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REVIEW

Effects of Dietary Chromium on Immune System

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ABSTRACT

Many studies were conducted on chromium (Cr) nutrition. Since earlier, Cr was accepted as an essential nutrient/mineral. Also, close relationship between dietary Cr and carbohydrate metabolism was revealed in detail. Although some effects of dietary Cr on immune response were revealed by earlier in vitro studies, interests on farm-based effects have been recently focused. In this review, the effects of dietary Cr on immune system have been emphasized.

Key Words: Immunonutrition, Immune response, Mineral nutrition, Trivalent chromium

Krom ile Beslemenin Bağışıklık Sistemi Üzerine Etkileri

ÖZ

Krom (Cr) beslemesi üzerine birçok çalışma yapılmıştır. İlk dönemlerde araştırmacılar tarafından esansiyel bir besin maddesi/mineral olarak kabul edilmiş ve karbonhidrat metabolizması ile yakın ilişkisi detaylı biçimde ortaya konmuştur. Erken dönemde Cr mineralinin bağışıklık sistemi üzerine bazı etkileri olduğu in vitro çalışmalar ile keşfedilmiştir. Son yıllarda ise bu etkilerinin çiftlik bazındaki yansımaları ortaya konmaktadır. Bu çalışmada, Cr beslemesinin bağışıklık sistemi ve yanıtına etkileri incelenmiştir.

Anahtar Kelimeler: İmmun besleme, İmmun yanıt, Mineral besleme, Trivalent krom

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INTRODUCTION

The Cr element has been defined as an essential mineral in rats by Schwarz and Mertz (1959) and in humans by Jeejebhoy et al. (1977). In the years that followed many studies have been carried out regarding the use of the Cr mineral in human nutrition especially in stress situations (Anderson et al. 1982, 1988). Eventually the mainstream research area transformed into an association between Cr and type 2 diabetes (Rabinowitz et al. 1983). During this period various animal trials were carried out also on Cr nutrition (Abraham et al. 1982a, 1982b, Schrauzer et al. 1986). Towards the end of the nineties the Cr mineral began to gain ground as an essential mineral in studies involving farm animals (cattle, sheep, pigs and poultry)(Pechova and Pavlata 2007). Furthermore, studies carried out throughout the years indicated that in general Cr is an essential nutrient increasing the efficiency of insulin which has an impact on the utilization of sugars, proteins and fats (Shrivastava et al. 2002). Therefore, it is fundamentally necessary for the normal metabolism of energy and protein sources (Mertz 1992, Xu et al. 2017). However, increasing insulin efficiency is not the only impact that chrome has. Studies are also available which indicate that feeding supplemental dietary Cr to dairy cows increases milk yield (Hayirli et al. 2001, McNamara and Valdez 2005) and/or strengthens immune response and resistance to diseases (Spears et al. 2012). Numerous biological active substances also containing heavy metals have a direct or indirect impact on the primary and secondary immune system. Many metals have biochemical, immunological and physiological impacts in the body as trace minerals. Although it is known that in terms of natural, humoral and cellular immune response the Cr mineral displays results in different contents, the intercellular and intracellular impact underlying this mechanism has not been fully manifested (Haq et al. 2016, Pechova and Pavlata 2007).

