Micronutrients, immunology and inflammation

Effect of vitamin A deficiency on the immune response in obesity

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Obesity has been associated with low-grade systemic inflammation and with micronutrient deficiencies. Obese individuals have been found to have lower vitamin A levels and lower vitamin A intake compared with normal-weight individuals. Vitamin A plays a major role in the immune function, including innate immunity, cell-mediated immunity and humoral antibody immunity. It has also been recognised recently that vitamin A has important regulatory functions. Vitamin A status has an important effect on the chronic inflammatory response. Vitamin A deficiency increases a T-helper type 1 (Th1) response, elevates levels of pro-inflammatory cytokines, increases the expression of leptin, resistin and uncoupling proteins (UCP) and promotes adipogenesis. The effect of vitamin A deficiency on obesity might be increasing the risk of fat deposition and also the risk of chronic inflammation associated with obesity. Supplementation with vitamin A in vitro and in animal models has been found to reduce concentrations of adipocytokines, such as leptin and resistin. In conclusion, vitamin A deficiency increases a Th1 response in the presence of obesity and thus, increases the inflammatory process involved in chronic inflammation and fat deposition. The metabolism of leptin and other adipocytokines may play a critical role in the effect of vitamin A deficiency in the inflammatory response observed in obesity.

Vitamin A: Immunity: Obesity

Micronutrients are necessary to have an adequate immune response and inflammatory processes, including the production of cytokines. Vitamin A and retinoids, vitamin A derivatives, are critical for the immune function, including innate immunity, cell-mediated immunity and humoral antibody immunity. It has been recognised for some time that retinoids have important regulatory functions. Of the existing retinoids, retinoic acid (RA) and retinaldehyde seem to have a major role in the immune response, but all-trans-RA is recognised to be the most active form of vitamin A.

The effect of micronutrient deficiencies, commonly present in protein-energy malnutrition, on the immune response has been widely documented and has been associated with higher risk of infectious diseases. Vitamin A deficiency has been shown to increase the risk to infections. Vitamin A supplementation has proven to be effective to reduce childhood mortality, and in some cases morbidity. In addition, vitamin A deficiency also impairs the inflammatory response and may be contributing to increase the risk of low systemic inflammation.

Higher prevalence of micronutrient deficiencies have been observed in obese individuals compared with normal-weight individuals, and may be increasing the risk of fat deposition and chronic diseases. Low concentrations of retinol have been found in overweight and obese individuals independent of age. In Brazil, for example, a high prevalence of vitamin A deficiency was found among overweight children; in adults with morbid obesity, vitamin A deficiency was significantly associated with insulin resistance. A negative correlation was also found between serum retinol concentration and...
Both RAR and RXR regulate the expression of hundreds of genes such as skin keratins, retinol-binding protein, leptin and IFN-γ. The regulation of gene expression by retinoids has been recently reviewed by Amann et al. (5). Transcription regulation by the retinoid receptors can be through two different pathways. The first direct pathway involves binding of RAR:RXR or RXR:RXR to specific response elements located in the promoter or enhancer region of a specific target gene. Also, the transcription of genes can be regulated indirectly by interfering with other transcription factors (5,33).

Retinoic acid and immunity

The role of RA on inflammation and immunity has been reviewed recently (41). Briefly, RA production is induced in tissue cells through retinol metabolism when an inflammation process begins. RA induces and regulates the expression of immune cells such as neutrophils, macrophages, dendritic cells and lymphoid cells, which include T-cells, T-regulatory cells and B-cells. B-cells are part of the immune regulatory response and are responsible for the production of antibodies. RA is necessary for the development and maturity of B-cells, B-cell proliferation, B-cell differentiation and antibody-secreting plasma cells (41–43). This effect that RA has on cell differentiation involves the RAR and RXR pathways. RA induces cell differentiation by binding to RAR, and thus induces gene transcription of transcription factors, signalling proteins, and interacts with RXR to activate the transcription of primary target genes (44,45). The RXR pathway seems to be the one involved in maintaining a Th2-type response (45,46).

RA has been shown to inhibit NF-κB activity in human cell lines and also repress the transcription of NF-κB genes such as IL-6, monoctye chemotactant protein-1 and cyclooxygenase-2, all involved in inflammation processes (47–51). Also, it is now recognised that RA is responsible for the down-regulation of the gene expression of IFN-γ and TNFα, contributing to the Th2 anti-inflammatory response (20,51,21,29,52).

