IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Insights Of Protein Deficiency Diseases – A Brief Review Literature

[1]Dr. Sandra Ann Alex, [2]Dr. Keerthana G, [3]Dr.Balasankari K, [4]Dr.Vinoth K, [5]Dr.Sathish Kumar M

[1]Under Graduate, [2,3]Post Graduate, [4]Senior Lecturer, [5]Head of the Department

Department of Oral and Maxillofacial Pathology

Karpaga Vinayaga Institute of Dental Sciences

Chengalpattu, India

ABSTRACT

Protein, with amino acids as its building blocks, plays a myriad of functions in the human body. Nearly eight billion people, or half of the world's population, suffer from protein deficiencies, according to the FAO and WHO. Protein deficiency gives rise to protein-energy malnutrition, mainly kwashiorkor and marasmus. These deficiencies can be dealt with by meticulous diet planning and ensuring the intake of protein supplements. Recently, RNA therapies for inherited metabolic disorders, including deficiency of proteins like phenylketonuria and neurodegenerative diseases like Huntington's disease, has been introduced.

Keywords: Proteins, Building blocks, Kwashiorkor, Marasmus, Phenylketonuria

INTRODUCTION

Every cell in our body needs protein, a macronutrient, for growth, maintenance, and repair[1]. An important nutrient, protein is a biopolymer made up of amino acids joined by peptidyl linkages. Jons Jacob Berzelius, a Swedish chemist, coined the term "protein" in 1838.Catalysis, hormones, immunology, cell structure and support, transport and storage throughout the body, and biological process coordination are just a few of the biochemical activities that proteins are involved in. The quantity of protein that the body needs in food is determined by its needs for nitrogen and essential amino acids. The body eliminates proteins throughout metabolic processes, most notably the urea cycle, rather than storing them as a reserve. Even in a condition of dynamic equilibrium, the body is constantly breaking down and re-synthesizing proteins. Significant functional impairments may result from a protein shortage. The Centre for Disease Control and Prevention's 2007 publication, "Protein and Amino Acid Requirements in Human Nutrition," states that the gastrointestinal system breaks down meal proteins and calculates the amount of protein that a person needs in grams per kilogram of body weight. The human body needs at least three times this amount of protein to get the necessary 14.72g/kg of essential amino acids. From this mass, the body will recover only 4.59g of essential amino acids, DMB, to repair and maintain muscle tissues, according to the American Dietetic Association and Dietitians of Canada [2].

KWASHIOKAR vs MARASMUS

Difference In Nutrition

From the beginning of the United Nations investigation, the dominant theory regarding the aetiology of marasmus and kwashiorkor was that the former was caused by inadequate energy from food, severe long-term food deprivation, or very early weaning, while the latter was linked to improper weaning and a diet lacking in protein. These opinions were formally supported by the FAO and WHO's third study, which said that whereas kwashiorkor is characterized by insufficient protein consumption, marasmus develops after protracted fat and carbohydrate deprivation (in addition to protein deficiency).

Then, in 1962, kwashiorkor, marasmus, and intermediate stages (marasmic-kwashiorkor) were classified as "protein-calorie deficiency diseases" in the 6th FAO/WHO report. Since then, kwashiorkor has been identified as a type of severe malnutrition associated with a diet that severely lacks protein (or high-quality protein) in relation to energy. On the other hand, marasmus is linked to either insufficient amounts of a high-quality diet or a balanced calorie and protein deficit [3].

Clinical Features

KWASHIORKAR:

The symptoms of kwashiorkor were described by Dr. Williams in 1933 as "constant and unique." These symptoms included oedema, especially of the hands and feet, followed by wasting, diarrhoea, irritability, frequent inflammation of the mucous membranes, and variable skin depigmentation with skin peeling. Children between the ages of one and four, regardless of gender, experienced the syndrome. One unique feature of children discovered after death was a "pale, fatty, and almost diffluent" liver .
The distinctive characteristics of large oedema and the particular alterations of the skin, liver, and hair in Kwashiorkor . The most common skin abnormalities in Kwashiorkor were dyspigmentation, "crazy paving" dermatosis, and "enamel paint" or "flaky paint." On the other hand, the "typical" newborn with marasmus has dry, wrinkled, and loose skin because of a significant loss of subcutaneous fat, and does not exhibit any of the skin changes linked to kwashiorkor. It is usually characterized by a large fatty liver, fibrosis, and malfunction of various organs (such as pancreatic, renal, and mental functions).

