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Artigo de Revisão

Estresse oxidativo e fenilcetonúria: uma revisão integrativa

Oxidative stress and phenylketonuria: an integrative review

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ABSTRACT

Phenylketonuria is an autosomal recessive disease. It is caused by an innate error that occurs in individuals where there is a change in the PAH chromosome 12q22-q24.2 gene, which encodes phenylalanine hydroxylase. Also known as PKU, the pathology consists of the absence of this enzyme or the lack of its full functionality, which can be detected in the first days of life. Treatment for PKU is essentially dietary and should be started as soon as it is diagnosed. The dietary restriction of phenylketonuric individuals is extensive, based on a limited diet that offers low content of, or free from phenylalanine. The decrease in phenylalanine levels in the blood aims to protect the patient from neurological damage caused by high levels of this amino acid. Commonly, diets are based on fruits and vegetables with low Phe levels accompanied by food formulas to achieve the necessary protein intake. Based on scientific studies, there is evidence that the restrictive diet, to which these patients have been submitted, results in a decrease in the body's antioxidant capacity and, consequently, contributes to the increase in oxidative stress caused by the presence of reactive oxygen species. Thus, the objective of the present study was to conduct an integrative review based on scientific studies regarding the correlation between oxidative stress in phenylketonuric patients and pathology. The analysis of selected studies showed a strong

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correlation between oxidative stress and neurological disorders in individuals diagnosed with PKU, being more common in patients with delayed diagnosis, showing that the restrictive diet is an essential factor in protecting patients.

Keywords: ROS; PKU; Phenylalanine; Neurological Damage.

RESUMO

A fenilcetonúria é uma doença autossômica recessiva. É causada por um erro inato que ocorre em indivíduos onde há uma alteração no gene 12q22-q24.2 do cromossomo PAH, que codifica a fenilalanina hidroxilase. Também conhecida como PKU, a patologia consiste na ausência dessa enzima ou na falta de sua plena funcionalidade, que pode ser detectada nos primeiros dias de vida. O tratamento da PKU é essencialmente dietético e deve ser iniciado assim que for diagnosticado. A restrição alimentar de indivíduos fenilcetonúricos é extensa, baseada em uma dieta limitada que oferece baixo teor ou isento de fenilalanina. A diminuição dos níveis de fenilalanina no sangue visa proteger o paciente de danos neurológicos causados por níveis elevados desse aminoácido. Comumente, as dietas são baseadas em frutas e vegetais com baixos níveis de Phe acompanhados de fórmulas alimentares para atingir a ingestão proteica necessária. Com base em estudos científicos, há evidências de que a dieta restritiva, à qual esses pacientes têm sido submetidos, resulta na diminuição da capacidade antioxidante do organismo e, consequentemente, contribui para o aumento do estresse oxidativo causado pela presença de espécies reativas de oxigênio. Assim, o objetivo do presente estudo foi realizar uma revisão integrativa baseada em estudos científicos sobre a correlação entre estresse oxidativo em pacientes fenilcetonúricos e patologia. A análise dos estudos selecionados mostrou forte correlação entre estresse oxidativo e distúrbios neurológicos em indivíduos diagnosticados com PKU, sendo mais comum em pacientes com diagnóstico tardio, mostrando que a dieta restritiva é um fator essencial na proteção dos pacientes.

Keywords: ROS; PKU; Phenylalanine; Neurological Damage.

INTRODUCTION

The first evidence that phenylketonuria could be differentiated from other forms of childhood “delay” was seen by Norwegian physician and biochemist Asbjørn Følling in 1934[1]. That same year, Følling was approached by a lady looking for an explanation to understand an apparent difficulty in her children’s mental development[2].

Studies describe that, after initial tests for detecting ketones in children’s urine, a change in the results was found. It was only later that this change was identified as the presence of phenylpyruvic acid, raising the hypothesis that this substance was related to the mental “delay” of these children[2,3]. Følling named the condition of patients with mental disabilities and high levels of phenylpyruvic acid “imbecillitas phenylpyrouvica.” A few years later, an English geneticist named Lionel Penrose came up with the term phenylketonuria or PKU, which was widely accepted[4].

