This study aimed to analyzeth effect of a low-carb diet on the body composition of body builders submitted to strength training. Methodology: The sample consisted of 24 male individuals, non-athletes, aged between 19 and 34 years, with training experience. Participants were divided into two groups, where in one group was submitted tostrength training with a normocaloric, normoproteic, normolipidicandnormoglycidic diet and the second group was submitted to strength training with a low carb, hypoglycemic, hyperproteic, hyperlipidic diet, during the period of four weeks. Results: When comparing the body composition of the group with the low-carbintervention in relation to the control group, no significant differences were observe dregarding the data of body fat percentage, lean mass percentage, body mass index. Conclusion: Given the previous evidence on the low-carbdietary strategy, further studies in this area are suggested toobta in new results and conclusions.

Keywords: Body composition, low-carb diet, low-carb diet, strengthbyweight lifting .

Efecto de una dieta baja en carbohidratos sobre la composición corporal de individuos que practican musculación con entrenamiento de fuerza

Resumen. Introducción: La dieta baja en carbohidratos ha sido estudiada, ya que ha mostrado resultados significativos en el beneficio de la reducción de peso, ya que está compuesta en su mayoría por proteínas y grasas naturales con bajo potencial inflamatorio, ayudando además a reducir y combatir la retención de líquidos. Esta dieta combinada con entrenamiento de fuerza podría ayudar con el crecimiento muscular y reducir la grasa corporal. Objetivo: Este estudio tuvo como objetivo analizar el efecto de una dieta baja en carbohidratos sobre la composición corporal de culturistas sometidos a entrenamiento de fuerza. Metodología: La muestra estuvo constituida por 24 individuos del sexo masculino, no deportistas, con edades comprendidas entre 19 y 34 años, con experiencia en entrenamiento. Los participantes fueron divididos en dos grupos, donde un grupo se sometió a un entrenamiento de fuerza con una dieta normocalórica, normoproteica, normolipídica y normoglicídica y el segundo grupo se sometió a un entrenamiento de fuerza con una dieta baja en carbohidratos, hipoglucemiante, hiperproteica, hiperlipídica, durante el período de cuatro semanas. Resultados: Al comparar la composición corporal del grupo con la intervención baja en carbohidratos en relación al grupo control, no se observaron diferencias significativas en cuanto a los datos de porcentaje de grasa corporal, porcentaje de masa magra, índice de masa corporal. Conclusión: Dada la evidencia previa sobre la estrategia dietética baja en carbohidratos, se sugieren más estudios en esta área para obtener nuevos resultados y conclusiones.

Palabras clave: composición corporal, dieta baja en carbohidratos, dieta baja en carbohidratos, fuerza por levantamiento de pesas.

Introduction.

The dietary basis of the individual plays a determining role in his or her physical condition, and every day new dietary proposals emerge that seek to modify the standard dietary basis in search of faster results (1,2).

In ancient times, being overweight was considered a condition of social status, since the person who presented a higher weight was considered more fortunate, thus showing his curves associated with his possessions (3). With the passage of time, society changed and in 1864, William Banting, in his quest for a lighter body, eliminated bread, potatoes, and sugar from his diet, eating basically meat, fish, and vegetables (4).

Over the years, diets have evolved and modernized according to new scientific findings regarding their efficacy. In 1972, later revised in 1992, Dr. Atkins' diet already recommended diets with a restricted amount of carbohydrates, with proteins and fats as the dietary basis (5). Then came Dr. Dukan's diet in 2000, where the basis was the same as that of Dr. Atkins, but the main difference was the priority given to monounsaturated and polyunsaturated fats, the famous good fats, and also that proteins should be lean and included physical activity in the weight loss program (6).

Currently, research has approached the efficacy of the ketogenic diet, which is given by the consumption of less than 10% of carbohydrates, and the low-carbohydrate diet, which in Portuguese would be a low-carbohydrate diet. The low-carbohydrate diet is characterized by a daily intake of 30 to 130g of carbohydrates (7). There is evidence that this dietary strategy favors the loss of body fat, by the mechanism of action of the insulin/glucagon ratio. It is known that carbohydrate is transformed into glucose and the same is absorbed by the liver, when many carbohydrate-rich foods are consumed, there is an increase in the release of insulin in the body, which in turn reduces the release of glucagon and is responsible for the burning of body fat. When foods rich in protein, quality fats, and fiber are consumed, there is a reduction in the amount of circulating insulin and, consequently, an increase in the release of glucagon. Thus, the individual can lose weight more quickly and effectively and, in parallel, obtains a decrease in the risks of developing cardiovascular diseases and other complications associated with overweight and obesity (8).

Nowadays, the routine with little time available has made the population increasingly sedentary and, consequently, more obese since the reduction of physical exercise associated with a poor-quality diet (based on processed and industrialized foods) leads to an increase in body weight, in addition to serious health problems. People show a certain urgency to obtain quick results and, considering that the low-carbohydrate diet is efficient in this sense, it has been one of the most applied and sought-after proposals nowadays when it comes to losing weight. On the other hand, strength training is more and more requested and takes precedence over aerobic training (2).

Strength training refers to an exercise or a sequence of exercises, which will help the individual's muscle building, aiming at the individual's anaerobic endurance. There is evidence that strength training associated with low-carbohydrate diets accelerates weight loss (6,9).

Methodology

The study consists of a non-randomized clinical trial (quasi-experimental).

This study was conducted from December 2020 to January 2021, with a total of four weeks of intervention. The study population was composed of students attending the Health and Movement gym, in the city of Balneário Arroio do Silva / SC, where the study was conducted. The sample was composed of 24 individuals. These correspond to 100% of the study population that fit the inclusion criteria, that is, non-athletes, in the age range of 19 to 34 years, male, with training experience, non-consumers of steroids. Participants were divided into two groups:

Group 1: Twelve individuals who underwent strength training with a normocaloric, normoprotein, normolipidemic, and normoglycemic diet.

Group 2: Twelve individuals who underwent strength training with a low-carbohydrate, hypoglycemic, hyperproteic, and hyperlipidemic diet, mainly rich in monounsaturated fat.

A non-probabilistic convenience sampling was performed in which the researcher uses subjective choice criteria. The participants were already practicing bodybuilding.

Inclusion criteria:

- Being a man

- No underlying chronic diseases

- Have experience in the practice of resistance training for a minimum of 90 days

- Not following a specific diet with nutritional control

- Sign the TCLE

Exclusion criteria:

- Being an athlete

- Being users of anabolic androgenic steroids

- Not agreeing with the study criteria and refusing to sign the TCLE

Measuring instruments and techniques

A digital scale (Omron HBF 514 model) used in the evaluation of body composition before and after the application of the dietary strategies in the intervention group and in the control group.

A tape measure stadiometer, without specific marking, was used in the evaluation of body composition before and after the application of the dietary strategies in the intervention group and in the control group.

The Cescorf adipometer was used in the evaluation of body composition before and after the application of the dietary strategies in the intervention group and in the control group. The adipometer was used to obtain the skinfold values of the participants in order to calculate the percentage of body fat and the percentage of lean mass of the participants.

The Cescorf tape measure was used in the evaluation of body composition before and after the application of the dietary strategies in the intervention and control groups.

The calculations and formulas to perform the physical assessment of individuals and determine body composition used the equation of Jackson and Pollock (10) published in 1978 [1.112- 0.00043499 x (Σ 7 folds) + 0.00000055 x (Σ 7 folds) 2 - 0.00028826 x (age)]. This equation was developed to estimate the body fat content of men (10).

Basal metabolic rate (BMR) and total energy expenditure (TEE) were determined using the Harris and Benedict formula (11), which for the male sex is TEE = 662 - (9.53 x I) + [NAF x (15.91 x P + 539.6 x A)], where P is weight, A is height, and I is age. The physical activity factor (PAF) ranks: sedentary 1.0, light 1.11, moderate 1.25, intense 1.48. Both for the age group 19 years and older (11).

The participants were divided into two groups. After the separation of the groups, an analysis of the body composition of the individuals was performed: percentage of body fat and muscle mass.

The intensity of the strength training was adjusted to 80% using the one repetition maximum (1RM) test for the main strength training exercises. The training was composed in the frequency of five times per week, where chest, shoulder, triceps, back, biceps, and lower limbs were worked. Multiple series system of three series with 8 to 12 repetitions for the exercises with 4 exercises for the chest, back, and lower limbs groups and 3 exercises for shoulder, triceps, and biceps, with interval of 45 seconds to 1 minute and 30 seconds, with the division of the weekly training in format A (chest, shoulders, and triceps), B (back and biceps), and C (lower limbs). All workouts were accompanied by a professional (12-14).

The caloric restriction to be followed during the research through the *low-carbohydrate* diet with 100 grams of carbohydrates per day is through the consumption of less than 200 grams of carbohydrates per day. The other macronutrients being in the range of 35 to 40 percent lipids and 35 to 40 percent protein calculated individually. Complex carbohydrates are used to replenish muscle glycogen stores and are consumed in the first meal after training and in 3 more meals.

Participants in the control group received a normocaloric (individually calculated GET value), normoglycemic (50% carbohydrate), normoproteic (30% protein), and normolipidic (20% lipid) diet also prescribed by the nutritionist (15).

The analysis was performed with the GraphpadPrism program, version 6.01, in which the *one-way Anova* analysis was chosen for paired dependent and independent samples, intergroup and intragroup with mean and standard deviation, using p-value <0.05 (level of significance considered).

Results

This study had as population sample 24 students, being 12 students from group 1, and 12 students from group 2, from a bodybuilding gym. The participants were male, with an age range of 19 to 34 years, who had experience in training and were not steroid users.