MARASMUS:

Marasmus is typified by a loss of subcutaneous fat, severe muscle atrophy, and atrophy of the majority of organs has little histological alterations despite the liver and other key organs being significantly smaller . Marasmus is more linked to HIV infection and rickets, kwashiorkor was more linked to bacterial infections, particularly bacteraemia and septicaemia[3].

Difference In Biological Features

Free radicals and Antioxidants

Golden and Ramdath's study was among the first to examine the role of antioxidants and free radicals in the pathogenicity of malnutrition[5]. The study found that while plasmatic zinc and vitamin E concentrations were low, ferritin, a storage form of iron, was particularly high in kwashiorkor; antioxidant enzymes like glutathione peroxidase were particularly low, and erythrocyte glutathione was very low . The results ushered in a new era for the study of malnutrition by successfully launching the theory that kwashiorkor is caused by an excess of free radicals and a depletion of antioxidants. In fact, a number of subsequent investigations have verified the low glutathione levels found exclusively in kwashiorkor but not in marasmus. Crucially, they were linked to a low NADPH/NADP ratio, which suggests that the cellular environment is becoming more oxidized due to a shift in cellular redox potential[3].

Protein and Amino acids Metabolism:

Manary (1998) showed that during acute infection, children with kwashiorkor have slower rates of whole-body protein synthesis and breakdown than children with marasmus. Then, in 2005, Jahoor verified this distinction and showed how children with and without oedematous malnutrition responded differently in terms of protein metabolism to food deprivation, indicating that only children with marasmus were able to maintain body protein breakdown at the same rate as well-nourished children, whereas children with kwashiorkor did not. According to research, children from Kwashiorkor have a high level of disruption in their amino acid metabolism, as evidenced by a steady and notable decline in their plasma levels of critical amino acids, with varying degrees of impact on particular amino acids . In the plasma of these children, certain non-essential amino acids either stayed at ordinary levels or may have been maintained at excessive levels.

Lipid Metabolism

Although the results were consistently greater in kwashiorkor children than in marasmic children, elevated plasma concentrations of free fatty acids (FFA) were frequently observed in both groups. Plasma phospholipids and total cholesterol were consistently and significantly lower in kwashiorkor than in marasmus. Generally, but not always, plasma fasting triglycerides are low in kwashiorkor; similarly, phospholipids and cholesterol are low, whereas triglycerides are normal or elevated in marasmus.
Manary (1998) showed that during acute infection, children with kwashiorkor have slower rates of whole-body protein synthesis and breakdown than children with marasmus. Then, in 2005, Jahoor verified this distinction and showed how children with and without oedematous malnutrition responded differently in terms of protein metabolism to food deprivation. This suggested that only children with marasmus were able to maintain body protein breakdown at the same rate as well-nourished children, whereas children with kwashiorkor lacked this ability. The fatty liver in kwashiorkor is more severe than in marasmus.
However, the fatty liver in Kwashiorkor could not be entirely explained by the elevated amounts of free fatty acids alone. Lewis proposed that in kwashiorkor, the liver was unable to eliminate fatty acids, which resulted in lipid buildup in the liver, while in marasmus, the liver responded to an excessive intake of fatty acids by producing more plasma lipoproteins. This has been linked to peroxisomal and mitochondrial dysfunction, as well as the absence of peroxisomes observed in Kwashiorkor livers observed by electron microscopy, which has been experimentally verified[3].

HOST IMMUNE RESPONSE IN PROTEIN ENERGY MALNUTRITION

The immune system has "built-in" checks and balances to control each antigen-specific reaction, making it incredibly intricate and well-integrated. This intricacy is indicative of a system that is extremely sensitive and accurate in identifying and detecting antigens, able to amplify information, highly responsive, and has an exceptional memory capacity. But this intricacy also makes it possible for a number of unrelated events to affect or compromise immune system performance. Among the most significant external influencing factors are nutritional condition and concurrent illnesses. Many organ systems can malfunction as a result of malnutrition. The amount and pace of protein synthesis, the rate of cell division, and the function of specific nutrients in the metabolic pathway are some of the variables that affect how severe the condition is in these organs.

