



Nutrition and Immune System in Livestock's: Mini Review



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Introduction

The relationship between nutrition and immunity are interlinked to each other that nutrient as a single or in a group affects immunity either directly or indirectly [1]. Directly nutrients affect the immune system by triggering the immune cell activation or altering immune cell interaction and indirectly by changing the substrates of DNA synthesis, changing, the physiological integrity of the cell, altering energy metabolism, or by altering the signals or hormones [2]. Specific nutrients like vitamins, minerals, antioxidants, etc. play a vital role in augmentation of immunity while deficiencies cause immune suppression [3]. The types of immunity, the role of different cells, their components, mechanism of action, measuring the immunity are described in brief to have a better understanding of the importance of the relationship between nutrition and immunity.

Types of Immunity

The immune system has evolved over a period of time to protect the host against the invading pathogens like bacteria, virus, protozoa, or fungus. Both innate and adaptive immune systems are interlinked and work together to provide immunity. The innate immunity acts as first line of defence followed by the action of adaptive immunity during the site of entry of the

pathogen. The phagocytes, NK cells, and granulocytes play a major role in innate immunity, while the lymphocytes, antigen-presenting cells (APC) play an important role in adaptive immunity. Phagocytes APC functions act as a linkage between the innate and adaptive immunity by presenting the antigens to the lymphocytes [4].

Innate immunity

The innate immune system is the primitive of the two immunities and is capable of destroying the pathogens non-specifically. This immunity is present in vertebrates, invertebrates, and plants also [5].

The innate cells includes the NK cells, mast cells, basophils, eosinophil, and the phagocytic cells including the macrophages, neutrophils, and dendritic cells while complement system and cytokines from other components of innate immunity and function within the immune system by identifying and by eliminating the pathogens that might cause infection [6]. Monocytes, macrophages, and neutrophils form the primary component of the innate immune system, in addition, the skin barrier, the mucous secretion etc. come under this immune system (Table 1) [14].

Table 1

S. No.	Innate Immune System Cells/Others	Functions
1	Macrophage/ Monocytes	Monocytes are those WBCs that are found in the blood, they migrate to the tissues, gets enlarged, granulates and become Macrophages. They phagocytosis the invading microbes and helps in antigen reorganization by the T cells [6].
2	Neutrophils	They are the first to migrate to the site of infection. These are granulocytes, uses respiratory burst with the help of free radicals, hydrogen peroxide, and hypochlorite to kill the pathogens. Play a vital role against parasitic and allergic reactions [7].
3	Dendritic cells	They resemble the same as that of neuronal dendrites. These are phagocytic cell who act as a connection between the innate and the adaptive immunity. They are considered as part of both innate and adaptive immunity [8].
4	Basophils	These cells are one among the granulocytes, producing histamine, which in turn increases the blood flow to the tissues [9].
5	Eosinophils	They engulf the bacteria and produces enzymes that cause perforation against the pathogen cells. They play a vital role in parasitic infection and allergic reaction [10].

6	Natural Killer cells	These cells are specialized to kill the infected cells like virus infected cells and cancerous cells without activation. They regulate the T cells, B cells, and macrophages by cytokine production [11].
7	gamma/delta T cells	These cells are a subset of T cells possessing a distinct T-cell receptor (TCR) on their surface, the gamma and the delta chain instead of the alpha and beta chain, which is usually present in normal T cells. They are considered as a component of both the innate and adaptive immune system [12].
8	Complement system	The complement system is a cascade of 20 different proteins that attacks the foreign cells surface. The term complement was termed to "complement" the killing of pathogens with the help of antibodies. Complement forms the humoral component of the innate immune response [6].
9	Cytokines	Cytokines are signalling molecules composed of proteins, peptides or glycoproteins produced by specific cells of the immune system like macrophages, T lymphocytes, B lymphocytes and mast cells, as well as from fibroblasts, endothelial cells, and various stromal cells [13].

Adaptive/Acquired immune system

Adaptive immunity is the second line of defence which develops once antigen is presented to both T and B cells. Both T and B cells play a vital role in adoptive/acquired immune system, where B-cell plays a vital role in humoral immune system whereas the T-cells play a vital role in cell-mediated cell-mediated immune response [15].

B cells: Antibody produced by B cells recognizes and bind to pathogens or destroy them with the help of macrophages. Such response is called humoral immunity [15].

Table 2: Types of T cells

S. No.	Sub-Groups/Types of T Cells	Functions	Surface Markers
1	T helper T cells	Maturation of B cell to plasma and memory cells Activation of cytotoxic T cells and macrophages	CD4+
2	Cytotoxic T-cell	To destroy the tumor cells and virus-infected cells	CD
3	Memory T cell	Provide memory against the infected pathogen's antigen after the infection	CD4+ or CD8+
4	Regulatory T cells or Suppressor T cells	To suppress the auto-reactive T cells [38].	CD4+, CD25+ and Foxp3+
5	Natural Killer T cells	Acts as both T helper and cytotoxic cells [35].	CD1D, CD1d
6	Gamma Delta T Cells	To produce functional diversity and will develop a memory phenotype. Phagocytosis functions in humans. Plays a part in both innate and adaptive immune system [36].	Lacks CD4+ and CD8+

Measuring the Immunity

Immunity can be assessed for both humoral as well as the cell mediated immunity. In humoral immunity, the basic principle is to measure the antibody titters whereas cell mediated immunity involves more complex techniques to measure the specific cell surface markers, specific memory T cells and lymphocyte proliferation etc [17].