The data in the tables are intended to present the mean, standard deviation, maximum and minimum values of variables such as age, height, weight before and after, and Body Mass Index (BMI) before and after sampling, as presented in Tables 1 and 2.

Table 1. General data of the control group

	Age (years) Group 1	*Height (m) Group 1*	*Weight (kg) Before Group 1*	*BMI (Kg/m²) Before Group 1*	*Weight (kg) After Group 1*	*BMI (Kg/m²) After Group 1*
Participants	12	12	12	12	12	12
Mean	27,5	1,76	85,62	27,48	85,75	27,52
Standard deviation	5,78	0,07	12,78	3,22	12,27	2,97
Minimum	19	1,68	65,3	23,14	66,7	23,63
Maximum	36	1,92	104	34,35	103	34,02

Grando (2021)

According to Table 1, the participants had a mean age of 27.5 years and a mean BMI value of 27.52kg/m^2 after the intervention. Being that the classification for BMI is less than 18.5 - Underweight, between 18.5 and 24.9 - normal weight and between 25 and 29.9 - Overweight (above the desired weight), Equal or above 30 - Obesity (16).

Table 2: general data of the intervention group

	Age (years) Group 2	*Height (m) Group 2*	*Weight (kg) Before Group 2*	*BMI (Kg/m²) Before Group 2*	*Weight (kg) Then Group 2*	*BMI (Kg/m²) Then Group 2*
Participants	12	12	12	12	12	12
Mean	27,7	1,76	85,75	27,96	84,25	27,44
Standard deviation	4,33	0,09	7,96	4,05	7,22	3,61
Minimum	19	1,68	75	21,83	73	21,83
Maximum	34	1,95	102	35,29	98	33,91

According to Table 2, the participants had a mean age of 27 years and a mean BMI value of 27.44kg/m^2 after the intervention. Being that the classification for BMI is less than 18.5 - Underweight, between 18.5 and 24.9 - normal weight and between 25 and 29.9 - Overweight (above the desired weight), Equal or above 30 - Obesity (16).

Figure 1 shows the graphical analysis of the BMI of the research participants. No significant differences were observed when comparing the groups before and after, nor between the groups after the four weeks of intervention. There were no significant differences between the same group and between groups.

Figure 1. Groups 1 and 2: Between control and intervention groups

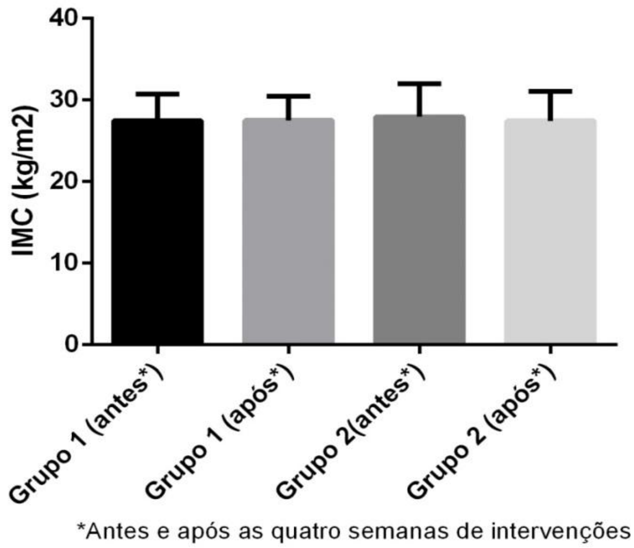


Figure 2 presents the graphical analysis of the body fat percentage of the research participants. No significant differences were observed when comparing the groups before and after, nor between the groups after the four weeks of intervention. Both groups remained with a body fat percentage similar to the initial assessment.

Figure 2. Groups 1 and 2: Between control and intervention groups

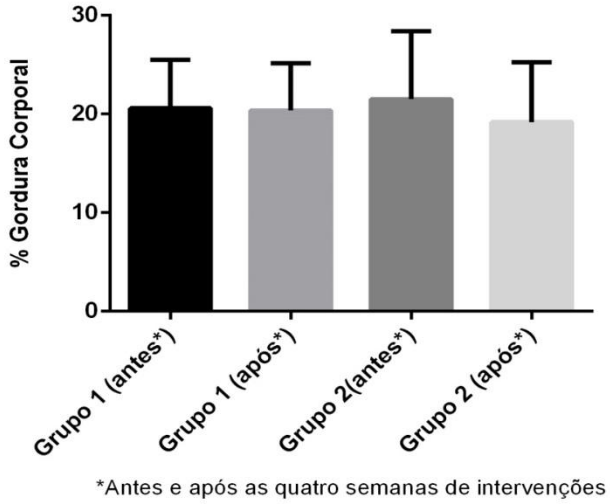
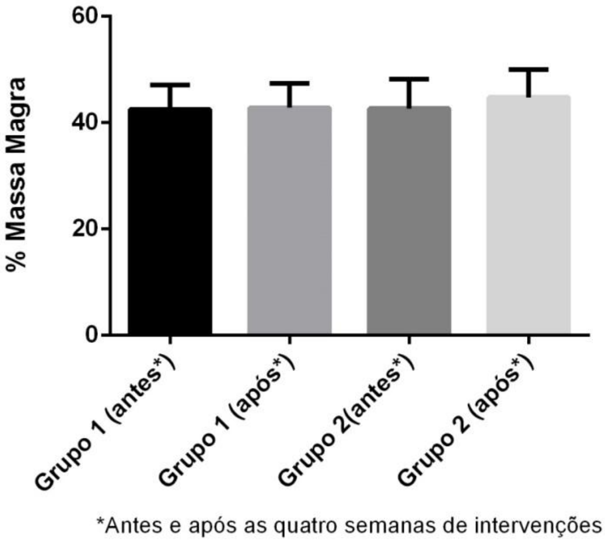


Figure 3 shows the evaluation of the percentage of lean mass of the overall sample of research participants. No significant differences were observed when comparing the groups before and after, nor between the groups after the four weeks of intervention. Both groups remained with a lean mass percentage similar to the initial assessment.

Figure 3. Groups 1 and 2: Between control and intervention groups



Discussion and conclusions

The BMI data before and after the intervention showed overweight in the participants as shown in Table 5.1. However, when measuring BMI and verifying that it is above normal, it is advisable to perform a body composition assessment. The objective is to verify if the excess weight is related to their amount of lean mass (muscle, bone, and residual weight) or adipose (fat) (15).

BMI should always be associated with the evaluation of the percentage of body fat and the percentage of lean mass in order to have a correct and more reliable physical evaluation (16,17). The present study aimed to evaluate BMI before and after the application of strength training and low-carbohydrate diet to complement the physical assessment, but no significant differences were observed in the comparison between groups. The study by Creighton et al. (17) observed in competitive runners that the metabolic profile obtained significant improvements with no change in the BMI of the participants.

Penteado et al. (16), who evaluated the BMI of 13 athletes of an indoor soccer team in 2009, reported that 61.4% of the participants were overweight and obese. However, the percentage of body fat was estimated between normal and below the recommended range, confirming that the assessment of nutritional status through BMI is not the most appropriate parameter since it is based on the relationship between weight and height. However, it is not an accurate measure of body fat content and, in this case, should be associated with another indicator of body composition (18).

Low-carbohydrate diets have recently become very popular due to their numerous health benefits. Several studies have been conducted on the impact of low-carbohydrate diets on improving exercise performance in athletes, reducing fat content, and decreasing the risk of dyslipidemia or insulin resistance in overweight and obese individuals (18-20).

Starting training with a low carbohydrate reserve promotes improvements that favor lipid metabolism as well as limiting performance for more intense workouts, just as a diet rich in fat can favor greater fat oxidation, but energy restriction is usually linked to the pursuit of aesthetic purposes and in strength sports athletes (9,12). The present study evaluated the percentage of body fat before and after group 1, which was the control group with fitness training associated with a standard diet, and before and after group 2, the intervention group, which performed strength training and received the low-carbohydrate diet, finding no significant difference in the comparison between groups. Michalczyk (21) conducted a study with competitive basketball players, where he used the low-carbohydrate diet for four weeks and obtained a significant reduction in the percentage of body fat contradicting the results found but also obtained no significant differences in the percentage of lean mass, which corroborates the results of this study, and was evaluated before and after in both group 1 and group 2.

The maintenance of lean mass is extremely important and it should be remembered that this component is directly influenced by the level of muscle glycogen, which is almost twice as high in competitive athletes compared to untrained individuals, so biochemical analysis is necessary in future analyses (22).

Rothschild and Earnest (23) observed in their study an improvement in mitochondrial enzyme activity, mitochondrial content, and fat oxidation rates; however, they did not observe any significant difference in physical changes on acute application of the low-carbohydrate diet, just as this study found no significant difference in this study, highlighting the importance of biochemical analysis in the future.

According to the research of Guimarães et al. (24), where tests and application of the low-carbohydrate diet were performed in 60 participants who practiced weight training to analyze weight reduction and lean mass gain, the result was an average weight reduction of around 2.5 kg and a reduction in BMI close to 0,9 kg/m^2, in addition to an increase in lean mass and a reduction in fat mass, highlighting the greater reduction in average body weight in men (-3.8 kg) relative to women (2.4 kg), which was not observed in the present investigation, as it did not include a sample of women. It is believed that, if the cited study had only analyzed the before and after, it would have the same results; however, a deeper analysis is necessary for this statement.