Phenylketonuria (PKU) is the most frequent inherited disorder of amino acid metabolism[5]. It is a rare disease caused by an innate autosomal recessive error originated by variants of the PAH gene that codes for the phenylalanine hydroxylase enzyme complex (PAH; EC # 1.14.16.1), located on chromosome 12q[6] in which the body’s ability to metabolize Phenylalanine (Phe) deteriorates[7-9].

PKU is characterized by the accumulation of phenylalanine (Phe) mainly due to the hepatic deficiency of phenylalanine hydroxylase (PHA), which converts Phe into tyrosine (Tyr), requiring the cofactor tetrahydrobiopterin (BH4), molecular oxygen, and iron[10,11]. Since PAH converts Phe to tyrosine (Tyr)[12], without the PAH enzyme or its full functionality, phenylalanine accumulates in the blood and other tissues. In high blood concentrations, Phe generates toxicity to the central nervous system and can cause severe neurological complications such as intellectual disability[7], microcephaly, motor deficits,

eczematous rash, autism, seizures, and developmental problems[12,13].

In Brazil, the diagnosis established by the Neonatal Screening programs is ideal. It allows early treatment, with the introduction of adequate dietary therapy, which will prevent the clinical condition's development. This detection is possible through the heel prick test. It is recommended to collect only after 48 hours of birth because, in order for the increase in Phe to be detected, the child must ingest a sufficient amount of protein[14].

According to data from the Center for Actions and Research in Diagnostic Support (NUPAD), from 1994 to 2017, 5.7 million children were screened for phenylketonuria; 348 children in outpatient follow-up and the incidence is one case for every 21,000 live births[15].

The intensity of the pathology can vary, depending on the tolerance of Phe ingestion for each patient. The normal circulating level of Phe in the blood for newborns is up to 120 μmol/L (~2 mg/dl)[16]. Several studies show that classical PKU has a Phe tolerance greater than 1,200 μM; the one classified as moderate with Phe of 900-1,200 μM; the light PKU with Phe levels of 600–900 μM and also a classification for mild hyperphenylalaninemia with Phe tolerance between 120–360 μM[17-19]. Classification is not always an easy task because phenylalanine concentrations are measured in individuals who are still newborns. However, classification can also be conducted based on tolerance to phenylalanine in the diet, which is still not always accurate and straightforward[10].

The dietary restriction of phenylketonuric patients is extensive. Treatment consists of a limited diet that offers low phenylalanine content[20], including protein, vegetable, and animal restriction, according to the daily requirements established by age and disease classification. The most common diets are those based on low-protein fruits and vegetables accompanied by food formulas[21].

These formulas are free from phenylalanine and composed of a mixture of several other amino acids[11] plus vitamins, minerals, fats, and carbohydrates[22]. Their function is to provide the necessary protein supply and maintain blood concentrations of the amino acid[23]. They should be administered in small portions throughout the day according to patient need.

Thus, with food formulas, it is possible to avoid blood phenylalanine increase and neurological damage, making satisfactory cognitive development correlated to pathology possible[20]. When the intake of these formulas is performed incorrectly, there is a loss of their biological use and, consequently, an increase in adverse effects (nausea, vomiting, dizziness, diarrhea), causing the quality of life, concerning this diet, to be compromised[24].

Intellectual and neurological impairments are the most important clinical aspects presented by patients with PKU[25]. When excluding foods rich in phenylalanine, such as meat, eggs, milk and dairy products, and some fruits and vegetables, from patient diets, there is also an exclusion of essential nutrients for the body. Thus, there may be a compromise of the intracellular balance between the antioxidant and oxidative capacity resulting in oxidative stress[20].

Oxidative stress is often described as a self-propagation phenomenon based on two observations, the presence of excessive oxidative release of reactive oxygen species (ROS) induced by stress and when there is a trigger of cellular damage, where the damaged macromolecules themselves can behave like and/or become ROS[26]. Reactive species are naturally produced in the body due to normal cell metabolism that performs positive functions in adequate concentrations. However, when in high concentrations, they produce adverse changes resulting in oxidative stress[27-29].

