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INTERACTION BETWEEN NUTRIENTS, PRO-INFLAMMATORY CYTOKINES AND INFLAMMATION: NUTRITIONAL MODULATION

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ABSTRACT

The pro-inflammatory cytokines interleukin 1 & 6 (IL-1 & 6) and tumour necrosis factor (TNF) and free radicals are released in infection, trauma, cancer and during inflammatory diseases. Free radicals and cytokines enhance each others production, thereby increasing pathological effects. Nutrients exert widespread modulatory effects on cytokine biology. Suboptimal nutrition during pregnancy may lead to long term changes in cytokine biology in the offspring. Dietary antioxidants (vitamin E and catechins) and precursors of antioxidant defences (sulphur amino acids), suppress up-regulation of cytokine production by free radicals. Fats rich in n-3 polyunsaturated fatty acids (PUFAS) suppress, and fats rich in n-6 PUFAs enhance, the production and effects of IL-1 and TNF.

Key Words: *Nutrients, antioxidants, inflammation, cytokines*

ÖZET

Besin Öğeleri Sitokin Etkileşimleri: Beslenme Modülasyonu

Organizmanını yaşamsal faaliyetlerinin devamlılığı, fizyolojik/metabolik gereksinmelerinin sağlanması ile mümkündür. Yaşamın değişik zaman dilimlerinde canlı büyüme, plasentanın oluşumu, anne sütü bileşenlerinin sentezi ve organizmaya giren patojenlerin yok edilmesi için gereksinim duyulan metabolik süreçlerin oluşumuna yönelmektedir. İnfeke olmuş organizmanın yöneldiği temel süreç infeksiyon kaynağı olan patojenin etkisizleştirilmesidir. Sözü edilen diğer fizyolojik süreçler ancak organizmaya giren patojenin etkisizleştirilmesidir. Sözü edilen diğer fizyolojik süreçler ancak organizmaya giren patojenin etkisiz hale getirilmesi ve oluşturduğu zararın yok edilmesini takiben yeniden önem kazanmaya başlar. Bunun nedeni patojenin organizmada üreme kabiliyetinin çok hızlı olmasıdır. Besin öğelerinin oganizmaya yeterli ve dengeli miktarlarda sunulması immün sistem fonksiyonlarının düzenli çalışmasına yardımcı olacaktır. İmmün sistem fonksiyonlarının değişmesi ve metabolik olarak aktivasyonu sonucu, sistemde düzenleyici olarak görev yapan sitokinlerin miktarı artmakta ve organizmayı artan besin öğelerinin ihtiyacını karşılamaya yöneltmektedir. Patojenik uyarım sonucu artan sitokin ve serbest radikal düzeyleri patojenin etkisizleştirilmesine yönelik olmasına rağmen varolan dengenin bozulması, organizma açısında son derece zararlı olabilmektedir. Organizmada oluşan zararın düzeyi, varolan antioksidant savunma sisteminin durumu ile çok yakından ilişkilidir. Antioksidant savunma sisteminin optimal düzeylerde bulunması patojenik uyarım sonucu oluşabilecek zararlı etkiyi azaltabilecektir. Gerek kalite gereksede kantite açısından sitokin biyolojisi, besin öğeleri ile yakından ilişkilidir. Vitamin E ve katekin gibi diyette yer alan antioksidantlar ve antioksidant savunmada öncü moleküller (kükürtlü amino asitler), serbest radikal uyarısı sonucu artan sitokin üretimini baskılamaktadır. n-3 poliunsatüre yağ asitlerinden zengin yağlar IL 1 ve TNF üretimini ve etkisini baskılarken, n-6 poliunsatüre yağ asitlerinden zengin yağlar arttırmaktadır. Yağ asitlerinin var olan bu etkisi inflamatuar hücre membranlarının özelliklerini değiştirmesinden kaynaklandığı ve dolayısıyla bu hücrelerde sitokinlerin etkilerini değiştirdiği düşünülmektedir. Bilimsel verilerin ışığında besin öğeleri ve sitokin etkileşimlerinin bilinmesi klinikte özel durumlarda uygulanan diyetin hastalığın klinik seyrinde son derece önemli olduğunu kanıtlar cinsdendir.

Anahtar Sözcükler: *Besin öğesi, antioksidantlar, inflamasyon, sitokinler*

INTRODUCITON

Since time immemorial humankind has experienced injury and invasion of the body by bacteria, viruses, fungi and parasites with the ensuing symptoms of fever, anorexia, pain and lethargy. Indeed, the fate of empires has hung upon such events. The symptoms are the consequence of activation of the immune sytem by antigenic challenge provided by the invasion. Activation of the system results in the release of pro-inflammatory cytokines, predominantly from phagocytic cells, which are widely distributed thoughout the body (1-3). Subsequently nitric oxide, hydrogen peroxide, and superoxide radicals are elicited.