It can be observed in the same way in the qualitative study conducted by Fiuza (25), where he makes a relationship between men and women, applying the low-carbohydrate diet during a period of one month, in 15 practitioners of resistance training. The age range of the participants was from 20 to 52 years, with a predominance of 20 to 28 years, and the female audience was 67% and the male 33%. The research revealed that, in both groups, there was loss of fat mass, but this significant reduction is only observed when comparing the groups between genders; however, it does not show the results within the same gender as in this study.

One of the factors that reduce the effectiveness of adherence to dietary reeducation diets is the difficulty in losing weight, sometimes related to sedentary lifestyle, poor eating habits, noncompliance with diet, and physical activities or individual comorbidities that cause patients to drop out before achieving significant results. In this sense, the choice of the low-carbohydrate diet promotes faster weight adjustment, thus favoring greater patient adherence to the therapeutic process (14).

In a study conducted by Francisco (26) for a year and a half, it was divided into 3 phases, the first and second being the phase of application of the low-carbohydrate diet that resulted in the desired weight loss, and the third phase, after one year of the first and second phases, the participants continued to maintain the weight achieved and the eating habits developed during the intervention. Of this participant population of 663 individuals, only 70 agreed to undergo the nutritional evaluation after one year, where it is observed that the BMI of the participants at the beginning of the research, being 60% of the individuals pre-obese and 27.8% with grade I obesity, and the rest presented grade II and III obesity. At the beginning of the maintenance phase, the participants were classified as 45.1% eutrophic, 44.7% pre-obese, and 8.6% grade I obese; and after one year, 35.8% of the 21 participants were eutrophic, 47.2% pre-obese, and 15% grade I obese. This study showed that the low-carbohydrate diet was effective in the application period. However, it needs an adequate period of application to observe a response to treatment. It is believed that this has been the most striking factor in the results presented in the current research, which was based on a short period of application made it possible to obtain significant results, suggesting that a longer period of application of the diet would have a promising result.

A nutritional research was conducted on the application of the low-carbohydrate diet in runners based on the energy expenditure of the group and sports performance before and after the test period. Having street running as an aerobic sport, Leite (27) understood in his research that the low-carbohydrate diet did not bring benefits to the participants of the project, where he did not find significant results with the diet. However, it is believed that associated with strength training the results are more promising, even not having found significant difference in this study.

Hashimoto et al. (28), during the first meta-analysis on the effect of the low-carbohydrate diet on fat percentage and body weight in patients seeking to lose weight, regardless of age and gender, observed that there was a greater loss of fat mass with the application of the low-carbohydrate diet compared to the other conventional control diets due to the higher protein intake. This study was one of those used in the search for material for the development of this work; however, the expected result was not obtained as shown in this meta-analysis.

According to Perroni et al. (29), although low-carbohydrate diets may provide metabolic benefits, when less than 50 g of carbohydrate/day is offered, it may result in ergolytic effects, i.e., it may end up compromising the individual's physical capacity or performance in activities such as strength training itself.

Lacerda (30) conducted a qualitative study with Crossfit practitioners to evaluate physical results. A reduction in hip and waist circumferences, loss of fat percentage and body weight was observed; however, there were no significant changes in the percentage of lean mass, and the participants continued with the nutritional diagnosis of overweight. The women's group presented a loss of about 4kg in relation to the initial weight and 4cm of loss in waist measurements, while the men showed a significant difference of almost 10kg in relation to the initial weight. There was also a reduction in BMI in both genders evaluated. This study, despite not considering a dietary intervention, was considered relevant as CrossFit is also classified as strength training. However, this work by Lacerda does not corroborate with the findings of this study in which no significant difference in body fat and body weight loss was observed, even using the same four-week training and diet application period.

According to Astrup and Hjorth (31), the efficacy of the low-carbohydrate diet depends directly on the metabolic system of each individual. Research conducted among individuals who were subjected to three types of diets, including the low-carbohydrate diet, indicated that the low glycemic index presented by the low-carbohydrate diet provides an improvement in the metabolism of individuals, such as the reduction of the lipid, glycemic, and hepatic profile; this being one of the key parts for the weight loss result. The study also revealed that most of the prediabetic individuals reduced their weight with a diet oriented to a lower quantity and higher quality of carbohydrates ingested, with a higher consumption of whole grains and fiber. This study reinforces the importance of biochemical analysis and new findings should be sought in the current research, and that physical assessment alone was not effective in obtaining significant results.

A very controversial study by Kabisch et al. (32), in 140 individuals with non-alcoholic fatty liver disease, indicated that there were no changes in hepatic fat with the application of the low-carbohydrate diet, but there were significant changes in the reduction of obesity indexes according to BMI and triglyceride parameters. Diets with fat reduction in the case of patients with hepatic fat showed more significant changes than the application of diets with lower carbohydrate intake (32). Other studies found in the literature show the efficacy of the low-carbohydrate diet in the reduction of non-alcoholic hepatic steatosis, reflected in the percentage of body fat (33), being what this study sought in its analysis.

Araujo et al. (34) conducted a test application of a high-protein, low-carbohydrate diet together with strength training in a group of 25 overweight older women. The diet consisted of protein (1.8g/kg/day x 1.0g/kg/day) and carbohydrate (2.0g/kg/day x 3.0g/kg/day) and similar amounts of lipids and fiber for a period of eight weeks. Compared to the traditional control diet (normo-glycemic, lipid, and protein), the hyperprotein diet with reduced carbohydrate intake showed no significant differences in fat mass loss and reduction in measurements. Similar to the results of this study, no significant differences were observed in the analysis of body weight and fat mass percentage.

Research was conducted with eight cyclists, comparing the efficacy of a Western diet with the low-carbohydrate diet. This research was applied for a period of four weeks for each diet, and the results showed that there was reduction of BMI, improvement of lipid and lipoprotein profile, and biochemical improvement of the participants (35), which differs from the BMI findings, but the biochemical analysis was not performed, and it is believed that, if it had been performed, the results would be significant as shown in other studies.

This study showed no significant changes in body fat percentage, lean mass percentage, body mass index, both in group 1 and group 2, which performed the application of the low-carbohydrate diet together with strength training. Regarding the BMI of the participants, there was a mean reduction of approximately 1.38 kg/m2 in relation to the maximum obtained before the intervention and after the investigation, which is not considered a significant reduction for the investigation. Regarding the weight of the participants, the mean reduction was 2 kg relative to the initial minimum weight in both phases and 4 kg relative to the maximum weight between them within standard deviation. Even without significant changes, it can be noted that, in numbers, the changes occurred were more visible in group 2, so the continuation of extension research on the subject of the effectiveness of low-carbohydrate diets with the help of strength training is necessary to have more material and knowledge on the subject.

After four weeks of intervention with a low-carbohydrate diet in individuals practicing strength training, no significant differences were observed in terms of BMI, fat percentage, or lean mass of the participants at the end of the application.

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E-HEALTH IN THE LONG-TERM NURSING FOLLOW-UP OF PATIENTS UNDERGOING BARIATRIC SURGERY - PREVALENCE OF METABOLIC RISK FACTORS

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Summary. To analyze the effect of bariatric surgery, physical activity and weight regain on the long-term prevalence of metabolic risk factors through telemedicine. Observational study with retrospective data collection. A total of 84 individuals who underwent gastric bypass bariatric surgery with a follow-up of more than five years participated in the study. Data collection was done by telemedicine to which data from the patients' medical records were added. An evolutionary analysis was performed regarding health data and associated comorbidities, namely metabolic risk factors (diabetes, dyslipidemia, and mean blood pressure) at baseline (before surgery), one year, and five years after surgery. We found a relative improvement in metabolic risk factors one year after surgery, which was maintained at five years after surgery with statistically significant values (p <0.007). The evolution of the prevalence of metabolic risk factors after surgery is not influenced by weight gain or physical activity. All comorbidities showed a significant decrease at the 1st and 5th year, related to the surgery itself, regardless of weight gain and the practice of physical activity, which confirms the effectiveness of surgery as the most effective factor in the treatment of comorbidities. We found no relationship between metabolic syndrome and physical activity or weight gain, which shows us how effective surgery is in reducing comorbidities.

Keywords: Physical Activity, Bariatric Surgery, Weight Gain, Metabolic Risk Factors

E-HEALTH NO ACOMPANHAMENTO DE ENFERMAGEM A LONGO PRAZO DE PACIENTES SUBMETIDOS A CIRURGIA BARIÁTRICA - PREVALÊNCIA DOS FATORES DE RISCO METABÓLICO

Resumo. Analisar o efeito da cirurgia bariátrica, atividade física e reganho de peso na prevalência dos fatores de risco metabólico, a longo prazo, através de telemedicina. Estudo observacional com colheita de dados retrospectivos. Participaram no estudo 84 indivíduos submetidos a cirurgia bariátrica de bypass gástrico com seguimento superior a cinco anos. A recolha de dados foi feita por telemedicina a que foram adicionados dados do processo clínico dos pacientes. Foi feita uma análise evolutiva relativamente a dados de saúde e comorbilidades associadas, nomeadamente fatores de risco metabólico (diabetes, dislipidemia e tensão arterial média) no baseline (antes da cirurgia), um ano e cinco anos após a cirurgia. Verificámos uma melhoria relativamente nos fatores de risco metabólico um ano após cirurgia, a qual se manteve aos cinco anos após a cirurgia com valores estatisticamente significativos (p <0,007). A evolução da prevalência de fatores de risco metabólico após a intervenção cirúrgica não é influenciada pelo reganho de peso nem pela atividade física. Todas as comorbilidades apresentam uma diminuição com significância ao 1º e 5º ano, relacionada com a própria cirurgia, independentemente do reganho de peso e da prática de atividade física, o que vem confirmar a eficácia da cirurgia como sendo o fator mais eficaz no tratamento das comorbilidades. Não obtivemos relação da síndrome metabólica com a atividade física nem com o reganho de peso, o que nos mostra o quanto a cirurgia é eficaz na diminuição das comorbilidades.