The effects of chromium on the immune system

Although the precise role of Cr on immune functions has not been fully elucidated yet a study carried out by Kafilzadeh et al. (2012) clearly reveals that the supplemental dietary Cr decreases the level of cortisol. It is known that cortisol which is the most important glucocorticoid has a negative impact on the generation of antibodies and their impact and on the function of lymphocytes as well as the leukocyte population (Munck et al. 1984, Roth and Kaeberle 1982). A study carried out by Mallard et al. (1994) revealed a sharp increase in the cortisol levels of dairy cows which did not receive Cr supplementation while a decrease in the plasma cortisol level of the group which received dietary Cr supplements in the 2nd week before calving until the first week of lactation was observed. Subiyatno et al. (1996) also determined that dairy cows which received supplemental dietary Cr had low cortisol levels after calving. In addition to the acute physical stress of calving dairy cows are subjected to chronic metabolic stress factors such as lactogenesis, galactopoiesis, negative and low energy balance as well as milk peak (Burton et al. 1993). In this period, the incidence of clinical mastitis increases in parallel with the lymphocyte and neutrophile functions that undergo severe changes (Guidry et al. 1976, Kehrli et al. 1989a, Kehrli et al. 1989b). Burton et al. (1993) reported that the ability of PBMC to respond to Con A stimulation in dairy cows during the calving and peak milk yield periods is weaker. In addition, the strength of the anamnestic antibody response to the OVA antigen is also impaired. However, according to researchers, supplementation of Cr into the rations of dairy cows fortified the blastogenic response of PBMC to Con A stimulation in dairy cows during the prepartum and calving period. This effect continued until the peak milk yield period. In addition, anti-OVA antibody response in Cr-treated cows was also stronger in dairy cows treated with Cr supplements compared to control groups (Burton et al. 1993). Villalobos et al. (1997) reported that a significant reduction in placental retention was observed in dairy herds in Mexico where retention incidence is observed with the addition of Cr picolinate applied as a dose of 3.5 mg/animal/day into silage-based rations 9 weeks prior to anticipated calving dairy herds. While a retention rate of 56% was observed in the control group, the value of the application group had been decreased by 16% (Villalobos et al. 1997). It is reported that this impact was achieved by supporting the immune system with Cr. The results of other studies on the effects of dietary Cr addition on immune system parameters in cattle can be summarized as follows. Burton et al. (1993) showed that the addition of Cr starting 6 weeks before calving and continuing up to the 16th week after calving generated a stronger blastogenic response to ConA stimulation. In contrast, peripheral blood mononuclear cells (PBMC) were isolated from cattle injected with ovalbumin in the same study and their blastogenic response to ovalbumin stimulation was investigated. Cr-treated animals showed a weaker ovalbumin-stimulated blastogenic response compared to control group animals. In a subsequent study by Burton et al. (1995), two PBMC cultures were generated by drawing blood from control group animals. Subsequently, blood from the treatment group was added in vitro into one of these two groups of blood. An increase in the blastogenic response to ConA stimulation was observed in the PBMC culture in which blood from the Cr supplemented group had been added in vitro. Chang et al. (1996) directly added Cr supplement in vitro into PBMC cultures isolated from control group animals; this

application also resulted in a similar increase. Burton et al. (1996) demonstrated that this ration supplementation induced lower IL-2, IFN-γ and TNF-α production in in vitro environment against ConA stimulation in PBMC cultures isolated from Cr-supplemented animals. The antibody produced in response to antigenic stimulation varied according to the antigen type (Pechova and Pavlata 2007). For example, while the addition of Cr generated a stronger antigenic response following ovalbumin administration, the same response was not generated against human erythrocytes (Burton et al. 1993). Furthermore, when Cr supplements are combined with commercial vaccines manufactured against IBR, Parainfluenza-3, BRSV and *Pasteurella haemolytica* infections, no impact was determined in terms of antibody response yet an increase in antibody titers against BVD infection was observed (Burton et al. 1993). However, other studies reveal that the supplementation of dietary Cr increases the production of antibodies against IBR (Burton et al. 1994) and tetanus toxins (Faldyna et al. 2003). Lien et al. (2005) studied the immune response of dietary Cr propionate (0.2 mg/kg) in weaned pigs; it was reported that a specific antibody titer against sheep red blood cells was higher in groups which had been supplemented with chromium. *E. coli* lipopolysaccharide (0.1 mg/kg) was administered as a stress inducing agent in the mentioned study. This treatment also increased the number of white blood cells in the Cr groups; higher concentrations of IgG and gammaglobulin were detected in the same groups in comparison to the others.

