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ORIGINAL COMMUNICATION

Obesity and immunocompetence

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The increasing worldwide prevalence of obesity is a major health problem since excessive body weight constitutes a risk factor in a number of chronic diseases. It has been reported that obese individuals are more susceptible to infection than lean subjects; however, the underlying factors are not fully understood. Limited and often controversial information exists comparing immunocompetence in obese and nonobese subjects as well as the cellular and molecular mechanisms involved, although much evidence supports a link between adipose tissue metabolism and immunocompetent cell functions. The complexity and heterogeneity of nutritional status and immune system interactions require an integral study of the immunocompetent cells, their subsets and products, as well as specific and non-specific inducer/regulatory systems in situations of human obesity. Additional research is needed to determine the clinical implications of these alterations on immunity and whether various interventions such as weight loss, exercise or nutrient supplementation could help to ameliorate them.
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Introduction

The immune system protects the organism against pathogens in two major ways: innate or natural immunity (non-specific) and acquired immunity (specific) that requires previous exposure to pathogens. Innate immunity includes physical barriers, lysozime, complement system, mediators of inflammation, macrophage-monocyte system, natural killer (NK) cells and others (Marti *et al*, 2001). Acquired immunity involves two different cell types: B-lymphocytes that produce and secrete different specific immunoglobulin subtypes (humoral immunity) and T-lymphocytes that regulate the immune response (T-helper lymphocytes; $CD4^+$) and destroy tumoral and viruses-infected cells (T-cytotoxic cells; $CD8^+$). These two principal branches act coordinately in order to develop an integrated defense. Examples of this interaction are the stimulation of T-helper cells by an antigen to produce cytokines (IL-2), which promotes proliferation and differentiation of macrophages as well as the interplay between T-helper and B-cells leading to immunoglobulin production of B-cells.

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Obesity, a disorder of energy balance in which energy intake is greater than energy expenditure, has been linked to a wide variety of health problems including hypertension, dyslipidemia, cardiovascular diseases, diabetes mellitus and certain types of cancer (Samartín & Chandra, 2001). In addition, obese individuals have shown increased susceptibility to infections, bacteremia and poor wound healing following surgical procedures. Obesity has also been associated with a poor antibody response to hepatitis B plasma vaccine. The mechanisms responsible for the increased risk of infection and poor antibody response among obese subjects are unknown, but may be linked to the negative effect that their metabolic milieu produces on immunity.

Another source of evidence comes from leptin, which is mainly derived from adipocytes and regulates appetite and energy expenditure. The leptin receptor is expressed in several immune cell types and appears to activate a number of cytokine-like signaling pathways. Studies in leptin-deficient *ob/ob* mice have revealed impaired phagocytosis and altered cytokine production, suggesting that leptin regulates macrophage function. Adipsin, which is secreted abundantly in adipose tissue, has complement factor D activity and catalyzes the first activation step in the alternative pathway of complement. Moreover, it is known that adipocytes produce factor D and C3 of the complement cascade. These observations suggest a link between adipsin and the complement alternative pathway with obesity.

The main problem in understanding whether obesity affects immunity is that the obese population is too heterogeneous in various aspects, including dietary patterns, individual microbial and social environments. As many of the observations in obese humans are supported by similar results in obese animals, these models may be helpful to examine the effects of obesity on immunity independently of the confounding heterogeneity in the human being.

Dietary lipids and immune function

The importance of dietary lipids on immune function has come under serious study only in the last few decades (Calder, 1998). Dietary fat may increase the prevalence of cancer by depressing the tumor control mechanisms of the immune system. It appears from animal studies that obesity and consumption of diets high in fat impair immune response and enhance the risk for serious infectious diseases. Dietary lipids are particularly important in maintaining tissue concentrations of polyunsaturated fats, including linoleic acid that cannot be produced in the body and is required by lymphocytes for optimal function (Ochoa *et al*, 2001).