Palavras-chave: Atividade Física, Cirurgia Bariátrica, Reganho de Peso, Fatores de Risco Metabólico

Introduction

Obesity is defined as a condition of the body characterized by excessive fat accumulation that poses a health risk. Characterized as a chronic disease, it is also a risk factor for numerous other diseases, subdivided into various levels depending on the body mass index (BMI) and responsible, on average, for about 3.5 million deaths per year.

The treatment of obesity can occur in several ways, with medical and surgical therapies. Thus, we have bariatric surgery, as a surgery for the treatment of obesity, being nowadays considered a safe and effective procedure in the long term, for the treatment of obesity and its comorbidities. Bariatric surgery is part of the surgical treatment of obesity (PTCO)program with certain criteria for approval, namely BMI of 50 kg/m2; BMI of 40 kg/m2 with or without comorbidities, with unsuccessful medical treatments and individuals with BMI>35kg/m2 with comorbidities and not responding to longitudinal clinical treatments [1].

Bariatric surgery started out as the treatment for severe obesity, when medical responses are not effective. There are several surgical techniques and some of them involve modifications of the gastrointestinal anatomy and physiology, which induces improvements in the metabolic syndrome, since this is a population with a high propensity for the prevalence of metabolic risk factors and other associated diseases [2].

In the long term, there remains a threat over the years to regain weight and behavioral influences are believed to play a modulating role in this weight regain. Predictors of significant postoperative weight regain after bariatric surgery include indicators of increased basal food cravings, progressively eating more than they used to, decreased well-being, quality of life, and concerns about addictive behaviors. Behaviors monitored and tracked postoperatively are strongly associated with avoiding weight regain. These data suggest that weight regain can be prevented, in part, during preoperative evaluation and potentially reduced with self-monitoring strategies after bariatric surgery [3].

A healthy lifestyle after bariatric surgery is essential to optimize and maintain weight loss. Observational studies suggest that physical activity after bariatric surgery may be associated with additional weight loss and maintenance of more effective weight loss over time. However, there is little experimental evidence on the effects of supervised exercise on obesity-related outcomes in this specific population [4].

The impact of bariatric surgery on metabolic diseases and other associated comorbidities began to emerge in the 1990s, but it was only towards the end of that decade that the remission of diseases such as diabetes could be independent of weight loss, when, incidentally, Rubino and Gagner [5] found that just one month after bariatric surgery there was a stabilization of blood glucose in patients with Type 2 Diabetes, before any significant weight loss. On the other hand, decreased insulin resistance is related to significant weight loss and increased secretion of hormones at the gut level, with glucagon-like action [6].

The first recommendations for bariatric surgery for the treatment of Type 2 Diabetes, and in 2015 guidelines recommending bariatric surgery for the treatment of Type 2 Diabetes, appeared in 2007 in patients fitting specific criteria [5].

This type of surgery, as a treatment for obesity, can have more than one objective, such as metabolic and bariatric surgery, where the latter is intended for cases with the primary objective of losing excess weight, as advocated by several authors. However, the primary goal may be metabolic surgery, if the primary intention is to improve the metabolic syndrome, in patients with a risk factor, regardless of BMI greater or less than 35Kg/m2 [5]. Whatever the goal of the surgery, the treatment guideline will always be the chronic disease, whether it is obesity or any of the associated comorbidities, such as diabetes, hypertension, or dyslipidemia.

The aim of this study was to analyze the effect of bariatric surgery, physical activity, and weight regain on the long-term prevalence of metabolic risk factors through telemedicine.

Methodology

In this study, retrospective data collection was done, with analysis and evaluation achieved by observing data over a certain period. These data were then complemented by a retrospective collection done in the present time, so this is a retrospective observational study.

Sample

The study was approved by the Ethics Committee of the Hospital where the patients underwent surgery, and had the participation of 84 individuals who had undergone bariatric surgery more than 5 years ago, with a sample power of 90% calculated by Gpower.

Participation was voluntary and participants who showed interest in participating in the study were asked for informed, free and informed consent, and were subsequently administered a questionnaire during the telephone interview. To complete the questionnaire record, clinical analytical data from the last 5 years after surgery were consulted.

The inclusion criteria for the sample indicated that participants were over 18 years of age, had no contraindications to exercise, had no surgical complications, and agreed to participate in the study. The exclusion criteria were locomotion problems, since they would be patients with no capacity or limitations for physical activity.

Instruments

The instruments used were a health questionnaire, with evaluation of analytical parameters and anthropometric measurements, and the International Physical Activity Questionnaire (IPAQ).

Procedures

Individuals who had surgery more than 5 years ago at this hospital from January to April 2021 were approached in order to assess their willingness to answer the questionnaire. Informed consent was obtained from all participants, ensuring data confidentiality, and health and clinical data were accessed through each patient's electronic medical record. The remaining data were collected by telephone interview and placed on a specially designed form to minimize data entry errors.

Statistical Analysis

The analysis was done using statistical software and characterization of the sample based on gender, age, and weight gain.

The statistical tests were appropriate for each type of variable and relationship to be studied, as well as in the result of the normality tests performed. Normality was analyzed using the Shapiro Wilk test and from this result the most suitable statistical tests were selected. The internal consistency of the dimensions of the questionnaires was checked.

The data collected was productive and several association and correlation analyses were performed between variables. The types of tests used for the various hypotheses were based on the results of the normality tests, so the Chi-square test and the repeated measures ANOVA were used.

Results

The characterization of the population can be seen in table 1.

Table 1 - Participants' characteristics

	Female		**Male**		**Total**	
	77 (91,7%)		7 (8,3%)		84 (100%)	
Age	Average	Standard deviation	Average	Standard deviation	Average	Standard deviation
	49,5	8,5	56,9	8,9	50,1	8,8

Physical activity was characterized in three levels, according to the description of the IPAQ questionnaire, and in the sample studied only two levels were present, sedentary and not very active. Its correlation with weight gain allows us to verify that most patients with weight gain had low levels of physical activity and through the Chi-square test, with p=0.005, it allows us to assume a statistically significant relationship, as presented in table 2.

Table 2 - Chi-square for comparison of weight gain as a function of physical activity levels

Level of Physical Activity					
Reganho Weight		*Sedentary*	*Not very active*	*Total*	*Sig*
	No	21 (54%)	18 (46%)	39	
	Yes	37 (82%)	8 (18%)	45	

Total	58 (69%)	26 (31%)	84	*p=0,005*

An evolutionary analysis was performed regarding health data and associated comorbidities, namely metabolic risk factors. This evolution comprises three assessments, the baseline (before surgery), one year after surgery, and five years after surgery.

We have mostly lower values in the first year after surgery, but increasing at five years after surgery, with statistically significant values (p <0.007), which implies that we have a positive effect regarding the surgery itself. Emphasize that the Vitamin D values are adjusted with pharmacological treatment, since the vast majority of patients had pharmacological Vitamin D support treatment during some period of the postoperative period (table 3).

Table 3 - Distribution of metabolic risk factors

Variables	***Baseline***	***1 year***	***5 years***	***Sig***
***Weight** (Kg)*	113,86±17,76	74,92±10,55	78,42±12,90	*p*=<0,001
***BMI** (Kg/m2)*	44,77±4,99	27,54±3,78	31,85±9,20	*p*=<0,001
***Cholesterol** (mg/dl)*	167,51±39,90	158,55±34,12	168,29±36,87	*p=0*,007
***Glucose** (mg/dl)*	95,93±25,70	86,26±10,17	94,13±20,31	*p*=<0,001
***TAM** (mmHg)*	96,24±13,40	86,86±8,93	86,66±10,29	*p*=<0,001
***Vit D** (ng/ml)*	19,10±6,16	18,90±7,46	21,78±6,70	*p=0*,001

Note: Statistically significant variation obtained by ANOVA test
TAM: Mean Blood Pressure
BMI: Body Mass Index

When we specifically evaluate each metabolic risk factor we have an initial assessment of 23 patients with medication controlled hypertension, which decreased to 8 after one year of surgery. At five years after surgery we have an increase to 12, of patients with disease taking medication to control their hypertension. It should be noted that after surgery there are no patients with uncontrolled hypertension.

In diabetes we have at baseline 10 patients with controlled disease with clinical measures, which decreases to 7 in the first year and to 4 in the fifth year after surgery. In dyslipidemia, we have at the first evaluation 21 patients taking medication to control the disease, which dropped to 7 at the first year, but by the fifth year rose to 9 patients needing clinical measures to control the disease.

We also evaluated the comorbidities of Obstructive Sleep Apnea Syndrome which there were 7 people with the disease controlled with clinical measures, which decreased to 2 in the first year and maintained at 5 years post surgery.

We can see in table 4 the relationship between metabolic risk factors, physical activity, and weight gain, whose p-values show no significant differences between the different levels of physical activity or weight gain as a function of time. We can only infer that there may be a biased relationship between cholesterol, mean blood pressure, and physical activity, where moderate levels of physical activity are related to lower levels of cholesterol and mean blood pressure.