Lymphoid tissues are particularly susceptible to these harmful consequences. Among, antigen-specific lymphocytes that are involved in humoral immunity, the beta-cell system of antibody synthesis, and the T-cell system of cell-mediated immunity are necessary for the host animals' resistance to bacterial infection. These systems cooperate with a number of nonspecific resistance factors, including complement, phagocytic cells, skin, mucous membranes, lysozyme, and the bactericidal ability of blood and tissue phagocytes. In addition to producing molecules that boost the phagocytic and bactericidal capacity of monocytic blood cells, T-lymphocytes and predetermined clones multiply and play a direct role in graft rejection, cytotoxicity against cancer cells, delayed-type hypersensitivity, suppression of the autoimmune phenomenon, and immune response regulation[4].

ACUTE MALNUTRITION

Acute malnutrition is a nutritional deficit brought on by insufficient consumption of energy or protein. Jelliffe coined the phrase "protein calorie malnutrition" in 1959, but "acute malnutrition" has now taken its place. Protein energy malnutrition is characterized by Olsen et al. as dietary deficit in children in underdeveloped nations. However, undernutrition in children is defined by all words as a nutritional state in which a lack of energy, protein, and other nutrients results in quantifiable negative effects on body processes and tissue, as well as a clinical outcome of growth deviation [9].

Pathophysiology

Inadequate energy intake leads to various physiologic adaptations, including growth restriction, loss of fat, muscle, and visceral mass, reduced basal metabolic rate, and reduced total energy expenditure. The biochemical changes in acute malnutrition involve metabolic, hormonal, and glucoregulatory mechanisms. The main hormones affected are the thyroid hormones, insulin, and the growth hormone (GH). Changes include reduced levels of tri-iodothyroxine (T3), insulin, insulin-like growth factor-1(IGF-1) and raised levels of GH and cortisol. Glucose levels are often initially low, with depletion of glycogen stores. In the early phase there is rapid gluconeogenesis with resultant loss of skeletal muscle caused by use of amino acids, pyruvate and lactate. Later there is the protein conservation phase, with fat mobilization leading to lipolysis and ketogenesis. Major electrolyte changes including sodium retention and intracellular potassium depletion can be explained by decreased activity of the glycoside-sensitive energy-dependent sodium pump to increased permeability of cell membranes in kwashiorkor.

Acute starvation impairs organ systems in different ways. Atrophy of the tonsils, lymph nodes, and thymus affects cellular immunity. Decreased secretory immunoglobulin A, poor phagocytosis, loss of delayed hypersensitivity, and decreased cluster of differentiation (CD)4 with normal CD8-T cells are all present. This increases vulnerability to invasive infections (e.g., gastrointestinal, urinary, and sepsis)[9].

Primary Acute Malnutrition

It is advised to treat primary mild acute malnutrition at home, which includes advising parents and emphasizing the continuation of breastfeeding and appropriate supplemental feeding (nutrition-specific therapies). These kids should ideally consume 25 kcal/kg more calories per day than their healthy classmates do, and their diets should include foods derived from animals that are high in important fatty acids and micronutrients like zinc, iron, and vitamin A.

According to WHO guidelines, ready-to-use therapeutic foods (peanut paste, milk powder, vegetable oil, and a mineral and vitamin mix) can be used to manage children with severe acute malnutrition in the community without any difficulties. Children with an appetite who have received treatment for problems can also receive ready-to-use therapeutic food in the hospital. Hospitalization is necessary until children are prepared to continue therapy at home for severe acute malnutrition sequelae, such as severe diarrhoea, hypoglycaemia, hypothermia, pneumonia, urinary tract infection, sepsis, etc. [9]

Secondary Acute Malnutrition

Finding the underlying condition through history collection, physical examination, and laboratory testing is essential for the treatment of secondary acute malnutrition. For preterm and low-birth-weight babies, iron supplementation combined with exclusive breastfeeding for the first six months is sufficient. Aggressive enteral feeding puts them at risk for necrotizing enterocolitis. A normal diet can be recommended for patients with mild inflammatory bowel disease or those whose condition is in remission. Some people with inflammatory bowel disease benefit from commercial, carefully produced liquid formulations. Protein restriction may be necessary in late chronic liver disease in order to prevent hyperammonaemia. It is best to utilize a mix of fats and carbohydrates and very little protein.