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The production of cytokines and oxidant molecules are part of highly effective mechanisms for creating a hostile environment, within the body, for pathogens (4).

Three pro-inflammatory cytokines, interleukin I (IL-1), interleukin 6 (IL-6) and tumour necrosis factor (TNF) orchestrate widespread metabolic changes, and mediate and modulate the enhanced level of activity of the immune system.

Cytokines and the metabolic consequences of infection

Infection is characterised by wasting of peripheral tissues. The wasting, which results from loss of tissue lipid, protein and micronutrients, is part of a coordinated, cytokine-mediated response, designed to enhance and support cytokine-mediated the activities of the immune system and protect the host.

Amino acids release from increase proteolysis in muscle, skin and bone, provide substrate for the synthesis of cells in the system. Glutamine, released from muscle, glucose derive from increased hepatic gluconeogenesis of amino acids and oleic acid from lipolysis, are major sources of nutrition for the system (5,6). Zinc, an important cofactor in DNA synthesis, is released from peripheral tissues, incorporated into metallothionein in liver and kidney, and subsequently utilised by the immune system (7). Thus IL1 and TNF orchestrate metabolism to provide nutrition for the immune system from endogenous sources. Such a change of nutrient supply is important, since anorexia, and lethargy are among the predominant features of infected subjects (8).

The widespread metabolic changes are designed to deliver nutrients to the immune system, to assist repair of tissues, control cytokine production, protect healthy tissue from the effects of free radicals and other oxidant molecules and remove nutrients from the bloodstream which might assist multiplication of the pathogen.

Damage to the host from the inflammatory response to pathogens.

Paradoxically, although cytokines play a pivotal role in the response to infection they can exert tissue damaging and lethal effects upon the host. Excessive, or inappropriate production, has been associated with morbidity and mortality in a wide range of conditions in which the immune system has become activated. These include sepsis, adult respiratory distress syndrome, malaria, meningitis, cystic fibrosis, systemic lupus erythromatsus, inflammatory bowel disease, rheumatoid arthritis and asthma (9-12). Indeed untimely production of proinflammatory cytokines have been implicated in the pathogenesis of atherosclerosis, multiple sclerosis and Alzheimers disease (13-15). The potential for damage to the host is increased by a number of biological events which enhance cytokine production. Oxidant molecules upregulate cytokine production by activation of nuclear transcription factors such as NFKB and NFIL6. The factors enhance transcription of genetic message for IL1 and TNF and IL6 respectively (16-18). IL1, IL8 and TNF are potent inducers of nitric oxide and other oxidant molecules from phagocytic cells. Further enhancement of cytokine production may occur since IL1 and TNF may induce production of IL6 and further production of themselves and each other.

Damage may also be exerted on the host by release of free radicals and other oxidant molecules that are also released from phagocytic cells in response to the inflammatory stimulus and IL1 and TNF.

Innate systems for regulating cytokine production.

A sophisticated array of control systems exist for modulating cytokine production and limiting their impact on the patient (19). Natural inhibitors to IL1 and TNF are produced in response to IL1 and TNF. The inhibitor for IL1 is produced by lymphocytes and that for TNF is the extracellular domain of TNF receptors that are shed into the circulation following binding of TNF to a small proportion of receptors on the surface of target tissues. The inhibitors are present in large concentrations and down regulate tissue responsiveness to the respective cytokines. IL1, IL6 and TNF increase the synthesis of a number of molecules which have antioxidant properties, thereby counteracting the ability of oxidants, generated as the consequence of cytokine action, enhance cytokine production (20). Glucocorticoids, secreted as a consequence of the action of IL1 and TNF on the hypophyseal adrenal axis, play a key role in suppressing cytokine production by enhancing lipocortin production and stimulating acute phase protein production (21,22).

Nutritional modulation of cytokine biology.

Cytokines may have beneficial or detrimental effects, depending upon the context and amounts in which they are produced. During infection they are mostly beneficial, in cancer, chronic inflammatory disease, or in individuals infected with human immu-

nodeficiency virus, they may be detrimental (23). Thus dietary manipulation of cytokine biology can be aimed at enhancing, suppressing and controlling cytokine production and actions, with potential benefit (4).

Modulation of cytokine biology throughout the life cycle.