Consumption of diets rich in monounsaturated fatty acids (MUFAs) has been associated with a lower prevalence of atherosclerosis (Yaqoob, 1998); however, less attention has been paid to the effects of MUFAs on the immune system. Cells of the immune system are an inherent part of the inflammatory events involved in atherosclerosis and studies show that a diet rich in MUFAs leads to a decrease in intercellular adhesion molecule-1 (ICAM-1) expression, a protein involved in leukocyte–leukocyte adhesion as well as leukocyte–endothelial cell adhesion. Also, it seems that MUFAs decrease the expression of another related protein, the primary fibrinogen receptor in leukocytes (Mac-1), which may play a role in the pathophysiology of inflammation. In contrast, MUFAs appear not to influence NK cell activity or the proliferative response of T-lymphocytes.

However, several studies have reported lower T-lymphocyte proliferation and decreased cytotoxic T-lymphocyte activity after feeding a high-fat rich diet in n-6 PUFAs (Calder, 1998). NK cell cytotoxic activity has also been found to be lower. An inverse linear correlation has been reported between the level of oleic acid or the oleic acid: linoleic acid ratio and spleen cytotoxic NK cell activity. Moreover, it has been shown that n-6 PUFAs intake reduces IL-2 production and IFN-γ.

Diets rich in n-3 PUFAs have been related to the inhibition of cell-mediated immune responses, but the mechanisms are still unclear (Ochoa *et al*, 2001). It has been postulated that n-3 PUFAs may inhibit the function of human antigen-presenting cells implicated in the recognition of antigens. This is supported by the findings that diets rich in n-3 PUFAs have lower capacity to present antigens to autologous lymphocytes related to a diminished expression of surface adhesion molecules. Interestingly, these data suggest a potential mechanism for the beneficial effect of n-3 PUFAs in the treatment of rheumatoid arthritis, an autoimmune alteration associated with elevated expression of MHC class II and adhesion molecules on antigen-presenting cells. Furthermore, diets rich in n-3 PUFAs have been reported to produce higher serum concentrations of IFN-γ during *Listeria monocytogenes* infection. IFN-γ positively regulates inducible nitric oxide synthase (iNOS), to enable macrophage-mediated killing of intracellular pathogens, and potentiate the expression of class I and II MHC molecules to facilitate the specific immune response.

Obese animal models and immune function

Different animal models are used to analyse how obesity influences the immune status: genetically obese rodents characterised by mutations in the leptin gene (*ob*/*ob* mice) or leptin receptor gene (*db*/*db* mice and *fa*/*fa* rats) and diet-induced obese rodents. These animals presented T-lymphopenia in all subsets and B-cell population is also diminished (Kimura *et al*, 1998). Lymphocyte responsiveness to different mitogens is lower in obese animals compared with lean ones. Obese animals also produce less IL-2 than lean animals which could partly explain the lower capacity of T cells to proliferate in obese animals (Tanaka *et al*, 1998). Elevated serum free fatty acid concentrations may inhibit T-lymphocyte signaling, while decreased lymphocyte proliferation may be due to the impairment of glucose uptake by lymphocytes (Moriguchi *et al*, 1998). In diet-induced obese animals (Table 1), similar results concerning the impairment of the immune function have been found, although the effects are less pronounced than in genetically obese animals.

Tumor necrosis factor-alpha (TNF-α) is a common link between obesity and insulin resistance/hyperinsulinemia. In genetically obese animals, TNF-α production from adipose tissue is reported to be higher (Samad *et al*, 1999), which may influence lymphoid tissue development and induce programmed cell death (apoptosis). A chronic elevation of

Table 1 Immune-related indicators and UCP2 mRNA levels in diet-induced (cafeteria) obese and control rats