Reduced bile salt excretion into the small intestine is another significant characteristic of chronic liver illness that can lead to malabsorption of lipids and fat-soluble vitamins. Since medium-chain triglycerides do not require bile salts for absorption, they can be used as a source of dietary fat to combat this. The vitamins A, D, E, and K, which are typically fat-soluble, should be used in water-soluble forms. High-energy and high-quality protein in amounts that won't cause or exacerbate uraemia may be beneficial for kids with chronic

renal illness. Enough protein and energy must be given to children with congenital heart disease without significantly increasing their fluid intake. Their recurrent lung infections, exhaustion, and dyspnoea have caused them to eat less.

A hypermetabolic condition brought on by heart failure and increased breathing effort raises the need for additional nutrition even more. Cachexia is frequently seen in children who have cancer, chemotherapy, radiation, surgery, and infections because of tumour necrosis factor-α and tumour metabolites. To meet the higher calorie requirements, the diet must be adjusted. When there is inadequate tolerance to high enteral feed volumes, parenteral nutrition may be utilized to enhance nutrition[9].

EFFECTS ON HEART FAILURE PATIENTS

Children's malnutrition is divided into two categories: kwashiorkor and marasmus. It is unclear, therefore, whether these factors have clinical significance in adult heart failure (HF) patients.2308 adult HF patients were separated into four groups based on the type of malnutrition they had: Group C (no malnutrition, n=1511, 65.5%), Group M (malnutrition of the marasmus type, n=133, 5.8%), Group K (malnutrition of the kwashiorkor type, n=554, 24.0%), and Group MK (malnutrition of the marasmic-kwashiorkor type, n=110, 4.8%).The blood pressure was lowest in Group M.B-type natriuretic peptide levels were greater in groups K and MK. The groups M and MK had the lowest right atrial pressure. Group MK had the lowest event-free rates of cardiac and all-cause deaths, according to Kaplan-Meir analysis. Groups M, K, and MK were linked to cardiac mortality (hazard ratios 2.053, 1.855, and 3.001, respectively) and all-cause death (hazard ratios 1.790, 1.657, and 2.313, respectively) in the multivariable Cox proportional hazard analysis when compared to Group C as a reference. Malnutrition of the Marasmus-Kwashiorkor type has the worst prognosis, and both types are linked to increased mortality[7].

COGNITIVE DEVELOPMENT IN MALNOURISHED CHILDREN

Compared to children who were properly nourished, malnourished youngsters performed poorly for their age. Design fluency, working memory, visual construction, verbal comprehension, learning, and memory for verbal and visual material are among the cognitive skills that showed little age-related improvement between the ages of 5 and 7 and 8 and 10. These cognitive capabilities also had an impact on the rate of growth

The performance on all three executive function tests—fluency, selective attention, and working memory for spatial locations—required cognitive flexibility and quicker information processing, all of which were impacted in undernourished youngsters. Additionally, the results reveal that children who were malnourished improved on these functions at a very modest rate.

On one level, both age-appropriate performance on executive function tests and the gains brought about by growing older are impacted. However, malnourished children performed poorly in verbal fluency, but their pace of improvement was higher than that of fully nourished children. When compared to youngsters that were fed properly, visuospatial functions such as visual perception, visual creation, and visuo-conceptual thinking performed noticeably worse, but their performance sharply improved with age. Malnourished children's performance on tasks such as visual perception (visual discrimination, perceptual matching, visual closure, and visuospatial relationships) and visual construction was significantly impacted, and their pace of progress with age was equally poor. Future behavioural consequences and brain growth and development are impacted by malnutrition. Compared to matched controls and, to a lesser extent, siblings, school-age children who experienced early childhood malnutrition typically had lower IQ levels, cognitive function, school achievement, and more behavioural issues. The drawbacks persist until adolescence at the latest. Consistent evidence of a particular cognitive deficiency is lacking. It is less evident whether certain cognitive processes are functionally sound[8].