It is well accepted that malnutrition has major deleterious effects upon immune function, particularly in the young and elderly. Infants who are born small for gectational age exhibit reduced proportions of circulating T cells and impaired delayed type hypersensitivity for a number of years after birth. In animal models, general food restriction or zinc or vitamin B6 deficiency can impair cell and humoral aspects of immunity for several generations (see 24 for review)

Recent evidence in animal models suggests that programming of the immune system by nutrients is also apparent for pro-inflammatory cytokine biology. Offspring of rats that were fed 12%, 9% or 6%, as opposed to 18% protein during pregnancy, showed reduced acute phase responses to LPS injections in adulthood. Furthermore the animals exhibited deranged activity of key enzymes in the metabolism of, the antioxidant, glutathione (GSH) (25). Peritoneal macrophoges taken from adult animals, whose mothers had consumed the 9% casein diet, also showed an impaired ability to produce IL1, IL6 and TNF in response to endotoxin (26).

Modulation of cytokine biology by fats.

Inflammatory symptoms are improved by fish oil or n-3 PUFAs in diseases such as rheumatoid arthritis, psoriasis, asthma, multiple sclerosis,Crohn's disease and ulcerative colitis (27). The oil also confers protection in animals against the lethal effects of endotoxin, burn injury and bacterial infection (28-31). γ-linolenic acid has also been shown to have a suppressive effect on plasma concentrations of a wide range of cytokines (IL1,IL2,IL4,IL6,TNF&γIFN) in patients with colorectal cancer (32).

Fats may exert modulatory effects by influencing the ability of cells to produce cytokines and on the ability of target tissues to respond to cytokines. The production and actions of proinflammatory cytokines are profoundly influenced by dietary fat intake. This topic has been reviewed in detail elsewhere (27,33). In essence, fats rich in n-3 polyunsaturated (PUFAs), or n-9 monounsaturated fatty acids, or poor in n-6 PUFAs reduce responsiveness to cytokines (27,34). Fats rich in n-6 PUFAs exert the opposite effect. Fish oil, which is rich in n-3 PUFAS, reduces the ability of leukocytes from healthy subjects and rheumatoid patients to produce IL1, IL6 and TNF (35). The ability of peritoneal macrophages from rats to produce IL1 and IL6 in response to TNF is greatly influenced by the dietary intake of linoleic acid and total unsaturated fatty acid intake respectively. IL1 production increases to plateau concentrations within a range representing 1-4% of dietary energy, whereas IL6 production is positively related to unsaturated fatty acid intake over a wider range of intakes (36)

An increasing body of evidence suggests that inappropriate cytokine production may be involved in the development of atherosclerosis (13). Studies on rabbits show that messenger RNA expression for IL1 and TNF in the aorta wall, in response to an endotoxin injection, is enhanced in by feeding cholesterol in diets containing saturated fat (37).

Many potential mechanisms exist whereby fats may exert their influence upon cytokine biology. The majority are a consequence of the well documented ability of fats to change the fatty acid composition of phospholipids (PL) within the cell membrane. As a cosequence, the fluidity of the cell membrane may change. Alterations in fluidity could, in turn, change the avidity with which cytokines bind to receptors and the kinetics of conformational change when G proteins become activated. Alterations in PL fatty acid composition will change the nature of substrate for the actions of phospholipase A2 and phospholipase C. Subsequently, modulation of the molecular species of diacylglycerols and eicosanoids generated when the respective phospholipases are activated will occur. Alterations in the proportions of PL classes in the membrane and concentrations of unsaturated fatty acids within the cell may modulate the actities of enzymes of the protein kinase C (PKC) family(36). The extent to which each of these potential mechanisms plays a part in the modulatory influences of fats on cytokine biology is at present unclear. Measurements of changes in macrophage and hepatocyte membrane fluidity, in response to feeding rats a variety of fats, suggest that alterations in sensitivity of either cell to inflammatory stimuli is not directly due to changes in bulk membrane fluidity (36).

Influence of protein and amino acid intake on cytokine biology.

Cytokine, acute phase protein and glutathione production is influenced, by the adequacy of both protein and sulphur amino acid intake. The ability to inc-

rease (α-2-macroglobulin in response to endogenous pyrogen in rabbits, and in response to TNF and turpentine abscess in rats, is impaired by low protein diets (38-40). In rats given a turpentine abscess, the concentration of α-2-macroglobulin increases over a wide range of protein intakes of various degrees of adequacy. The ability of rats fed low protein diets to increase serum α-l-acid glycoprotein and hepatic GSH concentrations, in response to TNF is enhanced by dietary supplementation with glycine and cysteine respectively (391.