	Control	*Obese*	P
Food intake (g)	19.3 ± 0.2	24.9 ± 0.2	< 0.01
Ratio $CD4^+/CD8^+$	1.50 ± 0.05	1.19 ± 0.05	< 0.05
LPS (cpm)	7882 ± 563	4140 ± 251	< 0.001
Con A (cpm)	10078 ± 563	9800 ± 853	NS
PHA (cpm)	15488 ± 752	5646 ± 430	< 0.001
Phagocytosis (%)	78.02 ± 2.11	83.37 ± 1.54	NS
Oxidative burst (%)	75.52 ± 4.47	61.93 ± 2.89	< 0.05
UCP2 mRNA	0.61 ± 0.09	1.25 ± 0.23	< 0.05

Spleen lymphocytes T $CD4^+$ and $CD8^+$, phagocytosis and oxidative burst were analysed by flow cytometry. Lymphoproliferation was measured by [^{3}H]-thymidine method (LPS, 100 μg/ml; Con A, 5 μg/ml; PHA, 50 μg/ml). UCP2 mRNA levels were measured by semiquantitative RT-PCR. Phagocytosis and oxidative burst were measured by flow cytometry. Data are expressed as mean ± s.e.m., $n = 9$, NS, non statistically significant differences.

TNF-α in obesity initiates a cascade of events (increased production of PAI-1 and TGF-β) that may facilitate the cardiovascular risk associated with this condition.

In obese Zucker rats, NK cell activity has been reported to be suppressed, and the effect found to be reversible through exercise training via improved lymphocyte glucose uptake and enhanced GLUT-1 expression. On the other hand, phagocytosis was not affected by obesity, but obese Zucker rats had diminished ability to kill phagocytosed bacteria as compared to control rats due to lower oxidative burst activity (Plotkin *et al*, 1996).

Poor oxidative burst activity was found in diet-induced obese animals (Table 1), which is related to increased uncoupling protein-2 (UCP2) mRNA levels in spleen of obese rats. Recently, a correlation (Arsenijevic *et al*, 2000) between the expression of the UCP2 gene and reactive oxygen species (ROS) production was reported. A mild uncoupling of respiration by UCPs may regulate ROS production by modulating proton leakage through the inner mitochondrial membrane, suggesting a greater capacity of macrophages to generate ROS with the absence of UCP2 in the mitochondria. Other genes implicated in obesity, such as peroxisome proliferator activated receptor (PPAR-γ), which are highly expressed in adipose tissue, seem to be a key modulator of adipogenesis, but also appear to be involved in macrophage and T-helper functions. Finally, leptin seems to be an activator of the immune system after starvation periods (Matarese, 2000); however, central administration of leptin stimulates CRH production which leads to urocortin secretion producing T-lymphocyte inhibition. Moreover, it seems that T-lymphocytes are able to produce urocortin so the role of the leptin in the regulation of the immune response remains unclear.

Table 2 Summary of the main immunological data in obese people compared to lean individuals

Situation	*Outcome*	*Reference*
Obese individuals	Higher total lymphocytes: helper cells ($CD4^+$) and cytotoxic T cells ($CD8^+$), IL-6 and IL-1alpha levels and C-reactive protein serum levels	Nieman *et al* (1999) Visser *et al* (1999) Raymond *et al* (1999)
Obese individuals	Lower lymphocyte response to mitogens related to TNF-a higher levels	Nieman *et al* (1999) Tanaka *et al* (1993)
Obese indivudals after moderate energy restriction	Lower proliferative responses to mitogens	Nieman *et al* (1996)
Obese individuals after weight reduction	Increased T cell response and higher proliferative responses to mitogens	Tanaka *et al* (1993 and 2001)
Obese individuals after fasting	Lower PHA counts and higher NK cell activity and IgM	Wing *et al* (1983)
Obese burn individuals	Higher bacterinemia, sepsis, duration of antibiotherapy and stay at hospital	Gottschlich *et al* (1993)