Effects of chromium on lymphocytes

There are many studies examining the effect of Cr on lymphocytes. There are some studies in which the response of peripheral lymphocytes isolated from the blood of animals with Cr-supplemented rations to stimulation with various mitogens in cell cultures has been examined. Burton et al. (1993) added Cr-amino acid chelates to the rations of dairy cows on a 0.5 mg/kg 6 weeks before calving and continued the application until the 16th week after calving. It was reported that blastogenic response as a result of mitochondrial stimulation of ConA in the cell culture of lymphocytes isolated from the animals had been increased by Cr. Furthermore, the same study (Burton et al. 1993) manifested that the treatment groups which had dietary Cr supplemented provided protection for the control group in which decrease of blastogenic response was observed 2 weeks before calving. In subsequent years the same researcher carried out a study in which cell cultures were combined with lymphocytes isolated from animals in a control group which did not receive any Cr supplements; when serum from animals which had received Cr additives in their rations was added directly into these cell cultures it was noted that again lymphocyte blastogenesis stimulated by ConA increased (Burton et al. 1995). It was also manifested that the increased blastogenesis did not change the presence of insulin and other hormones in the blood of the animals with Cr supplements (Spears 2000). In studies carried out by Chang et al. (1996, 1994) Cr amino acid chelates and $CrCl_3$ was added directly into cell cultures generated from lymphocytes isolated from cattle which had not received Cr supplements in their rations and it was noted that in both cases blastogenesis had increased as a result of Con A stimulation. Burton et al. (1996) conducted a cell culture study by isolating mononuclear cells from dairy cows in which Cr had been added in a Cr-amino acid form (0.5 mg/kg). A lower level of IL-2, IF-γ and TNF-α in oscillation was observed in the mononuclear cell cultures of the groups with Cr treatments following Con A generated simulation compared to the control group. However, Arthington et al. (1997) reported that no difference was observed in the TNF-α concentrations of calves supplemented with Cr (yeast with a high Cr content) compared with control groups both before and after BHV-1 inoculation. In a study carried out by Chang et al. (1996) neutrophils were isolated from dairy cows which had been supplemented with Cr on a 0.5 mg/kg ration or dairy cows without supplements. The ability of the isolated neutrophils to phagocytose was not affected by Cr supplements and did not differ from the control group. Similarly Arthington et al. (1997) reported that the supplemtation of Cr-enriched yeast to calf rations did not affect the ability of neutrophils to eliminate *S. aureus* microorganisms.

According to Kafilzadeh et al. (2012) animals which had been given Cr supplements during the prepartum period incurred a significant increase in the levels of neutrophils ($p<0.05$) while the number of lymphocytes remained low. Therefore the neutrophil/lymphocyte ratio has significantly increased in the treatment group ($p<0.05$). In addition, the number of neutrophils in the postpartum period was also higher in the treatment group. The increase in the number of neutrophils and N/L ratio in this study may be a reflection of the increasing level of insulin and the decreasing NEFA and cortisol levels in the treatment group. Insulin and cortisol have an antagonistic association in the metabolism and it is known that cortisol disrupts lymphocyte functions and decreases the leukocyte population.

Effects of chromium on macrophages

Lee et al. (2000) carried out in vitro studies and incubated alveolar macrophages in different cell culture media with and without insulin. As a result it has been demonstrated that subject to the dose, the addition of Cr chloride and Cr picolinate have an impact on intracellular glucose uptake, O_2 production, glucose-6-phosphate dehydrogenase production and *E. coli* phagocytosine production activities of macrophages.

Gatta et al. (2001) studied the impact on the immune response of adding Cr-yeast compound into the rations of rainbow trout. A positive effect on serum lysozyme activity has been determined in fish fed with high chromium-containing rations. In addition, chromium-fed fish in this study demonstrated significant changes in phagocytic activity and respiratory burst level. Jain and Kannan (2001) conducted a study on U937 monocyte cell cultures, in which a high-glucose media was established in cell cultures and Cr was added. The addition of Cr inhibits TNF-α secretion, which has a chemotactic impact on macrophages but also produces insulin resistance in normal cells.

Effects of chromium on cytokines

There are many studies examining the behavior of cytokines on the use of chromium ration additives. Myers et al. (1995) examined the effects of Cr picolinate and recombinant pig growth hormone as dietary supplementation on the growth performance and cytokine production in piglets. While very high levels of plasma IL-6 were observed in the Cr picolinate-fed group in the study no changes were observed in the IL-6 plasma levels of the groups which were administered only hormone and hormone + chromium picolinate. Peripheral blood mononuclear cells from Cr picolinate-treated animals generated more IL-2 production than the other groups.