Oxygen suffers a reduction in the ATP generation process and receives four electrons, which results in the formation of the water molecule. This process occurs in the mitochondria, and at the end of the electron transport chain, four cytochrome C molecules are catalyzed by cytochrome oxidase. This enzyme is responsible for controlling the generation of free radicals, removing one electron from each molecule of cytochrome C. These electrons are added to oxygen to give rise to water formation[30]. Thus, the oxygen metabolized in the mitochondria goes to the cytoplasm and to the cell membrane, where it will be reduced and give rise to the consequent formation of reactive species[31]. These radicals

formed are: the superoxide radical, hydroperoxyl radical, hydrogen peroxide (also considered a reactive oxygen species), oxide radical and, finally, the hydroxyl radical32. The process is only possible through the action of specific enzymes such as NADPH oxidase on the cell membrane and the use of iron and copper ions[33].

This stress can lead to the oxidation of several biomolecules such as proteins, lipids, and even DNA, with a consequent loss of their biological functions and homeostatic imbalance, causing potential oxidative damage in cells and tissues[34]. Also contributes to the development and progression of several diseases, such as neurological and cardiovascular diseases[35]. The antioxidant defense system has the function of inhibiting or reducing damage caused by the deleterious action of free radicals or reactive species, which can be achieved through different action mechanisms[30].

Organisms use endogenous and exogenous defense systems to protect cells against damage from ROS[31]. Enzymatic antioxidants are known as natural antioxidants. They are composed of the enzymes: superoxide dismutase (SOD), catalase (CAT), peroxiredoxins (Prx), glutathione (GSH), glutathione reductase (GR), and glutathione peroxidase (GPx). They neutralize excess ROS and prevent damage to the cell structure. Non-enzymatic compounds, in turn, are known as synthetic antioxidants. They consist of low molecular weight compounds, such as ascorbic acid, tocopherol, different selenium compounds, ubiquinones (coenzyme Q), uric acid, α-lipoic acid, glutathione, beta-carotene, and carotene, among others. These compounds can remove the oxidizing agent before it causes damage or repair the damage caused[36].

In the presence of a disorder in the antioxidant system, the body may need exogenous sources of these compounds with bioactive activity. This antioxidant source can often be obtained through a diet rich in phenolic compounds, vitamins, minerals, and carotenoids[29], naturally present in high concentrations in natural foods like fruits and vegetables. Animal derivatives can also contribute, mainly from marine organisms. Therefore, there is a great concern with the diet of individuals in general.

There is evidence that the diet to which PKU patients are submitted has a consequence of reducing antioxidant capacity[25]. Due to the fact that the diet of phenylketonuric patients is too restricted and the patients have a deficit in the intake of these compounds through food as well as the nervous system being the most affected in this pathology, the objective of the present study was to do an integrative review based on evidence scientific information about the oxidative stress of cells. This review was done taking into account *in vitro* and *in vivo* studies as well as the history of the pathology in order to clarify if there is a correlation between the phenylketonuric diet and oxidative stress.

MATERIAL AND METHODS

The present integrative review study was carried out based on a guiding question: “What is the correlation between phenylketonuria and oxidative stress?”. Based on this, consultations were carried out on studies correlating oxidative stress with phenylketonuria in the PubMed, Scielo, Web of Science, Science direct, and Open gray databases.

The search strategy was carried out using free terms with the help of Boolean operators “AND” and “OR” according to each platform (Table 1). Inclusion criteria were works in Portuguese, English, and Spanish, independent of publication year. Thus, the studies of interest to be retrieved should contain information on the effects of the pathology, having as a main focus the correlation between oxidative stress and PKU, which can be positive or negative, based on clinical studies, review, theses, and dissertations independent of age range, gender, classification, or stage of phenylketonuria. Thus, these were adopted as the selection criteria.

The exclusion criteria were considered those works that did not present data on the topic in a language other than Portuguese, English, or Spanish and that did not answer the guiding question.

Table 1. Search strategies used for each database.