Table 4 - Repeated measures ANOVA for comparison of the evolution of metabolic risk factors as a function of physical activity levels and weight gain

Level of Physical Activity (NAF)	***Weight gain (PR)***

		Sedentary	*Not very active*	*Time*NAF*	*Yes*	*No*	*Time*RP*
Cholesterol	*baseline*	173,29±41,13	154,61±34,29	*p= 0,059*	*174,36±39,10*	*159,62±39*,83	*p= 0,134*
	1 year	161,16±35,23	152,73±31,39		160,62±30,08	156,15±38,54	
	5 years	172,83±38,46	158,15±31,39		174,11±34,48	161,56±38,81	
Glucose	*baseline*	96,33±27,39	95,04±21,95	*p= 0,765*	*96,04±26*,44	*95,80±25*,17	*p= 0,701*
	1 year	85,48±8,27	88,00±13,53		84,76±8,21	88,00±11,92	
	5 years	93,86±19,35	94,73±22,70		93,67±18,98	94,67±21,98	
TAM	*baseline*	97,35±13,75	93,77±12,49	*p= 0,082*	*98,022±12*,53	*94,18±14*,23	*p= 0,224*
	1 year	87,31±9,47	85,85±7,65		87,47±7,86	86,31±10,11	
	5 years	88,57±10,82	82,39±7,54		88,65±10,58	84,36±9,56	

TAM: Mean Blood Pressure

Discussion and conclusions

The main objective of the present study was to analyze the effect of bariatric surgery, physical activity, and weight regain on the long-term prevalence of metabolic risk factors through telemedicine.

We can see that in the long term, the higher the levels of physical activity, the less weight gain, but we cannot say the same about metabolic risk factors, since it is not possible to verify a relationship between physical activity and weight gain.

When we approach weight gain in bariatric surgery, we consider a weight gain of more than 5% of the minimum weight achieved [7], which in our sample was mostly achieved in the first year after surgery. The correlation between weight gain, infers a strong connection with the practice of physical activity, as mentioned in other studies, changes in lifestyle, with monitoring or not, allows decreasing the rates of weight gain [3]. Already in 2011, Livhits (2001) reported that weight regain occurs on average 27 months after bariatric surgery and that it arises mostly and is greater in patients who have low levels of physical activity [8].

The characterization of our sample regarding the practice of physical activity showed that the levels of physical activity are only two and most practice it in a light way, which is in line with several studies that state that these patients, postoperatively, fall far short of the EASO recommendations regarding the practice of physical activity for the prevention of weight gain [9].

Although we only had patients with low and moderate levels of physical activity, the patients who practiced physical activity, regardless of the level, had no weight gain on average at 5 years after bariatric surgery, which is in line with what other authors have said, that physical activity allows for the maintenance of long-term weight loss [4]. However, those who had moderate levels of physical activity had fewer instances of weight regain. We emphasize that, in addition to none of the patients having vigorous or high activity, none had structured physical exercise, which reinforces the need for follow-up by an exercise professional in the multidisciplinary evaluation of these patients.

Metabolic risk factors, when present, infer important repercussions on comorbidities, namely diabetes, hypertension, dyslipidemia, and Obstructive Sleep Apnea Syndrome [10]. All comorbidities have a significance at the first and fifth year, related to the surgery itself. As stated in a recent study that bariatric surgery is the most effective treatment for comorbidities, regardless of weight gain and physical activity [11]. Only patients who underwent gastric bypass were included in our study, so we relate the positive resolution of comorbidities to performing combined surgical procedures with restricted and poor absorption [12].

Our data show that after 5 years there are no patients with uncontrolled pathology, however without any statistically significant relationship with weight gain or physical activity, which we can verify in several studies, which prove that the improvement of comorbidities is independent of weight loss [5]. These results are in line with other studies, namely a 2019 RCT study of 165 patients with an intervention program, in which there was no difference in metabolic risk factors between the control and intervention groups [13].

The results of this study allowed inferences to be made about how weight gain and physical activity may be related to metabolic risk factors in patients undergoing bariatric surgery.

Metabolic risk factors were addressed in our study with a lot of exploration of the whole framework, namely, regarding their improvement, or not, over the postoperative period. In fact, there are benefits, but we can only associate them with the surgical intervention, since we have no significant relationship that allows us to say that the metabolic risk factors decrease or maintain their decrease with the non-occurrence of weight gain or with the practice of physical activity.

Weight gain is one of the most important predictors of surgical failure, yet we have simple and useful tools to eliminate or decrease this factor. We noticed that the practice of physical activity is initiated autonomously, with no or little monitoring, which allows us to once again reinforce that the monitoring of these patients by professionals with the skills to do so would be an added value for all involved and for the national health system, since it will prevent several surgical procedures, several follow-up visits due to the deterioration of the patients' physical and psychological condition, as well as the development of new pathologies.

Metabolic risk factors respond well in the first year after surgery, but mostly can only be maintained with long-term levels of physical activity. It should be noted that diabetes is the pathology with the best response, that is, surgery has a strong potential for metabolic improvement, technically it is effective in resolving them, and the concomitant practice of physical activity does not seem to be significant or with contradictory results. This fact may be related to the level of the sample range used, in this case less than 95%.

Also in our study, the results were in line with this, as there was an initial decrease in metabolic risk factors and some increased one or two years after surgery with patients needing to resume medication and no positive relationship with physical activity and weight gain, only the mean blood pressure in some approximation.

This point is central and extremely relevant to the goal of our work, with the perception that these patients need guidance regarding the practice of regular physical activity, not only by prescription and monitoring, but by a whole referral in order to achieve the best results for all involved in this process, focusing on the patients and their needs. Bariatric surgery is successful in treating severe obesity, with great potential to be maintained if fueled by physical activity.

Regarding the limitations and future research of this study, we believe that the barriers and facilitators of physical activity, as well as the motivational profile, could be addressed during this post-surgical process. Also the fact that the study is retrospective, with self-reported data collection, becomes a limitation of the data collected, as well as the sample size and type.

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OMEGA-3 POLYUNSATURATED FATTY ACID SUPPLEMENTATION VS. A MEDITERRANEAN DIET AS A TREATMENT FOR NONALCOHOLIC FATTY LIVER DISEASE

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Summary. Introduction: Non-alcoholic fatty liver disease (NAFLD) is becoming increasingly prevalent and is the leading liver disease worldwide. The aim is to compare new dietary-nutritional strategies, such as the Mediterranean diet and omega-3 polyunsaturated fatty acids, to determine which is more effective as a treatment for this disease. Objective: To evaluate which nutritional management is more effective as a treatment for nonalcoholic fatty liver disease, omega-3 supplementation or a Mediterranean diet. Method: A bibliographic review was carried out, for which several scientific articles were consulted and selected from various databases, documents and the online information service provided by the National Library of Medicine of the United States (MedlinePlus), thus obtaining a total of 17 studies belonging to the PubMed database, which were analyzed in depth. Results and discussion: Both the Mediterranean diet and supplementation with omega-3 polyunsaturated fatty acids promote benefits on the clinical characteristics of patients with fatty liver disease. Following a Mediterranean diet seems to have greater benefits in the treatment of NASH by improving the clinical features of the disease such as hepatic steatosis, inflammation, fibrosis and non-alcoholic steatohepatitis, in addition to the metabolic syndrome.

Key words: omega-3 , NASH, Mediterranean diet, metabolic syndrome, NASH.

SUPLEMENTACIÓN CON ÁCIDOS GRASOS POLIINSATURADOS OMEGA 3 FRENTE A UNA DIETA MEDITERRÁNEA COMO TRATAMIENTO PARA LA ENFERMEDAD DEL HÍGADO GRASO NO ALCOHÓLICO

Resumen. Introducción: La enfermedad del hígado graso no alcohólico (EHGNA) cada vez es más prevalente y es la principal enfermedad hepática a nivel mundial. Se quiere comparar nuevas estrategias dietético-nutricionales, como la dieta mediterránea y los ácidos grasos poliinsaturados omega-3, para determinar cuál es más efectiva como tratamiento para esta enfermedad. Objetivo: Evaluar que manejo nutricional es más efectivo como tratamiento del hígado graso no alcohólico, si la suplementación con omega 3 o una dieta mediterránea. Método: Se realizó una revisión bibliográfica, para la cual se consultaron y seleccionaron varios artículos científicos de diversas bases de datos, documentos y el servicio de información en línea provisto por la Biblioteca Nacional de Medicina de los Estados Unidos (MedlinePlus), obteniendo asi un total de 17 estudios pertenecientes a la base de datos PubMed, los cuales fueron analizados en profundidad. Resultados y discusión: Tanto la dieta mediterránea como la suplementación con ácidos grasos poliinsaturados omega-3 promueven beneficios sobre las características clínicas de los pacientes con hígado graso. La realización de una dieta mediterránea parece tener mayores beneficios en el tratamiento de la EHGNA al mejorar las características clínicas de la enfermedad como la esteatosis hepática, la inflamación, la fibrosis y la esteatohepatitis no alcohólica, además, del síndrome metabólico.

Palabras clave: omega 3, EHGNA, dieta mediterránea, síndrome metabólico, EHNA.

Introduction

The National Library of Medicine (1) defines non-alcoholic fatty liver disease (NAFLD) as "the accumulation of fat in the liver that is NOT caused by consuming too much alcohol." It is characterized by an excessive accumulation of triglycerides (TG) and cholesterol in the form of lipid droplets in hepatocytes (2). NASH has different stages and can be divided into simple nonalcoholic fatty liver disease (NAFLD) or simple hepatic steatosis (NASH), which can be reversible through adequate nutritional treatment together with physical exercise for weight loss, or if it progresses it can become nonalcoholic steatohepatitis (NASH), with inflammation and cell damage. NASH can develop different stages of fibrosis, which can eventually lead to cirrhosis or liver cancer. Both NASH and cirrhosis are irreversible and the only existing treatment for them is liver transplantation. Therefore, it is necessary to find out more about the appropriate treatment for this disease (1,3–8).