Effects of chrome on immune response

Burton et al. (1993) have determined the efficiency of chromium added into the rations of dairy cows under physical and metabolic stress. The executed study indicated increases in the blastogenic response stimulated by mitogen-induced anti-ovalbumin antibody response in peripheral blood mononuclear cells of Cr-supplemented animals. Another study (Chang et al. 1996) demonstrated that Cr supplements had no impact on health status, mastitis-related parameters or the phagocytic activity of neutrophils. Van de Light et al. (2002) carried out a study to determine the impact of adding Cr tripicolinate to the rations of pigs on the immune response following the weaning phase. The researchers did not determine any impact on the overall performance and immune system during this process. The impact of supplemental dietary Cr on humoral response is carried out by specific antibody measurements following the introduction of a foreign protein or inoculation into the relevant organism (Spears 2000). In a study carried out by Burton et al. (1993) the primary and secondary antibody responses generated by control group dairy cows feeding on Cr rationed with amino acid chelates based on rations of 0.5 mg/kg against ovalbumin was higher than in the control group dairy cows. In this study the first injection for primary response was applied 2 weeks before calving and the second injection for secondary response was applied 2 weeks after calving. Furthermore, in this study the cows were also injected with human erythrocytes however chromium had no impact on the antibody response generated against this antigen. In a study conducted by Moonsie-Shageer and Mowat (1993), calves exposed to feed restriction and transport stress were fed with a yeast form with a high Cr content based on 0.2-1.0 mg/kg and while primary antibody response increased in these animals against human erythrocytes the response of the secondary antibody was not affected by the response application. On the contrary, Kegley et al. (1997) reported that the addition of Cr in the form of Cr-nicotinic acid on the basis of a 0.4 mg/kg dose to rations of stressed calves did not affect the antibody response resulting from pig erythrocyte injections. Similarly, Kegley et al. (1996) reported that neither the addition of $CrCl_3$ nor Cr-nicotinic acid to the milk of milk-fed calves increased the specific antibody response to porcine erythrocytes. A study carried out by Burton et al. (1994) demonstrated that the addition of ration Cr in the form of amino acid chelate form starting 6 days before inoculation and continuing for 28 days increased specific antibody response against IBRV however it did not influence specific antibody response against Parainfluenza virus Type 3.

Chromium and resistance against disease

Studies have demonstrated that Cr supplementation for cattle under stress conditions such as weaning, transport and feed restriction has had a positive impact on the performance and health of the animals (Spears 2000). Some studies indicate that adding Cr into the rations of stressed calves after transport decreases morbidity (Lindell et al. 1994, Moonsie-Shageer and Mowat 1993, Mowat et al. 1993) while other studies indicate no impact (Chang et al. 1995, Chang and Mowat 1992, Mathisonl and Engstrom 1995). A study carried out by Chang et al. (1996) indicated that the addition of Cr-amino acid chelate into the rations of dairy cows did not affect the health status of mammary glands. Kegley et al. (1996) reported that intratracheal Pasteurella haemolytica inoculation (in the form of Cr-nicotinic acid and $CrCl_3$) into the rations of calves in doses based on 0.4 mg/kg of Cr resulted in lower fever 5 days after the intranasal IBRV inoculation compared to the control group. In another study conducted by the same researcher, Cr supplements (in the form of Cr-nicotinic acid complex) on a 0.4 mg/kg basis were given to calves for 56 days prior to transport and it was reported that the body temperature or feed consumption of those animals which had been treated with Cr in response to an experimentally generated IBRV infection did not differ from animals which had not received Cr supplements (Kegley et al. 1997). Furthermore, no impact incurred in the rectal heat response of calves

with experimentally generated BHV-1 infection which had received Cr supplements in their rations (yeast form enriched with Cr) (Arthington et al. 1997). The serum concentrations of cortisol which is known to suppress the immune system increases during stress (Spears 2000). Various studies indicate that adding Cr into the rations of cattle decreases the concentration of serum cortisol (Chang and Mowat 1992, Kegley et al. 1996, Moonsie-Shageer and Mowat 1993). However there are also studies which report that cortisol levels are unaffected (Kegley et al. 1997, Kegley et al. 1996, Lindell et al. 1994). In a study by Arthington et al. (1997) a series of blood samples was collected at 4 hour intervals from calves in which experimental BHV-1 had been induced and it was reported that the Cr supplements (yeast form enriched with Cr) did not affect the serum cortisol level.

CONCLUSIONS

As a conclusion, dietary Cr has some remarkable direct or indirect effects on immune system as well as carbohydrate metabolism. However, all mechanism and pathways related to these effects have not yet been fully enlighted. Further researchs are needed for detailed evaluation on relationship between mentioned immune system effects and animal health/performance.

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