Database	Search strategies	Number of works
PubMed	((phenylketonuria[MeSH Terms]) OR (phenylketonuria[Text Word])) AND ((oxidative stress[MeSH Terms]) OR (oxidative st ress[Text Word]))	50
Scielo	(*phenylketonuria) OR (fenilcetonuria) AND (oxidative stress) OR (estresse oxidativo)	113
Open gray	((phenylketonuria OR phenylalanine)) AND ((oxidative stress))	6
Web of science	Phenylketonuria AND oxidative stress	671
Science Direct	oxidative stress AND phenylketonuria	79

Source: Authors (2020).

The selection of articles was carried out in two stages. The first considered reading titles and abstracts of works retrieved from the databases used throughout the review. The recovered works were listed, organized, and the duplicates were removed using the Mendeley software (version 1.19.6). The second stage is consistent with the complete reading of the articles selected in the first stage. Thus, a table was created with the aid of Microsoft office Excel software (version 16.40), containing the information: title, summary, identification number of the article Digital Object Identifier (DOI), when available, and complete reference the works.

Later, when reading the works in full for a more careful selection, only those which met the pre-established criteria were considered. Scientific articles with primary and secondary data were included, as long as these allowed a comparison of the data obtained with the selected articles.

RESULTS AND DISCUSSION

In total, 919 works were found, with 75 duplicates removed by the Mendeley software in the database search. A total of 6 articles published between 2002 and 2017 were retrieved and written in English (Table 2).

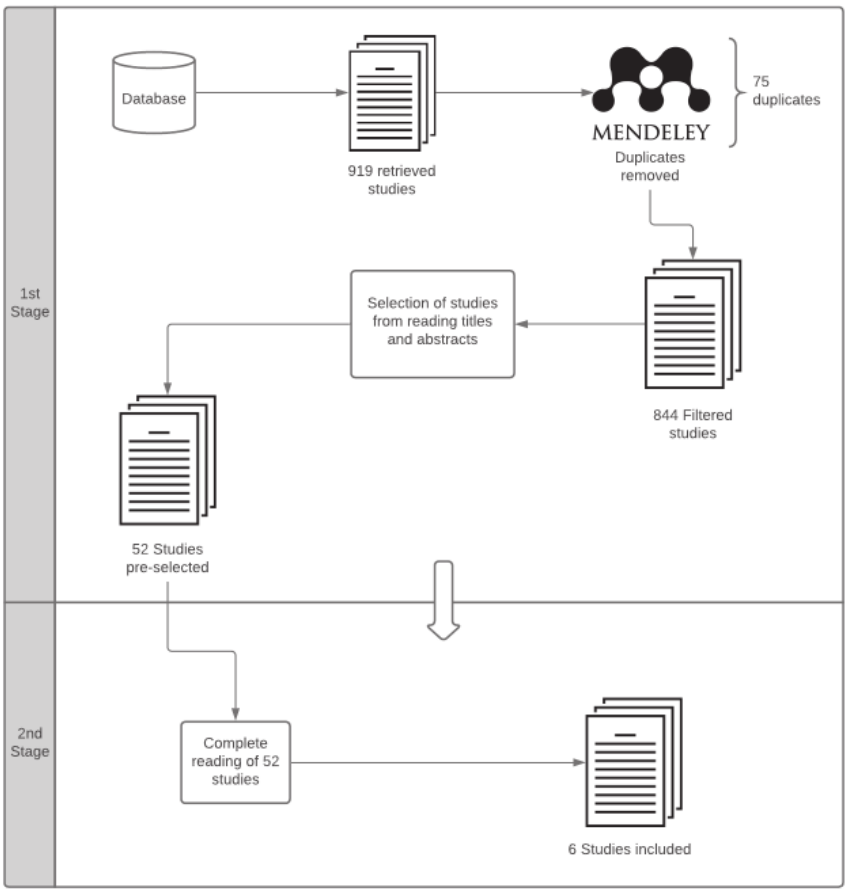
Table 2. Works retrieved from research in the databases.

Database	Number of works	Number of duplicates	Total
PubMed	50		
Scielo	113		
Open gray	6	75	844
Web of science	671		
Science Direct	79		

Source: Authors (2020).

The works were organized to elaborate the pathology review and its association with the oxidative stress caused in the patients in a qualitative way, with the selection process shown in Figure 1.

Figure 1. Flowchart for selecting studies in stages.