Measuring humoral immunity

Humoral immunity is measured based on quantification of immunoglobulin (Ig) concentrations. Various types of immunoglobulins include IgG, IgM, IgA and IgE, their level varies with nutrition and immunity [18].

T cells: Various T-cell sub groups exists and each has its own roles in adaptive immunity. The table below describes each sub-Groups of T cells (Various For instance, cytotoxic T cells (killer T cells) directly attack and kills the infected cells, while helper T cells aid in the function of other lymphocytes and enhance the responses. Regulatory T cells, sometimes called suppressor T cells, suppress immune responses. T cells possess T cell receptors on their surface which help them to get distinguished from B and NK cells [16].

Types of T cells (Table 2)

Assessing the Immunoglobulin concentration: Assessing the Immunoglobulin IgM and IgG concentrations helps to know the humoral immunity status. The presence of antibody against the specific pathogen provides information if immunity was developed or not against the specific pathogen. Their tier level will give substantial information about the immunity status.

Titre: Titre provides information about the concentrations of antibodies (whether IgM or IgG) produced towards a specific antigen.

Lymphocyte proliferation assay: Rate of cell division by T and B cell by using substances like pokeweed mitogen and oligosaccharide respectively provides an index of the ability of the humoral immune system to boost following an infection [19].

Measuring cellular immunity

Measurement of cell-mediated immunity can be undertaken by both in vitro and in vivo methods. It is, however, more problematic than humoral assessment as assays are plagued by difficulties in standardization, biological variability, imprecision and technical complexity [20].

Flow cytometry

The evaluation of cell-mediated immunity is to quantify circulating immune cells and their subsets by flow cytometric analysis. Fluorochrome-labelled monoclonal antibodies directed against cell surface molecules and analyzed by a flow cytometer, which measures light scatter and fluorescence emission from individual cells. The amount of fluorescence is directly proportional to the number of cells with the particularly targeted surface molecule. Different cell populations (B cells, and CD4/CD8T cells and natural killer cells) can be distinguished based on their scatter profile and surface molecule expression [21].

Delayed-type hypersensitivity skin testing

Delayed-type hypersensitivity skin testing provides cellular immunity assessment under in vivo condition. The test involves inoculation of antigen intradermally leading to local inflammation surrounding the site of injection after 1-2 days due to the recruitment of mononuclear cells (lymphocytes, monocytes) and neutrophils. Flow cytometry is usually done to test Mycobacterium and Brucella infection [22].

Cytokine production/concentration

Communication among cells that mediate immunity is carried out by a large number of hormones called "cytokines". Common signalling cytokines include IL-1, IL-2, IL-4, IL-5, IL-6, IL-10, tumor necrosis factor-alpha (TNF- α) and interferon-gamma (IFN- γ). Measuring concentrations of cytokines in biological samples can provide useful information on activities of specific aspects of the immune system [16].

Natural killer cell cytotoxicity assays

Natural killer cell cytotoxicity is assessed by a ⁵¹Cr-release assay in which patients' natural killer cells are incubated with ⁵¹Cr-labelled target cells. The target cells get lysed by natural killer cells led to the release of radioactivity which can be measured. Natural killer cell dysfunction may occur in patients with CD16 genetic mutations, chronic mucocutaneous candidiasis, severe combined immunodeficiency and other cellular immunodeficiency syndromes. These conditions need to be considered and excluded if natural killer cell dysfunction is confirmed. With respect to T and B lymphocytes, functional natural killer cell deficits can occur though the natural killer cell counts are normal. Natural killer cell assays are complex technically and seldom performed in diagnostic immunology laboratories.

Mechanisms of Immunity and Nutrition

Nutrition and immunity interact in a number of ways, many of which researchers are just beginning to understand. These include:

Nutritional immunity

The body can fight infections by withholding nutrients from pathogens; this concept is named nutritional immunity. For

example, iron, biotin, and manganese play a role in depriving pathogens of required nutrients [23].

Hormonal regulation

Certain vitamins, minerals, and macronutrients (substances required in large amounts) provide the molecules needed for hormonal regulation. Glucocorticoids are essential for mediating response towards the pathogens by the host. Hormones also regulate the activities of the lymphocytes. White blood cells play a central role in coordinating immune responses by responding to the presence of foreign material in the body [24].

Fatty acids and vitamins A, D and E

Fatty acids and vitamins have direct effects on the immune system by supporting the manufacture and function of cytokines - the chemical signalling molecules of the immune response [25,26].