NASH is the most prevalent chronic liver disease in the world, especially in Western countries, affecting both children and adults. Its prevalence increases along with that of obesity, approximately 20-30% of the general population suffers from it, being 2 times higher in men than in women. Of patients with NASH, approximately 20-25% have NASH, within this percentage, 20% will progress and develop liver cirrhosis (5,6,9–12). Within patients with NASH, those with NAFLD have a life expectancy similar to that of the general population, whereas patients with its more severe form, NASH, have a lower survival, due to cardiovascular problems and progression of liver damage (5,6,9,12).

Certain metabolic risk factors, genetic polymorphisms, an inadequate diet consisting of excess energy or changes in the composition of the intestinal microbiota (IM), which causes an increase in body fat and IR in peripheral tissues, are involved in the onset and progression of this pathology (13,14). It is mainly associated with metabolic syndrome (MS), which includes type 2 diabetes mellitus (DM2), dyslipidemia, arterial hypertension (AHT) and obesity. Often patients do not present with symptoms; if they do, they may present with ascites and fluid retention in the lower extremities, among others (1,6,15).

According to several publications, a change in lifestyle through the control and reduction of risk factors, especially associated metabolic comorbidities, is the current treatment for this disease. Weight loss is important in the case of overweight or obesity, along with physical exercise and a diet appropriate for the pathology. In addition, to reduce liver fat it is necessary to lower cholesterol and TG levels. Hepatitis A and hepatitis B vaccines need to be given to NASH patients (1,5,10,16,17). As for pharmacological treatment, its use is not very clear and further studies would be necessary. If used, these vary depending on the stage of the disease, comorbidities, grade and phenotype. They are usually used for people with worse prognosis such as patients with NASH and fibrosis (5,10).

Linked to all this, in recent years new lines of research have emerged regarding nutritional treatments for this disease. On the one hand, the Mediterranean diet (DietMed) generally combined with physical activity and, on the other hand, supplementation with omega-3 polyunsaturated fatty acids (PUFA ω-3) are investigated. Both nutritional treatments are currently being studied and considered a suitable course of action due to their numerous beneficial effects as a treatment for this disease (15,18–20).

The main objective of this review is to evaluate which nutritional management is more effective as a treatment for NASH, whether ω-3 PUFA supplementation or a DietMed.

Methodology

A search for scientific articles related to the topic was conducted, giving priority to relevant human studies and clinical trials, systematic reviews and meta-analyses using the databases of: Pubmed, Scielo and Science Direct.

The literature search for articles began in January 2022 and ended in April 2022.

To locate the articles used in this review, inclusion criteria of 5 years old were applied, with the exception of relevant articles from previous years; articles with a significant sample and journals indexed with an impact factor greater than 1.5.

The following keywords were used in the databases to search for articles in the different sections:

- Fatty liver: "Fatty liver.
- Non-alcoholic fatty liver disease: "NASH", "gut microbiota", "metabolic syndrome", "NASH", "weight loss", "physical activity", "diet", "developmental mechanism"
- Mediterranean diet: "NASH", "NASH", "Mediterranean diet", "cardiovascular problem".
- Omega 3 polyunsaturated fatty acids: *"EHGNA", "EHNA", "omega-3 PUFA", "EPA", "DHA".*

The exclusion criteria were: articles older than 5 years, that did not fit the topic of interest, that the sample was not significant or that it was impossible to read beyond the title/abstract.

Finally, of all the articles found, a total of 17 were selected and included in the review: 4 studies cover the relationship between DietMed and NAFLD; 4 studies cover the relationship between DietMed, physical activity, and NAFLD; 7 studies cover the relationship between ω-3 PUFA supplementation and NAFLD; and 2 studies cover the relationship between DHA supplementation and NAFLD. All of them were analyzed in depth.

Results

Mediterranean Diet

DietMed is a type of diet characteristic of the Mediterranean region that is mainly composed of monounsaturated fatty acids from olive oil; plant-based foods such as fruits, vegetables, grains, nuts, legumes; and to a lesser extent meats and dairy products. This diet has been attributed numerous health benefits: it decreases MS and cardiovascular risk by reducing cholesterol and TGs. DietMed is associated with a healthy lifestyle and the practice of physical exercise (18,21–23).

The following sections will discuss the side effects and beneficial effects of this dietary pattern on NASH.

Adverse effects of the Mediterranean diet

Caution should be exercised when following a DietMed since, being composed mainly of fats, there is a risk of weight gain. Low levels of iron, vitamin C and calcium may also result from consuming fewer foods that contain them (23).

Beneficial effects of the Mediterranean diet

This type of diet is characterized by its reduced content of refined sugars and fructose. Corn syrup is a refined sugar with high amounts of fructose, and its consumption has been shown to increase the risk of NASH, since high fructose consumption produces an accumulation of lipids in the liver, therefore, this low-fructose dietary pattern reduces the probability of suffering from this disease. It is also characterized by the absence of processed foods, such as soft drinks, which are rich in fructose and added sugars. This type of food promotes fat accumulation in the liver through de *novo* lipogenesis of fructose in the liver (24,25). In patients with NASH this mechanism is altered. Therefore, the absence of processed foods, rich in fructose and refined sugars in the diet, prevents the accumulation of fat in the liver and the development of liver disease (4,7,24,26).

Unlike other types of diets, DietMed is rich in complex carbohydrates, especially whole grains, and fiber. This type of food has a lower energy density than refined carbohydrates and is very satiating, which favors a lower accumulation of fat in the liver due to excessive energy intake. In addition, high fiber intake can favor the enrichment of certain bacteria in the intestine, such as *Firmicutes*, which are responsible for degrading fiber, leading to an increase in SCFAs such as butyrate, which is responsible for eliminating inflammation in the liver (27). It should be noted that whole grains improve postprandial glycemic control, which has a protective effect against associated problems such as MS (obesity and DM2) and cardiovascular risk (18,24,27–29).

Reducing meat consumption is beneficial, especially red meat, because meat contains cholesterol and saturated fatty acids that are deposited in the liver in the form of fat, increasing the risk of MS and cardiovascular problems. Therefore, the performance of the DietMed has an inverse association with this pathology (21,24,28).

DietMed does not speak of a specific consumption of coffee, therefore, based on current scientific evidence, it is possible to consume 2-3 cups per day. Coffee has cardioprotective effects, reducing the appearance of MS due to its caffeine and polyphenol content. It also has a hepatoprotective effect by reducing liver fibrosis (24,26,30).

This diet is characterized by the consumption of large quantities of foods with antioxidant and anti-inflammatory properties such as fruits, vegetables, nuts, whole grains, olive oil and fish rich in omega 3. These foods, thanks to their characteristics, prevent cell damage, oxidative stress and delay the development of hepatic steatosis, in addition to improving metabolic diseases (18,21,28). In addition, high nut consumption is associated with health benefits such as reduced cardiovascular risk, DM2, MS and insulin resistance, all of which are characteristic of NASH (31).

Therefore, this dietary pattern based on fats, fruits, vegetables, legumes, complex carbohydrates, fiber and to a lesser extent simple carbohydrates, refined sugars and meats, especially processed and red meats; is a type of diet that manages to reduce cardiometabolic risk factors, such as cholesterol and TG, and clinical events *(Figure 1)*, which is very important for the loss of fat in the liver and therefore, for the treatment of NAFLD (18,23,24,28,31,32). The combination of DietMed with physical exercise improves hepatic fat accumulation, increases lipid oxidation and insulin sensitivity. In addition, when combined with probiotics *(Lactobacillus)* , it provides better liver health by controlling dysbiosis and restoring altered IM(33–35,31,26,18).