Source: Authors (2020).

The analysis works identified that the accumulation of toxic metabolites leados to the excess production of free radicals, and restricted diets can influence the antioxidant status[37]. High concentrations of Phe in the brain correlate with the neurological signals and brain dysfunctions characteristic of PKU, even though the exact mechanisms are still uncertain[35]. Thus, it is considered that the decrease in neurotransmitters and protein synthesis in the brain, as well as high levels of Phe and increased oxidative stress, are responsible for the neurological damage that occurs in phenylketonurics[38].

It has already been demonstrated that the restrictive diet to which patients with PKU are submitted has the consequence of a reduction in antioxidant capacity[25] as well as the fact that high concentrations of Phe and neurotoxic derivatives are directly responsible for the increase in brain oxidative damage or indirectly, causing mitochondrial dysfunction or alteration of the antioxidant defense system (6). Thus, several experimental studies (Table 3) have demonstrated a relationship between oxidative stress and PKU[25,39-41].

Table 3. Synthesis of selected works.

Kind of study	Sample group	Analysis type	Results	Reference
Human model	20 patients with a mean age at diagnosis of 25 ± 10 days. Patients were divided into two groups according to diet A (good adherence: Phe levels in the last 2 years within the recommended limits) and B (low adherence: blood Phe levels in the last 2 years above the recommended limit). The control group, with 10 people, was composed of healthy individuals of similar ages. This study excluded patients without a diagnosis of classical PKU, receiving treatment with BH4. Patients who were breastfed at the time of the study were also excluded.	The analyzes took place through blood collection in the patients. Tests were carried out to assess blood levels of Phe and L-carnitine, total antioxidant status (TAS), total oxidant status (TOS), paraoxonase 1 (PON1), erythrocyte GSHPx and Q10 level.	The results showed differences in the levels of GSHPx, Q10, Q10 / cholesterol, and L-carnitine in patients with phenylketonuria and the control group. GSHPx, Q10, Q10 / cholesterol levels decreased in patients with low adherence. L-carnitine levels increased significantly in patients with good adherence than in patients with low adherence and decreased in patients with low adherence than in healthy controls. No correlation was observed between the concentrations of Phe and L-carnitine in the low adherence group.	([38])
Animal model	Newborn Wistar rats, 8 animals per group: control 0.4 µM; 0.5 µM Phe; 1.0 µM Phe; 1.5 µM Phe.	The animals had free access to water and standard commercial feed. After 72h biochemical tests (global mitochondrial function, cell viability, ROS production, GSH content, enzymatic activity, quantification of total Phe) were performed on astrocytic cells to check for changes in the various oxidative stress parameters	There were changes in the various oxidative stress parameters evaluated, indicating that phenylalanine induced free radicals' production.	([41])
Review article	_____	Discussion of oxidative stress parameters in patients with PKU.	PKU patients are susceptible to oxidative damage, and the literature suggests that oxidative stress can contribute to neurological disorder in this pathology.	([25])
Human model	Samples (plasma from 20 patients and erythrocytes from 4 patients) were obtained at the time of diagnosis of index cases. Plasma and erythrocytes were also obtained from healthy individuals of the same age used as a control group.	For the analysis, samples were used whose plasma Phe levels were at least 600 µmol/L, and the average value for PKU samples was 1160 µmol/L. The period between blood collection and analysis was always less than two weeks. Species reactive to thiobarbituric acid (TBA-RS), total antioxidant reactivity (TAR), activities of antioxidant enzymes (GSH-Px, SOD), and protein determination were analyzed.	There was a significant increase in the TBA-RS dosage (290%) in PKU, a 56% decrease in ART, as well as a decrease in the activity of the erythrocyte GSH-Px enzyme by 70%. It is proposed that the generation of free radicals is involved in the pathophysiology of tissue damage found in PKU.	([40])