RA is also produced at high concentrations in the intestine and at the mucosa, and has been shown to promote epithelial integrity to produce mucosal secretion, and induces immunity to protect the intestine after immunisation in animal models (53–54). In addition, RA is known to modulate transforming growth factor β in the epithelial intestine cells and this contributes to an anti-inflammatory response in the gut (28,55).

Vitamin A and the adipose tissue

Vitamin A actively participates in the adipocyte metabolism. It is estimated that 15–20% of total retinoids are located in the adipose tissue (56). The role of vitamin A in adipose tissue development and metabolism has been previously reviewed (57–59).

During obesity, the adipose tissue undergoes an important expansion and cell differentiation as well as adipocyte maturation. PPARγ is the major regulator of adipogenesis and its expression is mediated through several pathways, one of which involves retinoids. Vitamin A, retinaldehyde...
and RA are all present in the adipocyte and are actively involved in cell differentiation, as well as transcription of PPARγ(59,60). Also, vitamin A is involved in the production of anti-inflammatory cytokines in the adipocyte promoting a Th2-type response(27,29).

White adipose tissue (WAT) and brown adipose tissue (BAT) regulate retinoid metabolism, and differentiation between WAT and BAT is associated with the amount of intracellular retinoids(57,61). Both RAR and RXR are expressed differently in WAT and BAT, and thus, there are different gene expressions depending on the type of adipose tissue(62). In BAT, for example, RA induces transcription of the uncoupling protein (UCP)-1 gene mediated through RAR and RXR and the response element located at the enhancer; UCP-1 is the protein responsible for the thermogenic function attributed to BAT(63-67). In vitro, RA increased 1-6 times UCP-1 mRNA expression in the BAT and slightly decreased its expression in WAT adipocytes(68).

In addition to the UCP-1 gene transcription, RA has been found in vitro to decrease preadipocyte survival time and to inhibit or promote adipose cell differentiation depending on the dose, probably regulated by RA intracellular lipid-binding protein-II(59,69-72).

In addition to RA, retinaldehyde can also play an important role in gene expression through nuclear receptors, similar to RA(89). Both in vivo and in vitro adipogenesis have been shown to regulate retinaldehyde metabolism. In addition, Zouzenkova et al.(8) demonstrated in rodents that retinaldehyde inhibits adipogenesis and suppresses PPAR and RXR response.

**Retinoids and leptin**

Leptin is an important adipocytokine that actively participates in the regulation of energy homeostasis and its importance in body weight control has been demonstrated in human subjects and animals(73-75). High leptin concentrations are associated with an increase in adipose tissue observed in obesity(73-75). Also, leptin is induced as part of the acute phase response in response to inflammation, but it is also part of the chronic inflammation response associated with obesity(76,77). It is now recognised that leptin regulates both the innate and adaptive immune response; low leptin concentration is associated with a higher risk of infections and high leptin concentration is responsible for increasing pro-inflammatory cytokine levels(77,78). Thus, leptin is a key modulator of inflammation and obesity.

Leptin is involved in the activation and infiltration of macrophages into WAT, the activation and development of natural killer cells, induces chemotaxis of neutrophils, suppresses the proliferation of T-regulatory cells and regulates the Th1 and Th2 response(72,79-83). Leptin has been shown to induce a Th1 response with an increased production of IFN-γ and TNFα(82,84). In ob/ob mice, decreased secretion of pro-inflammatory cytokines, such as TNFα, IL-6, IFN-γ and IL-1β, was observed, which is reversed when leptin is administered(85). The interactions between leptin and other pro-inflammatory cytokines is complex, and leptin can help modulate the inflammation response(86). Therefore, leptin plays an important role in the pathways leading to chronic inflammation.

Of the different active metabolites of vitamin A, RA has been shown to participate in leptin’s metabolism in both mice and human tissue(87,90). Different isomers of RA seem to have different effects on leptin expression and adipogenesis. In vitro, leptin expression is inhibited by both 9-cis- and all-trans-RA(89,90). However, Menendez et al.(90) found that all-trans-RA has a more potent inhibitor of leptin secretion compared with 9-cis-RA. In addition, all-trans-RA increases adipogenesis in a dose-dependent way through the activation of RXR and PPARγ, while 9-cis-RA has no effect(89).