FOOD PROTEIN

Nearly eight billion people, or half of the world's population, suffer from protein deficiencies, according to the FAO and WHO. The world's most significant dietary issue is protein insufficiency. Depending on where they come from, proteins can be categorized into five groups: microalgae, insects, vegetables (cereals, legumes, oilseeds), microbiological (from fungi, yeast, and bacteria), and animals (meat and offal, fish, and milk eggs). Plant and animal proteins are used to make amino acids. Due to factors like animal diseases and the overall state of the economy, the costliest proteins are those derived from animals. The problem of

systematically including alternative proteins in the human diet is becoming more urgent as meat prices grow globally. The human diet contains vegetable proteins.
Nevertheless, these vegetable proteins are characterized by the presence of antinutrient elements, an average degree of digestibility (about 62–80%), and a lack of important amino acids. Depending on the type of cereal, the protein level on a DMB might range from 5 to 25%. In addition to its common use as a cereal, oatmeal is also used to make oatmeal coffee, pancakes, kissel, and malt for making alcohol. Traditionally, barley is used to make pearl barley (9.5g/100g), fine-ground barley (10.0g/100g), and flour (10.5g/100g).On a DMB, corn has a high carbohydrate content, 65–70% starch, up to 8% fat, and about 10% protein. In addition, trace levels of free amino acids like lysine are present in corn.
Moreover, butrichin carotene, calcium (0.05%), and vitamins B, F, A, and E are all essentially absent from corn. Essential amino acids (1.56g/100g), bulgur (12.29g/100g), buckwheat (13.25g/100g), semolina (1.3g/100g), couscous (12.76g/100g), and millet (11.2g/100g) are among the other grains with the following protein content on a DMB. On a DMB, soybeans have the highest protein level of any legume (up to 30g/100g); edamame and green soybeans, which are collected before they ripen, have somewhat lower protein contents (around 22g protein). In addition, soy has the highest concentration of practically every kind of important amino acid. Protein is also abundant in nuts and seeds.

For human nutritional needs, microalgae are regarded as a great source of biologically active and useful nutrients. The two most widely used microalgae on the market today are *Arthrospira platensis* and *Chlorella vulgaris*, which are both sold as standalone functional foods that are high in proteins, vitamins, and minerals. The protein content of insects as dietary sources ranges from 20 to 75 percent. In 2020, about $350 million was invested in companies that produce plant-based meat. By 2023, the FAO projects that the edible insect market will grow to a value of $1.2 billion. The current food business is increasingly using all of these different protein sources to produce high-protein foods and dietary supplements[2].

HEALTH COMPLICATION CAUSED BY PROTEIN DEFICIENCY

Kwashiorkor

Kwashiorkor is a type of protein deficiency that affects children. An enlarged liver, a swollen belly, pedal oedema (swollen feet), skin depigmentation, skin irritation, diminished hair, and tooth misfortune are some of its many symptoms. Finally, it can inhibit the development of a child's mind and body.

Marasmus

Marasmus is a kind of protein inadequacy that can prompt weakness, muscle squandering, and lessened muscle versus fat levels, decreased vitality levels and weight reduction. It additionally diminishes the viability of the invulnerable framework and makes sufferers more helpless to infections.

Impaired Mental Health

Chronic protein deficiency can affect your mental health in a number of ways. In addition to causing tension, irritability, sadness, and grumpiness, it can create mental impediment, particularly in children.

Oedema

Oedema (liquid maintenance) can be brought on by a lack of protein. This may result in swelling in the hands, feet, and stomach, among other areas of the body. In addition to swelling, oedema can result in stiff joints, hypertension, discoloured skin, and pain in the appendages.

Organ Failure

Many bodily functions depend on protein for growth and maintenance. Protein deficiencies can result in many body organs not functioning properly.

Wasting and Shrinkage of Muscle Tissues

Your body starts obtaining protein from other sources when you don't receive enough of it from your diet. Your muscles are one of the main sources from which your body swings. In the unlikely event that your muscles lose protein, they will deteriorate and shrink.

Weak Immune System

The production of antibodies, a crucial component of the safe framework, depends on protein. Your body won't be able to make these antibodies if you end up being noticeably protein deficient. Your body will fight against distant objects, making you more vulnerable to illness[4].

PROTEIN REPLACEMENT THERAPY

Traditional treatments for illnesses caused by genetic flaws and inborn metabolic abnormalities typically focus on treating the symptoms rather than the underlying cause. Hence, the scientific community has long sought treatments that target the underlying cause of the issue, such as DNA and, more recently, RNA therapies.