Kind of study	Sample group	Analysis type	Results	Reference
Human model	46 phenylketonuric patients aged 6 months to 34 years, not including patients with chronic diseases, undergoing pharmacological treatment during the study, without food control, and with late diagnosis of PKU with severe neurological impairment. These were separated into two groups: 1-24 patients (age range: 6 months to 22 years under good metabolic control (mean IDC value 279 μM; SD 107); 2-22 patients (age range: 11-34 years; mean: 19.2 years) showing low adherence to the diet during the study (mean IDC value 734 μM; SD 164) and a control group with 58 individuals of the same age.	The levels of selenium, ubiquinone-10 (Q10), and antioxidant enzymes were analyzed over 3 years of metabolic monitoring. Antioxidants were measured by atomic absorption spectrophotometric, chromatographic, and spectrophotometric procedures.	The values of Q10 and CAT activity decreased throughout the study, showing a correlation between PKU and oxidative damage and that selenium levels were not affected in patients undergoing dietary treatment.	(42)
Animal model	2-month-old female Wistar rats and a control group	The effects of maternal hyperphenylalaninemia on the morphological and biochemical development of the brain and cerebellum of the young rats were evaluated. As well as the formation of adult Ehrlich, lipid peroxidation, reduced and oxidized glutathione levels, the activities of the enzymes glutathione peroxidase and glutathione reductase, and the effects of daily administration of melatonin vitamins E and C until partum.	PKU affected pup development, causing a significant decrease in body and brain weight. Oxidative stress markers increased in PKU rats. Daily administration of melatonin, vitamin E, and vitamin C until delivery prevented oxidative biomolecular damage to the rat brain and cerebellum and prevented morphological changes in the pups.	(37)

Source: Authors (2020).

Preissler and collaborators (2016)[41] investigated the effects of phenylalanine on oxidative stress and other metabolic parameters in cultures of astrocytes (cells of great importance for brain function) in newborn rats. The results suggested that Phe in concentrations usually found in PKU induced oxidative stress and, consequently, cell death in astrocyte cultures, which may be related to the brain damage found in patients with PKU[41].

Vargas, Wajner, and Sitta (2011)[25] observed through a review study that, according to the literature, it is possible that there is an important relationship between selenium deficiency and decreased antioxidant capacity. This can be related to the decrease in glutathione (GSH), an endogenous antioxidant substrate of the enzyme GSHPx corroborating with a study by Kumru et al. (2017) that used this enzyme as one of the markers for assessing oxidative stress in PKU[38]. There is also a likelihood that low selenium levels are associated with decreased total antioxidant status in the plasma of hyperphenylalaninemia individuals with PKU. Suggesting that, as observed in the literature, oxidative stress may contribute to neurological disorder in PKU[25].

Sitori et al. (2005), when faced with the fact that oxidative stress is observed in some innate errors and may result from restrictive diets in antioxidant status, focused the objective of their study to evaluate various parameters of oxidative stress in the plasma of patients with PKU[40]. The results reported that patients showed an increase in the plasma measurement of TBA-RS (species reactive to thiobarbituric acid), indicating that lipid peroxidation is induced in PKU patients' plasma, probably secondary to the generation of free radicals. This fact corroborates with a study carried out years later, in 2017, which says that lipophilic antioxidants prevent lipid peroxidation[38] and this is related to the generation of ROS. The decrease in plasma TAR (total antioxidant activity) was also observed, reflecting a deficient ability to deal quickly with an increase in reactive species. There was also a decrease in the erythrocyte activity of GSH-Px (glutathione peroxidase), interfering with the antioxidant system's ability to protect essential proteins and membranes from potentially harmful effects of reactive oxygen and lipid peroxides. Thus, with these results, it was assumed that oxidative stress is involved in the pathophysiology of tissue damage found in PKU and retaining, as a consequence, the deficiency in the ability to deal quickly with an increase in reactive species[40].

A longitudinal study conducted by Artuch and other researchers in 2004[42] sought to investigate the implications of three factors of the antioxidant system already reported about oxidative damage in phenylketonuric patients (selenium, ubiquinone-10 (Q10), and antioxidant enzymes) along 3 years of metabolic monitoring. It was observed that TAC (total antioxidant capacity) activities were lower when assessed in patients with PKU compared to the control group. Likewise, there was a decrease in the value of Q10 throughout the study in both groups. However, when assessing plasma selenium concentrations, no significant difference was observed between the groups of PKU patients compared to the control. On the other hand, Vargas, Wajner, and Sitta (2011) suggest that there is probably that selenium levels are indeed associated with a decrease in the antioxidant status of PKU patients[25]. Thus, they concluded that there is a correlation between oxidative stress and PKU, with CAT activity being negatively associated with plasma phenylalanine values in patients with PKU and Q10 values tend to decrease with increasing patient age, probably as a consequence of high phenylalanine levels and due to low food intake of Q10 by these individuals. The level of selenium was not affected in patients undergoing dietary treatment in this study[42].

