Experimental malnutrition: A systematic review

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Abstract

The protein-energy malnutrition (PEM) is an important public health problem. This study aimed to perform a systematic review of articles published in English and Portuguese in the last decade, aimed at research on experimental malnutrition. It was selected studies published from January 2006 to August 2015. The descriptors used were from "modelo de desnutrição" and "model of malnutrition". The databases consulted were Scielo, PubMed, Lilacs and Cochrane Library. In 17 articles, positive and negative outcomes of malnutrition were searched in different databases. Among these, 8 articles researched the correlation of malnutrition with immune system or gastrointestinal system and 5 articles analyzed the hematopoietic system and the skeletal system. Only 1 paper analyzed the cardiovascular system, 1 analyzed the cutaneous system and 2 the malnutrition itself. Experimental malnutrition articles need to standardize models for malnutrition in more details throughout his writings. Furthermore, it was observed that the studies about malnutrition did not search the relation between surgical stress and malnutrition.

Introduction

The protein-energy malnutrition (PEM) is a major public health problem that affects millions of people worldwide and can be described as a form of malnutrition where there is inadequate calorie or protein intake. Extreme cases induces in the individual a series of biochemical and organic changes, causing changes in bodily function, and is associated with worsening of the diseases [1].

The PEM has been a statistically significant problem in surgical patients, affecting 22-58% of cases, and is related to higher hospital costs, longer hospitalization, predisposing to a variety of complications, higher incidence of infections and mortality [2]. Clinically, the PEM can be classified into marasmus (deficiency in calorie intake), kwashiorkor (protein malnutrition predominant) or a combination of both, marasmus-kwashiorkor [3].

In this context, laboratory animals have been used increasingly to assess the effects of malnutrition degrees variables in susceptibility to infections and also in the various parameters of the immune response, as well as in several pathologies related to malnutrition [1]. The big advantage of using animal models is to allow highly controlled evaluation of each nutritional parameter, considering that is not possible in the case of human populations.

In this scenario, the present study was to conduct a systematic review of articles published in English and Portuguese in the last decade, aimed at research on experimental malnutrition.

Materials and method

The included studies were about experimental malnutrition, published from January 2006 until August 2015. Keywords used were “modelo de desnutrição” and “model of malnutrition”. Data bases consulted were Scielo, Pubmed, Lilacs and Cochrane Library. It was established the following criteria for inclusion: studies which used extratermeros animals (post-natal) and articles which were published 10 years ago. As criteria for exclusion: articles with incomplete information and review articles (only original articles were included).

Results

According to elegibility criteria, 17 articles were identified during the study period and are presented in Table 1, and 9 of these ones were published since 2011, showing that the issue is still current. As the place of origin of the articles, 8 of them are from South America, 4 from Europe, 1 from North America and 2 in Asia.

In 17 articles, there was the analysis of different systems in search of positive and negative impacts of malnutrition. It was found 8 articles researching the relationship between malnutrition with the immune system and/or gastrointestinal system, while 5 articles analyzed the hematopoietic system and the skeletal system. Only one paper analyzed the cardiovascular system, one analyzed the cutaneous and 2 studies, just the malnutrition process.

About the experimental animals used, 16 used mice and the pig was used in only one study. The time for induction of the malnutrition was 21 days in 4 studies, while less than 21 days in 5 studies and two weeks or less in 6 studies.

To induction to malnutrition was used the low protein diet or less in 6 studies.

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## Table 1. Articles about experimental malnutrition published from January 2006 until August 2015.