These days, cell-free systems can synthesize mRNA for protein replacement therapies using the in vitro transcription reaction (IVT).The IVT is conducted in a continuous or batch bioreactor that monitors and regulates reaction parameters like temperature and pH. NTPs that will act as RNA building blocks, a DNA-dependent RNA polymerase that carries out the transcription, the linearized DNA plasmid that serves as the template from which mRNA is to be transcribed, and in certain situations, a 5cap analogue. A cornucopia of extra reagents can be used to protect the integrity of the reaction and the end product, resulting in higher yields. RNA inhibitors, pyrophosphatase, and polyamines are examples of such agents.

The architecture and chemical makeup of the resultant mRNA, which are determined by the design of the plasmid exposed to IVT and the IVT agents utilized in the procedure, determine its translational efficiency. An adequate 5cap analogue must be present in mRNA that is suitable for protein replacement therapy. RNA-based protein replacement therapies have the potential to treat a number of diseases, some of which are still treatable today. Both preclinical and clinical investigations have investigated these treatment techniques, and some intriguing findings have surfaced.

Mutations in the phenylalanine hydroxylase (PAH) gene result in impairments in phenylalanine metabolism, which causes phenylketonuria (PKU), an autosomal recessive illness. To create an mRNA replacement therapy for PKU in mouse models of the condition, a study was carried out. More specifically, a mouse model was given a full-length mRNA encoding for human PAH that was encased in a lipid nanoparticle (LNP) and carried a missense mutation in the PAH gene. High amounts of human PAH protein were produced in the hepatocytes as a result, reestablishing the metabolism of phenylalanine. Interestingly, either after single or repeated doses of treatment (in both males and females), the reduction in phenylalanine did not coincide with any adverse clinical indications. These findings unquestionably demonstrate the feasibility of using RNA-based protein replacement therapy to treat PKU. Despite the vast potential of the mRNA technology not only to revolutionize former therapeutic and diagnostic practices, but also to amend the rules of the pharmaceutic market through its cost-effective and widespread development, its applications are still mainly at the stage of assessment through clinical trials that are currently under way[10].

REFERENCES

1.Khan, Alamgir & Khan, Salahuddin. Health complication caused by protein deficiency, Int. J. Food Sci.2017; Nutr.2017,1. 1-2.

2.Dolganyuk, V.; Sukhikh, S.; Kalashnikova, O.; Ivanova, S.; Kashirskikh, E.; Prosekov, A.; Michaud, P.; Babich, O. Food Proteins: Potential Resources, 2023; Sustainability, 15, 5863.

3.Thi-Phuong-Thao Pham, Maryam Tidjani Alou, Michael H. Golden, Matthieu Million, Didier Raoult, Difference between kwashiorkor and marasmus: Comparative meta-analysis of pathogenic characteristics and implications for treatment, Microb Pathog.2021; Volume 150,104702

4.Amir, Mellova Amir "EFFECTS OF PROTEIN-ENERGY MALNUTRITION ON THE IMMUNE SYSTEM," Makara J. Sci.2003;Vol. 7: Iss. 2

5. Golden MH, Ramdath DD, Golden BE. Free Radicals and Malnutrition. In Dreosti I.E.(Ed), Trace Elements, Micronutrients and Free Radicals, Humana Press, Totowa, New Jersey. 1991;199-222.

6.Joosten,K.F.;Hulst,J.M. Prevalence of malnutrition in pediatric hospital patients. Curr.Opin.Pediatr. 2008, 20, 590–596.

7.Sato, Y., Yoshihisa, A., Sugawara, Y. et al. Malnutrition stratified by marasmus and kwashiorkor in adult patients with heart failure. Sci Rep 2024;14, 19722

8.Kar BR, Rao SL, Chandramouli BA. Cognitive development in children with chronic protein energy malnutrition. Behav Brain Funct. 2008 Jul,24;4:31.

9. Dipasquale V, Cucinotta U, Romano C. Acute Malnutrition in Children: Pathophysiology, Clinical Effects and Treatment. Nutrients. 2020 Aug 12;12(8),2413.

10.Vavilis T, Stamoula E, Ainatzoglou A, Sachinidis A, Lamprinou M, Dardalas I, Vizirianakis IS. mRNA in the Context of Protein Replacement Therapy. Pharmaceutics. 2023 Jan 3;15(1):166.