Martinez-Cruz and collaborators (2002)[37] studied the oxidative stress caused by PKU in rats. The effects of maternal hyperphenylalaninemia on the morphological and biochemical development of the brain and cerebellum of young rats were evaluated, as well as different markers of oxidative stress. This study was able to demonstrate that PKU strongly increased most of the markers of oxidative stress studied (adult Ehrlich proteins and OLP). When evaluating the GPx and GRd activities, it was observed that PKU caused a loss of both enzymatic activities. The pathology was also able to induce significant morphological damage, such as the decrease in pup body and brain weight. The same parameters were observed when melatonin, vitamin E, and vitamin C were administered. These substances were able to improve the results by preventing oxidative biomolecular damage in the brain of the rat and

cerebellum as well as preventing morphological changes in the pups. In this way, the authors observed that PKU induces a clear state of oxidative stress involved in the brain and body damage. However, by administering antioxidants to mice, they are able to prevent PKU-induced damage altogether[37], as well as another study that suggests the use of antioxidants as adjuvant therapy[38].

Thus, there is an association between PKU and oxidative stress, since studies show that observation. This oxidative stress can be measured by tests to assess blood levels of Phe and L-carnitine, total antioxidant status (TAS) or total antioxidant capacity (TAC), levels of GSHPx, Q10, GSH, TBA-RS and selenium, GPx and GRd activity, and ROS production. The most common markers observed were GSHPx, Q10, TAS or CAT, possibly the best.

The main factors associated with oxidative stress in PKU are the levels of Phe in the blood and the deficiency in the intake of some essential compounds correlated with the diet of these individuals. It was observed that both in human[38,40,42] and animal[37,41] models that high amounts of Phe in the blood lead to an increase in this imbalance and, consequently, to neurological disorders resulting from the pathology, being more observed in late or untreated patients.

As new data emerges, this correlation may become more robust. However, it is already possible to understand that there is a deficit of antioxidant factors in the body of individuals with PKU, as well as evidence of its relationship with a restrictive diet where the administration of exogenous antioxidants can minimize the consequences. Thus, research is suggested that deal with the conditions of administration and dosage of exogenous antioxidants according to the classification of the pathology, tolerance levels, age, sex and pre-existing diseases.

CONCLUSION

Given the results obtained through the literature, it was possible to verify that there is evidence of a correlation between the neurological disorders of individuals diagnosed with PKU and oxidative stress. This phenomenon is more observed in patients with delayed diagnosis or with blood phenylalanine levels outside those recommended as satisfactory, as demonstrated in animal models and a study with patients.

Due to the fact that the diet is very restrictive, it interferes with the amount of essential components such as vitamins, minerals, and antioxidant compounds, the low intake of the latter especially being the cause of the imbalance and accumulation of reactive oxygen species. Thus, in addition to the early diagnosis and treatment of PKU, it is suggested, based on scientific studies, to introduce these antioxidant compounds in the treatment of patients to increasingly reduce the damage caused by oxidative stress. Furthermore, such introduction can contribute to nutritional aspects and prevent other diseases since antioxidants belong to a group of compounds essential for diet and healthy living. The need for further studies is also stressed in order to assess the administration conditions, dosages of exogenous antioxidants according to the pathology classification by levels of tolerance, age sex, and pre-existing diseases.

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Contributions

ALCCR: Article search and article writing.

RCSS: Article structuring and critical review.

ECM: Critical review.

LTSD: Critical review.

RAL: Review and article structuring.

JOFM: Assistance in the search and selection of articles, critical review, and structuring of the article.

RLBA: Assistance in the search and selection of articles, critical review, and structuring of the article.

Declaration of interest

No conflict of interest.

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