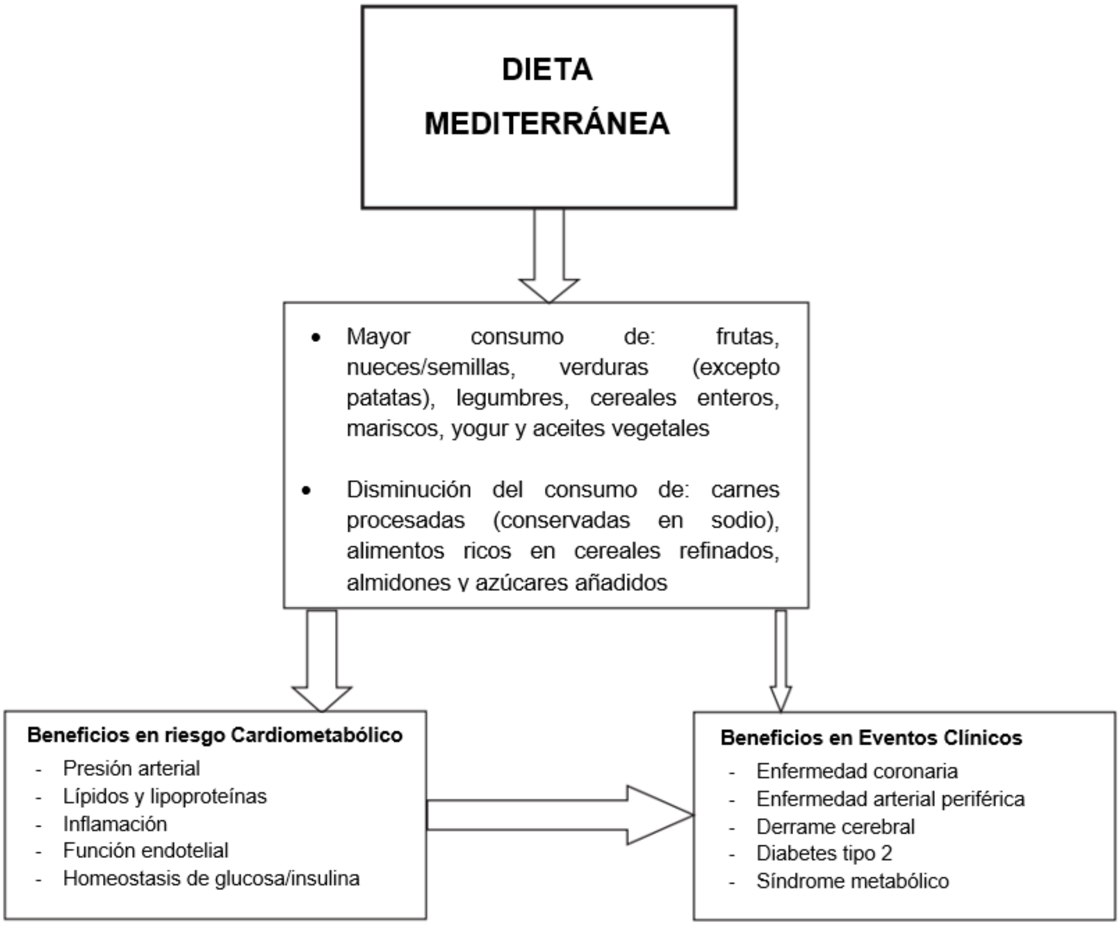

Figure 1. Characteristics of the DietMed and its benefits at the cardiometabolic and clinical event level. Improving cardiometabolic risk factors associated with DietMed consumption may lead to the prevention of clinical events. The thickness of the arrows is not proportional to the observed benefits (cardiometabolic or clinical), but may indicate a different hierarchy of effects (34).

Polyunsaturated omega-3 fatty acids

The PUFA ω-3, are a type of polyunsaturated fat essential for different processes in our body, such as maintaining stable cholesterol levels. These are of the essential type, i.e., the body cannot synthesize them, so they have to be obtained through the diet. These ω-3 PUFA are found in few foods, therefore, habitual intake is often deficient, which is associated with increased hepatic fat (HD) (36). Omega-3s have been shown to be beneficial in preventing cardiovascular problems due to their anti-inflammatory effect, improving insulin sensitivity and reducing oxidative stress (16,19,24,37,38).

Within PUFA ω-3, there are different types of long-chain fatty acids: α-linolenic acid (ALA), stearidonic acid (SDA), docosapentaenoic acid (DPA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). In the case of NASH treatment, we are only interested in the last two, DHA and EPA, modulators of hepatic gene expression. Both reduce TG and very low density lipoprotein (VLDL) levels, converting them into low density lipoproteins (LDL) and intermediate density lipoproteins (IDL) (16,19,39).

The following sections will discuss the side effects and beneficial effects of ω-3 PUFA on NAFLD.

Adverse effects of omega-3 polyunsaturated fatty acids

Supplementation with ω-3 PUFA can produce gastrointestinal problems such as: heartburn, stomach pain, nausea, vomiting, constipation, diarrhea or belching. It can also produce changes in the sense of taste (37).

Beneficial effects of omega-3 polyunsaturated fatty acids

It has been seen that patients with this disease have a low intake of ω-3 PUFA and a high intake of omega-6 PUFA, which may favor lipid production and IR. Therefore, supplementation with ω-3 PUFA would help to compensate for this imbalance and diminish its negative effects (20,39–41). These fatty acids are used for different processes in our organism, such as maintaining stable cholesterol levels, in addition, they decrease the amount of TG in the liver, which would justify their use in NASH for the loss of fat in the liver (37,42).

The use of ω-3 PUFA supplementation produced improvements in MS risk factors, at the hepatic level in fat content, pancreatic enzyme levels, blood lipid levels and degree of steatosis. DHA has greater efficacy in ameliorating both steatosis and liver fibrosis (43) *(Figure 2)*. But in NASH, supplementation with ω-3 PUFA did not result in any improvement (19,20).

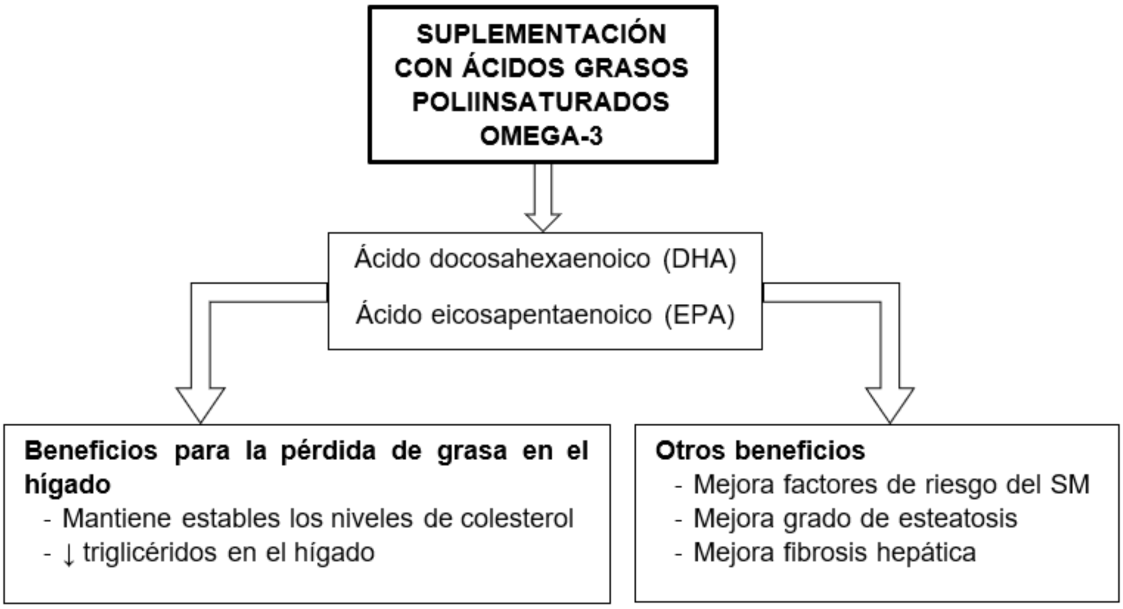

Figure 2. Types of ω-3 PUFA and their benefits for liver fat loss and other risk factors (37,42,43).

Discussion

Regarding DietMed, 3 studies cover the relationship between DietMed and NASH, and 3 other studies cover the relationship between DietMed, physical activity and NASH.

Table 1 shows in more detail the characteristics and results found in each study based on the clinical criteria of the disease. These studies show that the use of DietMed, both on its own and in conjunction with physical activity, improves disease parameters, especially those related to MS (11,15,29,31,32,44).

Table 1

Summary of the characteristics and results of the studies included in the discussion that address the relationship between DietMed alone or in conjunction with physical activity and NASH (11,15,29,31,32,44).

Author, year (Ref.)	**Type of study**	**Sample size**	**Features**	**Results**
DietMed and EHGNA				
Chen et al., 2019 (31)	Retrospective case-control study	n = 1068 (534 with NASH and 534 without) (31.8% female)	Age 18-70 years old	- No association between nut consumption and NASH risk in the overall sample - Significant inverse association between ↑ nut consumption and EHGNA in the highest quartile of the male sample
Georgoulis et al., 2015 (29)	Retrospective cross-sectional study	n = 73 with NASH (31.5% female)	Age 34-56 years	- 46.5% sample with SM, ↑ waist circumference and ↓ HDL - Positive association between MS and consumption of red meats and refined grains - Negative association between MS and DietMed score (MedDietScore) and consumption of whole grains.
Aller et al., 2018 (11)	Cross-sectional study of adherence to DietMed	n = 203 with biopsy-proven NASH (43.3% female)	Age 44-49 years	- ↑ Serum adiponectin levels and ↓ resistin and leptin concentration in overweight vs obese participants - ↑ Frequency of NASH in obese participants - Adherence to the Mediterranean diet as an independent protective factor for liver fibrosis and NASH in overweight participants.
DietMed, physical activity and EHGNA				
Konerman et al., 2018 (44)	Cohort study	n = 403 who completed the MetFit program at the University of Michigan between 2008 and 2016 (37.5 % female)	Age 45-63 years Duration = 12 and 24 weeks	The main group were men with severe obesity and NASH - 30 % ↓ weight ≥ 5 % - 62 % resolution of hypertriglyceridemia - 33 % low HDL resolution - 27 % resolution of fasting glucose disturbance 43 % ALT normalization
Bullón-Vela et al., 2019 (32)	Cross-sectional study	n = 328 patients with MS participating in the	Age 55-75 (men) and 60-75 (women) years old	- ↓ noninvasive hepatic steatosis index values with ↑ tertiles of physical activity - Adherence to the Mediterranean diet inversely associated with

		PREDIMED-Plus study (45.1% women)		noninvasive hepatic steatosis index values ↑ tertiles of legume consumption inversely associated with the highest tertile of the noninvasive hepatic steatosis index
Gelli et al., 2017 (15)	Observational study	n = 46 with NASH (37% female)	Age 26-71 years Duration = 6 months	- ↓ 93 % to 48 % of the percentage of participants with steatosis grade ≥ 2 - Regression of steatosis in 9 participants - 25 of 46 participants achieved a 7% weight reduction or maintained a normal weight - ↓ Liver enzymes (especially ALT) Improved waist circumference, BMI, waist-to-hip ratio, LDL/HDL, total cholesterol/HDL, triglycerides/HDL, serum glucose, HDL, fatty liver index, HOMA-IR insulin resistance index, Kotronen index, EHGNA liver fat score, visceral adipose index and lipid accumulation product

In the work of Gelli et al (15)the authors demonstrate that DietMed and a more active lifestyle can be considered a safe therapeutic approach to reduce the risk and severity of NASH and related diseases.