Substrates

These provide the molecules required for metabolism. All nutrients provide the amino acids and energy that help build and maintain the components and the metabolic processes of the immune system. For example, vitamin A helps with the development of B- and T-lymphocytes (key parts of the immune response) [27].

Antioxidants

These are molecules that reverse the chemical process of oxidation by stabilizing the number of unstable oxygen atoms (free radicals) that can cause cell damage over time. At the molecular level, the oxidation that free radicals produced can damage DNA, RNA, and the cell lipids (fat molecules that make up the cell membrane), which are essential for the cell membrane integrity. The weakening of the lipid layers can hasten cell death [28]. Important antioxidants are vitamins E, C, and A, and minerals such as zinc and selenium, as mentioned above.

Vitamins A and E, in particular, have antioxidant effects in the horse. For instance, vitamin A might direct lymphocyte development and maintenance of the mucous membranes, which help fight off challenges from pathogens.

Specific Nutrients and its Effect on Immunity

In non-ruminants, essential amino acids, folic acid, vitamin B6, vitamin B12, vitamin C, vitamin A, vitamin E, linoleic acid, iron, zinc, selenium, and copper affect one or more indexes of immunity. In ruminants, their capability to synthesize amino acids and vitamins with the help of microbial population had refrained scientist to study their effects. But few reported that cobalt, copper, selenium, chromium, vitamin E and A have regulated the immune system in ruminants [29].

Nutrients with antioxidant properties have shown to protect the cell membrane of the immune system as they are susceptible to Reactive Oxygen Species (ROS) - mediated damage. Hence antioxidant properties of vitamin C, E, carotenes and zinc and selenium minerals support the cell membrane which in turn strengthens the immune system as a whole [30].

Carotenoids

Carotenoids include β -carotene, lutein, canthaxanthin, lycopene, and astaxanthin are potent source of vitamin A. In ruminants, supplementation with β -carotene at dry periods

reduced mammary gland infections with increased lymphocyte blastogenesis and increased neutrophil killing activity [31].

Vitamin E and selenium (Se)

Feeding elevated levels of Se to ruminant animals reduces the incidence of diseases. Feeding of Se enhanced neutrophil killing activity. Se deficiency increases neutrophil adherence and could affect the ability of neutrophils to attack and sequester pathogen [32]. Vitamin E prevented the peripartum reduction in neutrophil superoxide anion production and impaired IL-1 production by monocytes and increases lymphocyte proliferation. Injection of Se either alone or in combination with vitamin E significantly improved the production of specific antibodies against *E Coli* and that the production of specific antibodies was greater after the administration of Se alone [33].

Omega-3 and 6 fatty acids (ω -3 and ω -6)

Fatty acids affect immunity through the production of cytokines, eicosanoids (e.g., prostaglandins) and leukotrienes. Diets rich in the ω -6 fatty acids, such as linoleic acid (C18:2), lead to the formation of arachidonic acid, whereas diets rich in the ω -3 fatty acids (such as linolenic acid, C18:3, flaxseed and fish oils) lead to the formation of, eicosapentaenoic acid (EPA). Eicosanoids synthesized from arachidonic acid tend to have stronger inflammatory potential whereas those synthesized from EPA have lesser potential. Hence, feeding fatty acid mixtures which are enriched in the ω -3 fatty acids reduces inflammatory reactions and reduces production of proinflammatory cytokines including IL-1, IL-6, and TNF- α . Studies on flaxseed increased progesterone and PGE4 concentrations increased TNF- α and nitric oxide [34].

Chromium (Cr)

The addition of Cr to livestock diets improves immunity. Chromium increased blastogenesis in the lymphocytes recovered from sick calves. However, the same effect was not detected in healthy calves' lymphocytes. A common theme among studies has detected the benefit to Cr supplementation could be due to the presence of a stressor (shipping, parturition, weaning). It is possible that stress and consequent immuno suppression can be suppressed with Cr supplementation [35].

Copper (Cu)

Natural Cu deficiency increases the susceptibility of ruminant animals to disease. However, experimental models of Cu deficiency often fail to increase the incidence of disease. Supplementation of Cu-deficient diets augments markers of immune function whereas others do not. Cu or Zn affected the humoral immune response to albumin immunization [36].

Zinc (Zn)

Zn plays an important role in transcriptional control through its action as a Zn-finger motif. Cells deficient in Zn have reduced ability to proliferate. The immune response requires a rapid proliferation of cells (e.g., T- and B-lymphocytes) in response to specific antigens and, therefore, Zn deficiency prevents this aspect of immunity from developing.

Spears (2000) reported that, in contrast to studies with humans and laboratory animals, marginal Zn deficiency has little effect on immune function in ruminant animals while Zn supplementation could be beneficial [37,38].

Conclusion

Nutrition plays an important role in determining the immunity of the animal in its life time. Their role is crucial during early and late stages of the animal's life span. Deficiency of protein-energy tend to affect the immune status of the animals. Deficiency of single or group of vitamins, minerals has influence on immune system. Identification of specific nutritional deficiency and supplementation with the respective deficient nutrition is the key to alter the immune status and to boost the immunity of the animal.

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