| Year | Title                                                                 | Country   | Author(s)                  | Studied system | Animal          | Model                              | Induction time to malnutrition | Effects                                                                 | Sex | Number of animals |
|------|------------------------------------------------------------------------|-----------|----------------------------|----------------|----------------|------------------------------------|-------------------------------|-------------------------------------------------------------------------|-----|--------------------|
| 2006 | Preventive strategy for Candida gut translocation during ischemia-reperfusion injury supervening on protein-calorie malnutrition | China     | Murota et al. [15]         | Gastrointestinal | Rat Sprague-Dawley | Low protein diet (2,5% casein)      | 7 days                        | Significant increase in permeability of the colon malnourished rats. The groups treated with Compound showed partial improvement of this parameter | Uninformed | 90                |
| 2007 | Rapid restoration of colonic goblet cells induced by a hydrolyzed diet containing probiotics in experimental malnutrition | Brazil    | Dock -Nascimento, Junqueira e Aguilar-Nascimento [12] | Gastrointestinal | Rat Wistar      | aprotic (Rhüster)                  | 12 days                       | Malnutrition decreased the number of goblet cells throughout the colon. | Male | 26                |
| 2007 | Reduction of erythroid progenitors in protein-energy malnutrition      | Brazil    | Borelli et al. [19]        | Hematopoietic   | Rat swiss       | Low protein diet (20 g/kg - casein)  | 14 days                       | Anemia of protein-energy malnutrition was the result of ineffective erythropoiesis. | Male | 38                |
| 2007 | Contribution of polyunsaturated fatty acids to intestinal repair in protein-energy malnutrition | Spain     | Nieto et al. [14]          | Gastrointestinal | Rat             | Low protein diet and hypocaloric (rich in lactose) | 14 days                       | Polyunsaturated fatty acids in the diet can influence the intestinal repair in chronic diarrhea due to protein-energy malnutrition. | Male | 80                |
| 2007 | Restoration by dietary glutamine of reduced tumor necrosis factor production in a low-protein-diet-fed rat model | Japan     | Komatsu et al. [10]        | Immune          | Rat Domryu      | Low protein diet (3% casein)        | 21 days                       | TNF production by reduction malnourished rat macrophages.                  | Male | 24                |
| 2008 | Protein-energy malnutrition modifies the production of interleukin-10 in response to Lipopoly saccharide (LPS) in a murine model | Brazil    | Fock et al. [6]            | Skeletal system | Rat Swiss Webster | Low protein diet (4% proteina)      | 14 days                       | Increased circulating levels of IL -10 in response to LPS.                | Male | 84                |
| 2009 | Protein-energy malnutrition decreases immune response to Leishmania chagasi vaccine in BALB/c mice | Brazil    | Malafaia et al. [8]        | Immune          | Rat Balb/c      | Low protein diet and isocaloric (3% casein) | 6 weeks                       | Malnutrition can alter the response to L. chagasi vaccine in rats even following nutritional supplementation. | Male and female | 40                |
| 2010 | PTH improves titanium implant fixation more than parimidine or renutrition in osteopetenic rats chronically fed a low protein diet | Switzerland | Dayer et al. [18]          | Skeletal system | Rat Sprague-Dawley | Low protein diet and isocaloric (2,5% casein) | 6 weeks                       | Reduction of malnourished rats force and PTH reversed the deleterious effects of malnutrition in mechanical fastening and microarchitecture. | Female | 41                |
| 2011 | Animal model of undernutrition for the evaluation of drug pharmaco kinetics | Spain     | Merino-Sanjuán et al. [22] | Malnutrition only | Rat Wistar      | Low protein diet and hypocaloric (5% protein) | 26 days                       | The proposed mathematical model allows the body weight of animals to be predicted at a given time taking into account the diet followed in the experimental period. | Male | 133               |
| 2011 | Modelos experimentais de desnutrição e sua influência no trofismo cutânio | Brazil    | Leite et al. [3]           | Cutaneous       | Rat Wistar      | Marasms (half the standard diet) and Gelatine | 60 and 30 days                | Dermis thinner , lighter weight and less collagen.                      | Male | 120               |
| 2011 | Avaliação da gasometria arterial de ratos desnutridos submetidos a anestesia inalatória por éter etilico em vaporizador artesanal | Brazil    | Pantoja et al. [20]        | Malnutrition only | Rat Wistar      | Low protein diet (“polvilho”)        | 21 days                       | The process of malnutrition was effective in reducing weight , serum albumin and bicarbonate. | Male | 20                |
| 2012 | Post-Weaning protein malnutrition increases blood pressure and induces endothelial dysfunctions in rats | Brazil    | Belchior et al. [21]       | Cardiovascular  | Rat Wistar      | Low protein diet and hypocaloric (9% protein ration RHD) | 3 months                       | Protein malnutrition after weaning increases blood pressure and induces vascular dysfunction. | Male | 20                |

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2012 Modulation of the nuclear factor-kappa B (NF-κB) signalling pathway by glutamine in peritoneal macrophages of a murine model of protein malnutrition
Brazil Lima et al. [7] Immune Rat Balb/c Low protein diet (2% protein) 21 days The malnourished animals showed anemia, leukopenia, lower concentration of glutamine in the state of malnutrition. The plasma interferes with the activation of macrophages and higher concentrations of glutamine, in vitro, can negatively affect the NF-κB pathway.