While cytokines bring about major changes in protein and amino acid metabolism whereby amino acids are released from peripheral tissues for nutrition of cells of the immune system and the synthesis of acute phase proteins and glutathione by liver, the supply from the periphery may not always match demands. There may be an enhanced requirement for sulphur and related amino acids following infection and trauma (4). Severe trauma and infection cause large decreases in plasma glycine, serine, and taurine. These changes may be due to enhanced utilisation of a closely related group of amino acids, namely glycine, serine and the sulphur amino acids methionine and cysteine. Many substances produced in enhanced amount in response to cytokines, are particularly rich in these amino acids. These substances include glutathione, which is comprised of glycine, glutamic acid and cysteine, metallothionein, which contains glycine, serine, cysteine and methionine to a composite percentage of 56%, and arange of acute phase proteins which contain up to 25% of these amino acids in their structure. Following surgery of uninfected patients, a decrease in the ratio of urinary sulphate to nitrogen occurs, indicating preferential retention of sulphur amino acids into tissue components (20). In studies in rats given TNF, the partitioning of cysteine into hepatic protein and glutathione may depend upon the dietary sulphur amino acid intake. At low levels of intake, incorporation of cysteine into protein is favoured over incorporation into GSH, at high levels of intake, the situationis reversed (41). An insufficient intake ofsulphuramino acids may exert a proinflammatory influence. In protein depleted rats given TNF, enhancementof lung GSH concentrations is only possible, if cysteine and methionine are added to the diet. Furthermore the infiltration of inflammatory cells into the lung, which occurs in the malnourished rats in response to the cytokine, is prevented by the addition of sulphur amino acids to the diet (41). The ability to maintain and enhance tissue GSH may be of particular importance in controlling cytokine production in response to inflammatory stimuli, since the stimulatory influence of oxidant molecules and TNF, on NF*K*B activity, is decreased by glutathione and other sulphur containing compounds (42,43).

TNF may play a role in the extensive weight loss observed in patients with cancer and AIDS. It is thus interesting to note, that in asymptomatic HIV- infected individuals, substantial reductions in GSH concentrations in plasma and lung epithelial fluid occur (44). Furthermore the decrease in plasma and tissue GSH, observed in AIDS patients, may indicate a requirement for sulphur amino acids which is not being satisfied by diet or endogenous sources. In such patients urinary malonaldehyde excretion is enhanced indicating increased free radical damage (45,46). Alveolar macrophages are present in an activated state in such patients and exhibit exaggerated production of oxidants (47).

Protein and amino acid supplementation do not invariably produce benefit in situations which cytokines and inflammatory agents are acting upon wellfed or malnourished subjects. Beneficial effects on immune function, morbidity and mortality were observed in burned children when additional protein in the form of whey protein was fed. The unsupplemented and supplemented diets contained 16.5 and 23% of energy as protein and provided 87 and 73% of the energy requirements respectively. Improvements in neutrophil opsonic index, plasma acute phase proteins, survival and number of days with bacteraemia were noted in children fed the whey protein supplements (48). In malnourished elderly patients showing an impaired ability to produce cytokines, dietary protein supplementation restored and enhanced production (49). Furthermore asymptomatic infected malnourished children often become febrile during nutritional rehabilitation. The appearance of fever may indicate an enhancement of cytokine production, previously held in check by the malnourished state (50). Such an enhancement carries benefits as well as dangers for the host if it is not part of a carefully coordinated metabolic response which disadvantages the pathogen but protects the host. Indeed enhanced mortalities have been noted in malnourished infected populations once nutritional supplementation is commenced (51). Furthermore, in rats a non-lethal dose of TNF becomes lethal if the ability of the animal increase and maintain GSH synthesis is prevented by administration of diethylmaleate (52).

In studies in animals, mortality from malaria and bacterial infection is modified by alterations in spe-

cific amino acid and protein intake. Mortality in rats from *Plasmodium berghei* malaria was reduced by low protein diets but enhanced by dietary supplementation with a mixture of threonine, valine, leucine and isoleucine (53). Likewise mortality in guinea pigs, from *Escherichia coli* and *Staphylococcus aureus* infection, was increased from 15 to 54%, over a range of protein intakes from an inadequate 5% of total dietary energy as protein, to 20% of energy (54). Similar deleterious effects on mortality from bacteremia were observed in guinea pigs when animals received increased quantities of an adequate diet. While 62% mortality occurred when an adequate quantity was fed (125 kcal/kg/d) increasing intake to 150 or 175 kcal/kg/d resulted in 100% mortality (55). Enhanced cytokine production rather than increased virulence may underly these paradoxical effects of dietary supplementation.