**Vitamin A deficiency and the immune response in obesity**

**Vitamin A deficiency**

Vitamin A deficiency is a major public health concern worldwide. Clinical signs of vitamin A deficiency include xerophthalmia, and also an increase of infectious diseases(3,9,92). According to the World Health Organisation, the global prevalence of vitamin A deficiency, defined as serum retinol concentrations <0.7 μmol/l (<20 μg/dl), is 33.3 (95% CI 31.1, 35.4)% for preschool children and 15.3 (95% CI 7.4, 23.2)% for pregnant women(93). These numbers represent 190 million children and 19-1 million pregnant women worldwide.

The clinical manifestations of vitamin A deficiency are due to its effect on the immune system, mainly lymphopenia, impairment of the mucosal barriers and a decrease of the T-cell response(3,19,94). Since the immune response is compromised, vitamin A deficiency increases the risk of parasites, bacterial and viral infections. In vitamin A deficiency, normal regeneration of the mucosal epithelial barriers is impaired and the resistance to infections is diminished. In animal models, vitamin A deficiency impaired both the humoral and cellular immunity of the intestinal mucosa probably through the modulation of the dendritic cells(95).

**Vitamin A deficiency and T-helper types 1 and 2 response**

Vitamin A deficiency impairs both Th1 and Th2 response(9,96). However, Th2 immune response is affected the most. Vitamin A deficiency down-regulates the Th2 response and up-regulates Th1 response(21,23,52,96). In vitamin A deficiency, the antibody-mediated immunity is impaired and there is an increase of pro-inflammatory cytokines that promotes a Th1 type inflammatory response, while the production of anti-inflammatory cytokines, such as IL-4 and IL-10, is reduced(21,52,97,98). It has been observed that vitamin A-deficient children had a markedly Th1 response with low concentrations of IL-10 compared with non-deficient children(25). In Indonesian children, for example, vitamin A deficiency was associated with a Th1 response(99). A population of children in Venezuela with a high prevalence of vitamin A subclinical deficiency had lower IL-10 concentrations, an anti-inflammatory cytokine, compared with a group with adequate vitamin A status(100).
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Table 1. Vitamin A functions, major roles in the immune system and effects of vitamin A deficiency in undernutrition and obesity (adapted from Maggini and Stephen(94) and Maggini and co-workers(54))

<table>
<thead>
<tr>
<th>Vitamin A functions</th>
<th>Vitamin A functions in the immune system</th>
<th>Vitamin A deficiency and obesity</th>
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<tbody>
<tr>
<td>Vision</td>
<td>Innate and cell immunity</td>
<td>Down-regulation of leptin expression</td>
</tr>
<tr>
<td>Development</td>
<td>Antibody response</td>
<td>Down-regulation of resistin expression</td>
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<tr>
<td>Epithelial integrity</td>
<td>Epithelial tissue differentiation</td>
<td>Increased Th1 type response</td>
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<tr>
<td>Tissue cell growth</td>
<td>Gene expression</td>
<td>Increased pro-inflammatory cytokines</td>
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<td>and differentiation</td>
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<tr>
<td>Reproductive function</td>
<td>Critical for Th1 and Th2 lymphocytes differentiation</td>
<td>Increased UCP mRNA and reduced thermogenesis in BAT</td>
</tr>
<tr>
<td>Gene expression</td>
<td>T- and B-cell differentiation in the intestine</td>
<td>Promote adipogenesis</td>
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<td>Immune function</td>
<td>Supports a Th2 anti-inflammatory response</td>
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<td></td>
<td>Supplementation decreases morbidity and mortality due to infectious diseases</td>
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<td></td>
<td>Supplementation improves vaccine response</td>
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Thus, even in subclinical vitamin A deficiency, Th2 response is compromised. The elevated Th1:Th2 ratios observed in vitamin A deficiency lead to inflammation and low capacity of the body to fight infections. In animal models, vitamin A deficiency shifts from a Th2 response to a Th1 response, decreasing antibody production and Ig maturation(21). This increase in the inflammatory response is due to a higher production of IFN-γ by T lymphocytes(101,102).

In addition to its effect on the T-cells response, vitamin A deficiency also diminishes the activity of neutrophils, macrophages and natural killer cells(103,105). Animal models have shown that chronic marginal vitamin A status decreases number of natural killer cells and lymphocytes, affects both T-cells distribution and function, and thus increases the risk of infections with aging(103–105).

Vitamin A deficiency and the adipose tissue

The increase of the adipose tissue observed in obesity produces an increased secretion of adipocytokines, such as leptin, that, as mentioned earlier, induces an inflammatory response. Vitamin A deficiency is highly prevalent in obesity and this may produce inadequate Th1:Th2 ratio, increased leptin concentrations, and elevate pro-inflammatory cytokines levels(18,106,107). Vitamin A deficiency reduces not only RA levels but also retinaldehyde, and therefore may be contributing to fat deposition.