In the prospective cohort study (27) comparing DietMed with a healthy diet, it was found that DietMed resulted in a greater loss of liver fat, weight and likelihood of developing NASH than the consumption of a healthy diet. This diet is rich in fruits and vegetables that contain high amounts of water and fiber, contributing to satiety and improved weight control by reducing energy intake. In addition, thanks to fiber, liver inflammation is also reduced. Of note, preliminary evidence suggests that nut consumption may promote fat oxidation and reduce ectopic fat mass in the viscera, although supporting studies are limited.

In the meta-analysis conducted by Akhlaghi et al. (28) on DietMed for NASH patients, we found 7 observational studies and 6 clinical trials. In observational studies there was an inverse association between DietMed and NASH. However, only 4 of the clinical trials proved the positive effect of DietMed on HD, showing a significant drop in BMI, weight, TG and total cholesterol, but no effect was found on LDL and HDL cholesterol, blood pressure, fasting blood glucose and insulin. Overall, the available data from these studies indicate an inverse association between DietMed and HD with a drop in BMI, and plasma TGs, but no significant improvement in waist circumference, cholesterol, glucose or insulin resistance was observed. Although the results are promising, further observational and interventional studies are needed to reach firmer conclusions.

In relation to ω-3 PUFA supplementation, 4 studies cover the relationship between ω-3 PUFA supplementation and NAFLD and 1 study covers the relationship between DHA supplementation and NAFLD. *Table 2* shows in more detail the characteristics and results found in each study based on the clinical criteria of the disease. Three of these studies show that supplementation with ω-3 PUFA improves disease parameters, especially hepatic fat content, with the exception of the trial by Sangouni et al., 2021 (38)in which no significant effects on any parameter were seen.

Table 2

Summary of the characteristics and results of the studies included in the discussion addressing the relationship between ω-3 PUFA and NASH (38,41,42,45,46).

Author, year (Ref.)	**Type of study**	**Sample size**	**Features**	**Results**
Scorletti et al., 2014 (46)	WELCOME randomized, double-blind, placebo-controlled trial	n = 103 adults with histologically confirmed NASH or imaging evidence of clinical features	Age >18 years old Duration= 15-18 months Omacor (DHA 380mg+EPA 460mg)= 4 g/day Placebo (olive oil)= 4g/day	Treatment with DHA+EPA: - Enrichment of DHA in erythrocytes - ↓ of mean % liver fat in patients with NASH.
Hodson et al., 2017 (42)	Pilot study, pre-specified substudy of the randomized, double-blind, placebo-controlled WELCOME trial	n = 24 adults with NASH (from the WELCOME study)	Age >18 years old Duration = 15-18 months Omacor (DHA 380mg+EPA 460mg) = 4g/day Placebo (olive oil)= 4g/day	Individuals who achieved a change in erythrocyte DHA enrichment of ⩾2 %: - Favorable changes in hepatic fatty acid metabolism and insulin sensitivity - ↓ hepatic fat content.
Capanni et al., 2006 (45)	Pilot study with ω-3 PUFA and placebo, for a future double-blind randomized controlled trial	n = 56 adults with NASH	Age 32-77 years Duration = 12 months PUFA ω-3 (EPA0,9/DHA1, 5)= 1g/day Placebo = control patients without therapy	- ↓ Serum TG and ALT level - Improved ultrasonographic characteristics (↑ Doppler perfusion index (DPI), ratio of hepatic artery blood flow to total liver blood flow) - Improved hepatic blood flow by ↓ intrahepatic fat accumulation.
Sangouni et al., 2021 (38)	Double-blind, randomized, placebo-controlled trial	n = 60 diabetic patients with NAFLD	Age 18-65 years old Duration = 12 weeks PUFA ω-3 (EPA360mg + DHA 240mg) = 200mg/day	Omega-3 supplementation (2000 mg/d) compared to placebo had no significant effect on cardiometabolic risk: plasma atherogenic index (AIP), Castelli I risk index, Castelli II risk index and atherogenic coefficient (AC).

			Placebo (liquid kerosene) = 200mg/day	
Pacifico et al.,2015 (41)	Double-blind, randomized, placebo-controlled trial	n = 58 children with NASH	Age <18 years old Duration = 6 months PUFA ω-3 (DHA) = 250mg/day Placebo (linoleic acid) = 290 mg	DHA supplementation: - Change in hepatic fat fraction estimated by MRI and visceral MRI. - Changes in visceral adipose tissue, epicardial adipose tissue, ALT, TG and insulin sensitivity. - Improving metabolic abnormalities in children with NASH

The double-blind, randomized, placebo-controlled clinical trial (43) shows evidence that supplementation with ω-3 PUFA, specifically DHA, was effective in reducing steatosis and liver fibrosis, thus the dose and duration of supplementation used were able to ameliorate the liver damage occurring in NASH patients.

Musa-Veloso et al (19) demonstrated according to the meta-analysis performed of several studies that supplementation with ω-3 PUFA resulted in statistically significant improvements in 6 of 13 metabolic risk factors, in the levels of 2 of 3 liver enzymes, in hepatic fat content and in the steatosis score. Although histological disease measures (fibrosis score, hepatocellular ballooning score, steatosis score, lobular inflammation score, and NAFLD activity score) assessed in NASH patients showed no improvement by ω-3 PUFA supplementation, this could be due to a low sample of patients in the study and a very low dose (0.345 g/d) of the supplement provided.

However, in the randomized controlled trial, a significant reduction in liver fat content was observed between the placebo group and the intervention group (40)however, in the randomized controlled trial, a significant reduction in liver fat content was observed between the placebo group and the intervention group, which masked any effect produced by ω-3 PUFA supplementation. Along the same lines Parker et al. (36) found that, using noninvasive techniques for the assessment of intrahepatic lipid concentration and composition, and a dose of ω-3 PUFA that had previously demonstrated reductions in hepatic fat, neither hepatic benefit nor a decrease in hepatic fat could be observed. We also found no effect of ω-3 PUFA supplementation on ALT levels, volume of subcutaneous or abdominal visceral adipose tissue compartments after supplementation. Further studies in which the level of HD is higher in participants are needed in order to observe more significant effects on liver-related outcomes.

Based on the current evidence, when comparing the performance of a DietMed with ω-3 PUFA supplementation for the disease studied, it can be seen that, in the case of DietMed there are a greater number of studies, trials and topical reviews in favor of its use that evidence improvements in the clinical characteristics of NASH. An inverse association can be seen between DietMed and SM; a reduction in weight, TGs, cholesterol, liver fat, visceral fat, liver inflammation, waist-to-hip ratio, BMI and HD index; normalization of some enzymes, including ALT; resolution of impaired fasting glucose. In addition, DietMed has been shown to be a protective factor against liver fibrosis and NASH. However, in the case of ω-3 PUFA, a smaller number of studies, trials and current reviews can be seen that evidence their use in the treatment of this pathology, likewise, the improvements found in the different clinical parameters are lower. These are the following: reduction in hepatic fat, visceral fat and TG content; normalization of some enzymes, including ALT; improvement of blood flow by reducing hepatic fat, insulin sensitivity, improvement of metabolic risk factors and metabolic abnormalities in children. Therefore, concerning the benefits obtained from the performance of the DietMed versus PUFA ω-3 it can be determined that, in the case of the DietMed multiple improvements in the clinic of the disease have been demonstrated due to its different components, among them the high consumption of foods rich in PUFA ω-3, which would justify the better results of this diet, since it is one of the pillars of this dietary style. The ω-3 PUFA alone as supplements have benefits, although in some studies they are indistinguishable from placebo. At a general level, greater benefits are found with DietMed treatment than with ω-3 PUFA supplementation (11,15,19,27–29,31,32,36,38,40–46).

With respect to limitations, although some of the studies do not have any limitations, in most of them the number of samples in the population is very small and the study time is very short. In addition, some of them lack a control group or are not prospective in nature. It is important to note that each research group uses different markers to assess the progression or improvement of NASH in both the DietMed studies (SM, waist circumference, HDL, serum adiponectin levels, etc) and the ω-3 PUFA studies (hepatic fat content, serum TG level, Doppler perfusion index (DPI), etc), which makes it difficult to compare the results.

With a view to conducting future studies, the following recommendations are proposed: improving the design of future studies with ω-3 PUFA supplementation, extending the study time to a minimum term of 3 months and establishing a higher dose; further investigating the results of these interventions in NASH populations; and the development of future studies on treatment for NASH with a DietMed together with ω-3 PUFA supplementation.

Conclusions

Based on the current literature, we can conclude that in terms of the nutritional approach the best option as a treatment for this disease is the adoption of a DietMed. This diet is usually associated with a Mediterranean lifestyle, which includes physical activity. With this, in addition to obtaining multiple benefits on the clinical characteristics of NASH, especially at the level of the MS, weight loss is achieved, which is important in the treatment of this pathology by achieving an improvement in the liver, decreasing HD and slowing the progression of the disease by reducing inflammation, fibrosis and NASH. Within this diet, it should be noted that one of its fundamental pillars is the consumption of foods rich in PUFA ω-3, which provides better results on the clinic of the disease than with only the supplementation of these fatty acids, this is due to the sum of the benefits of the different components of the diet. Therefore, it would be interesting to conduct future studies in which a Mediterranean diet is evaluated together with omega-3 PUFA supplementation to see if supplementation with these fatty acids could enhance the positive effects of these fatty acids in synergy with those already demonstrated in the Mediterranean diet.

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