These observations suggest that nutritional strategies concerning the supply of amino acid substrate to individuals responding to cytokines, should go beyond consideration of all protein as simply being a provider of protein N, the amino acid proportions in that provision should also be taken into account.

The anorexia induced by cytokines may be an attempt to selectively avoid the intake of nutrients which might disadvantage the response of the host to pathogens. Indeed, rats given ILlß and a choice of casein, lard or a mixture of sucrose and cornstarch, reduced intakes of the protein and fat by 57 & 68% respectively, whereas carbohydrate appetite was unaffected (561.

Modulation of cytokine biology by oxidants and antioxidant status.

Alterations in antioxidant status may change the intensity of cytokine production and responses to inflammatory agents by modulating the interaction between free radicals, hydrogen peroxide, and NF*K*B and NFIL6. Activation of NF*K*B can be reduced by endogenous antioxidants such as glutathione (GSH) and synthetic antioxidants such as n-acetyl cysteine. It is unknown whether nutrient antioxidants, such as vitamin E, C or ß-carotene exert a similar effect. However enhanced plasma concentrations of acute phase proteins and IL6 were observed in vitamin E deficient rats given endotoxin (57,58). Cigarette smoking raises plasma acute phase protein concentrations suggesting pro-inflammatory cytokine production. Indeed blood samples from smokers contained higher IL6 concentrations than samples from nonsmokers and produced more TNF when stimulated with endotoxin. Vitamin E may modulate cytokine mediated effects of smoking as acute phase protein concentrations correlated negatively wit vitamin E intake (59). Cellular GSH content is enhanced following exposure to cytokines, however the response is dependent upon dietary sufficiency of sulphur amino acid intake (41). It is unknown whether an inability to enhance GSH in response to cytokines, due a dietary insufficiency of sulphur amino acids, has a pro-inflammatory effect. However as indicated earlier increased numbers of polymorphs were noted in rats which are unable to maintain lung GSH content in response to TNF (41).

Micronutrients are involved in responses to cytokines in a number of roles. These include incorporation into substances that are synthesised in increased amounts during inflammation, components of antioxidant defences and modulators of immune cell function. Trace elements are present in metallothionein (Zn), caeruloplasmin (Cu), transferrin (Fe), superoxide dismutases (Cu,Se,Zn) and glutathione peroxidase (Se).

Copper deficiency, in rats, impairs the ability of rats to increase plasma caeruloplasmin (CP) and copper-zinc superoxide dismutase in lung, in response to the dual stress of endotoxin injection and exposure to high concentrations of oxygen. Likewise the ability of IL1 to increase plasma concentrations of CP with fully functional oxidase activity is also suppressed by copper deficiency (60). Deficiencies in zinc impair the ability of IL1 to induce metallothionein synthesis in rats (61).

Iron status may influence the production of cytokines, by its ability to catalyse free radical formation. The production of TNF by mice and IL1 production by rats, in response to endotoxin, is suppressed by desferrioxamine (an iron chelator) and by iron deficiency respectively (16,62). Furthermore inflammatory symptoms, in rheumatoid arthritis, are exacerbated by intravenous iron dextran (63).

CONCLUSIONS

The essence of survival, of an individual or species, lies in the ability to prioritise physiological processes, particularly those processeses which exert a large metabolic demand. Thus at various times throughout the life cycle mammals will focus metabolic processes upon achieving growth, the construction of placenta and foetus, the synthesis of milk components and the combating of invasion by pathogens. For the infected individual, the marshalling of reso-

urces to combat the invading pathogen must assume a priority over all other physiological events. These other physiological processes can continue once the invasion has been repulsed and the damage done by the invader, repaired. The high priority given to combating pathogens is necessary because of the speed with which pathogens multiply, once established within the host. The immune system with which the individual combats the invader is likewise capable of rapid cellular growth. The provision of nutrients to allow the immune system to function correctly cannot be left to happenstance. Thus cytokines act as modulatory agents by which the activity of the system is changed and metabolic activity of the host directed towards provision of nutrients for the system. The enhanced level of cytokines and free radical production which follows pathogenic invasion, although designed to combat the invader, carries the potential to damage the host. Damage however is limited by concurrent enhancement of the antioxidant defences of the host and activation of systems for retaining cytokine production within healthful confines.

As has been discussed earlier, previous and concurrent nutrient intake modulate cytokine biology in quantitative and qualitative terms s a consequence of the modulation, the host will experience depletion of resources and damage which ranges from mild and temporary in nature, to severe, chronic and lethal.

The future challenge for the clinician and scientist working within the nutrition domain will be in detennining how the nature of the nutrient cytokine interactions, identified in the experimental context, can be employed to achieve a healthful diet and clinical benefit (64-66).

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