In a mouse model, vitamin A deficiency increases the expression of UCP-1 mRNA and UCP-2 mRNA expressions, thus promoting reduced thermogenesis in BAT, increased body weight and increased leptin concentrations(108). In addition, vitamin A deficiency might promote adipogenesis, adipocyte differentiation through PPAR and increased preadipocyte survival time.

Vitamin A deficiency might increase leptin expression and thus, increase the production of cytokines, contributing with the low-grade systemic inflammation observed in obesity. For example, in mice, vitamin A deficiency increased body weight, BAT, adiposity and leptin mRNA expression(108). Low RA concentrations increase leptin and resistin expressions in brown and white adipocytes(108,109).

Resistin is an adipocytokine that inhibits adipocyte differentiation and an insulin resistance factor in both cell and animal models. In vitro, RA inhibits resistin expression in both brown and white adipocytes through RAR and RXR pathways(109). Thus, vitamin A deficiency in obesity increases Th1 type response, increases the expression of leptin, resistin and UCP, and promotes adipogenesis. Vitamin A deficiency in obesity might be increasing the risk of fat deposition and also the risk of chronic inflammation associated with obesity.

The main activities of vitamin A, the role of vitamin A in the immune function and the effect of vitamin A deficiency on the immune function in obesity are summarised in Table 1.

Vitamin A supplementation and the immune response in obesity

Supplementation of vitamin A has proven to be an effective strategy to reduce specific mortality from diarrhoea(12,13). Pooled results of twelve trials showed that preventive vitamin A supplementation reduced diarrhoea mortality by 30% in children aged between 6 and 59 months(13). A meta-analysis that included seven trials found a 28% reduction in specific mortality from diarrhoea when supplementing vitamin A in children aged 6 months to 5 years of age and a decrease in the incidence of diarrhoea mortality(12).

The effect of vitamin A supplementation on leptin and inflammatory cytokines has been studied in both in vitro and in animal studies. In vitro, vitamin A supplementation has been shown to down-regulate the inflammatory response inducing a Th2 response, with a dose-dependent increase of mRNA and protein levels of IL-4, IL-5 and IL-13(98,110). Leptin expression is inhibited by RA supplementation. Supplementing mice with RA reduces leptin mRNA concentrations, in both BAT and WAT independently of adiposity and the fat content of the diet(27,87,111). Similarly, in human adipose tissue, RA inhibits both leptin expression and secretion(88,90). Furthermore, it has been observed that RA supplementation and dietary vitamin A reduce both resistin mRNA and resistin circulating...
concentration in animals\(^{(109)}\). Also, RA supplementation and vitamin A status are involved in the expression of transcription factors involved in adipogenesis and UCP1 in WAT and BAT in animal studies\(^{(65,108,111–112)}\). In rats, a high-fat diet down-regulated PPARY and RAR mRNA expression and up-regulated cyclooxygenase-2\(^{(51)}\). When supplementing with RA, production of cyclooxygenase-2 was inhibited.

No studies have looked at the effect of vitamin A supplementation alone in inflammation markers in obese populations. Our group found that supplementing with low-fat milk with added micronutrients, including vitamin A, of women from rural communities in Mexico with a high prevalence of micronutrient deficiencies, reduced more body weight, BMI and total body fat compared with a control group\(^{(113)}\). Similarly, supplementing obese women in China with micronutrients, that also included vitamin A, resulted in less body weight and body fat than women receiving Ca supplementation alone\(^{(114)}\). In both studies, vitamin A and the other micronutrients may be having an effect on leptin concentrations, and also may be reducing pro-inflammatory cytokine concentrations. Supplementing obese individuals with vitamin A may be important in populations with high vitamin A deficiency, high prevalence of obesity and chronic inflammation.

Conclusions

Retinoids are important to regulate critical pathways of the immune functions. Vitamin A deficiency has important consequences on the immune response. In obesity, vitamin A deficiency seems to increase a Th1 response and elevate adipocytokine levels, and thus, may participate in the inflammatory process involved in chronic inflammation and fat deposition. The metabolism of leptin and other adipocytokines may play a critical role in the effect of vitamin A deficiency in the inflammatory response observed in obesity. To understand how vitamin A deficiency affects the immune system in obese populations provides new insights into treatment of chronic inflammation processes.

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