2013 An animal model of Kashin-Beck disease induced by a low-nutrition diet and exposure to T-2 toxin
China Kang et al. [4] Skeletal system Rat Sprague-Dawley Low protein diet, rich in barley (10,2% protein) 4 weeks Radiographic and histological abnormalities of the tibia. Male and female 120

2013 Acute effects of rotavirus and malnutrition on intestinal barrier function in neonatal piglets
United Jacobi et al. [13] Gastrointestinal Pig Low protein diet and hypocaloric (half the standard diet) 3 weeks Lower weight, diarrhea. In infected villi and reduction of lactase activity and increased crypt depth . Male and female 24

2013 Effect of a probiotic fermented milk on the thymus in Balb/c mice under non-severe protein-energy malnutrition
Argentina Núñez et al. [17] Immune and hematopoietic Rat BALB/c Low protein diet 21 days Increase of immature thymocytes in malnourished rats and influence of probiotic in the histological and functional recovery of the thymus. Male and female 35

2013 Protein energy malnutrition decreases immunity and increases susceptibility to influenza infection in mice
England Taylor et al. [9] Immune Rat C57BL/6 Low protein diet and isocaloric (2% protein) 3 weeks The malnourished mice exhibited more severe disease following infection with influenza and lower specific antibody response against the virus. Female 72

The other most studied system was the gastrointestinal which is markedly affected by the effects of PEM. In general, PEM affects the gastrointestinal tract causing atrophy of the gastric and intestinal mucosa. In the stomach causes hyperplasia, ulcерated lesions, decreased hydrochloric acid, weakening of gastric barrier to bacteria. In the intestines, there is a reduction of crypts, villi and intestinal microvilli, size of enterocytes, decreased intestinal transit may generally to constipation, and due to attenuation of the immune system, it is usual to observe infections and diarrhea [11-15]. Interestingly, other studies, malnutrition was not significantly contribute to the worsening of the intestinal barrier in rotavirus infection, or to decrease the potency of the vaccine against this pathogen [13,16]. The loss of thymocytes was identified in a study, this loss, as well as changes in the intestinal mucosa, can be ameliorated by supplementation with probiotic fermented milk [17].

In addition to the immune, and gastrointestinal systems have also been studied bone and hematopoietic system, the main findings loss of bone cells leading to defects like deficient hematopoiesis, lacking blood cells. It has been evidenced histological and radiographic abnormalities in mouse models with Kashin-Beck disease induced malnutrition [4]. Treatment with parathyroid hormone is effective in reversing the deleterious effects of malnutrition long term [18]. In malnutrition, anemia is caused by deficient erythropoiesis as the serum iron and erythropoietin in malnutrition do not change [19].

Although all the selected works have placed on your method data related to diet adopted by the animals, few jobs that have adopted an explicit model of induction to malnutrition, which could easily be replicated by other authors. This was the case of the work of Pantoja et al. [20] and Leite et al. [3], both studies could be considered innovative. At first, it was used as food biscuit flour, “pouvilho”, (totally devoid of protein) in Wistar rats diet to check for changes that malnutrition can result in blood gas analysis. Leite et al. used two models to arrive

Discussion
On the analysis of studies of this review, it can be seen that the experimental malnutrition has become an important area for the better understanding of the pathophysiology of malnutrition. In this regard, several systems have been the subject of research around the world. In China, for example, a study investigated radiographic abnormalities [4]. However, it was the gastrointestinal and immune systems were revealed as the main targets of interest of the scientific community nowadays.

It is noteworthy that the most prevalent cause of immunodeficiency worldwide is severe malnutrition which affects up to 50% of the population in poor countries. The immunological changes resulting from malnutrition can affect both the innate immunity in respect of specific. It has been noted that the availability of components of the complement system and phagocytic function are compromised in malnutrition and this hampers the elimination of pathogens. Both the C3 level, which is the main component opsonic, and the ability of phagocytes to internalize and destroy pathogens, appear reduced in states of desnutrição [5]. Such statements have been exemplified in the studies that correlate immune system with malnutrition, where the main roads studied were the NF-κB and inhibiting macrophages by interleukin 10 [6-10].
malnutrition: marasmus model which was to halve the mice food portions and the gelatin model, which would correspond to normal protein diet associated with low protein quality [20,3]. In the skin, malnutrition causes loss of collagen with less dermal thickness and negatively influences the tropism cutaneous [3].

As the cardiovascular system, malnutrition induces endothelial dysfunction, an increase of superoxide and nitric oxide in addition to the increased blood pressure [21].

Merino-Sanjuan et al. [22] used the pharmacokinetic study for malnutrition in animal model. Conclusion was the body weight of animals can be predicted at a given time takin in account the diet followed in the experimental period.

It is believed that, as the main characteristics for a model malnutrition, are practicality, the induction time and the adequacy of the animal studied. The evaluated articles, however, can see a significant discrepancy between the induction time in the researched articles, which would justify closer future studies to validate the best induction time for certain species.

Conclusion

It was observed that it is necessary that the experimental malnutrition articles standardize models for induction malnutrition in more detail in the course of his writings, so that other authors may have access to these techniques and can replicate them. In addition, it was noted that the scientific arsenal is lacking in research correlating malnutrition to one of its main causes today: surgical stress.

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