Obese individuals and immune function

Epidemiological data support the idea that obesity is associated with alterations in immune function, but data are controversial for some parameters (Samartín & Chandra, 2001). One of the problems in analyzing immune function in obese individuals is that the effect of obesity itself on immune system can be hidden by the coexistence of hyperglycemia and dyslipidemia. Studies in which obese individuals with diabetes, insulin resistance or hyperlipidemia are excluded may eliminate these confounding factors. As occurs in animal models, most investigations confirm a lower capacity of lymphocytes to proliferate in response to mitogen activation (Table 2). Insulin receptor synthesis on T-lymphocytes after *in vitro* stimulation is reduced in obese subjects (Nieman *et al*, 1999) and it is possible that this lower expression may play a role in the impairment of T-lymphocyte functions.

Several studies showed that leukocyte and lymphocyte subsets are elevated in obese individuals (Nieman *et al*, 1999). However, other investigations revealed a T-lymphopenia in obese patients (Tanaka *et al*, 1993). This lymphopenia is apparently related to higher body mass index and *in vitro* TNF-α production. It appears that obesity is related to a reduced activity of natural killer cells in elderly men and women. A negative correlation between body fat and natural killer cell activity in elderly women and adult men has been established (Nieman *et al*, 1999). In infants, a positive relationship between body weight and lower respiratory tract infections has been observed. Possible reasons for the higher incidence would include mechanical factors that affect pulmonary functions and impaired immune status concerning cell-mediated immunity and phagocyte function. Monocyte and granulocyte phagocytosis were not influenced by obesity, while basal and activated monocyte and basal granulocyte oxidative bursts were higher in obese subjects.

Moreover, there are several studies that assess the immune response in obese patients after weight loss or nutritional deprivation, suggesting that immune impairments can be corrected with adequate weight control (Table 2). Obese patients after a moderate energy restriction have a lower mitogen-stimulated proliferation response and decreased monocyte oxidative burst as well as NK cell counts, but not T- and B-cell counts (Nieman *et al*, 1996). While total lymphocyte numbers did not change after a weight reduction program, the response of T-lymphocytes to different mitogens was increased as well as B-lymphocyte blastogenesis at the end of the dietary restriction period (Tanaka *et al*, 2001). During the slimming period, fasting blood glucose and serum triglyceride concentrations were slightly reduced. Therefore, these results suggest that an improvement in the physiological milieu may contribute to an improvement in

immune function during weight loss. A positive effect on immune response might be observed over the long-term period after subjects have achieved and maintained normal weight. Further research is warranted in this area before meaningful conclusions can be drawn because most of the studies have analyzed the effects of short-term weight loss on immunity in obese subjects. Moreover, the interactive effect of changes in psychological stress with weight loss on immune function need to be addressed. These results indicate that nutritional restriction appears to enhance certain effector functions of the host defense system in the obese patient.

Final conclusions

In summary, obesity diminishes the immune response, but the mechanisms implicated in this process remain unclear. While, the excessive intake of dietary fat has an important role in the responsiveness of immunocompetent cells and a lower consumption is desirable, more research is needed to understand the influence of dietary fat intake on immune function. Data about the role of weight loss in the improvement of immune response in obese patients are actually confusing and further investigation is required. New approaches are the immunomanipulation of the adipose tissue with specific antibodies against adipocytes and dietary patterns that potentiate the immune system.

References

Arsenijevic D, Onuma H, Pecqueur C, Raimbault S, Manning BS, Miroux B, Couplan E, Alves-Guerra MC, Goubern M, Surwit R, Bouillaud F, Richard D, Collins S & Ricquier D (2000): Disruption of the uncoupling protein-2 gene in mice reveals a role in immunity and reactive oxygen species production. *Nature Genet.* **26**, 435 – 439.

Calder PC (1998): Dietary fatty acids and lymphocyte functions. *Proc. Nutr. Soc.* **57**, 487 – 502.

Gottschlich MM, Mayes T, Khoury JC & Warden GD (1993): Significance on nutritional, immunologic, hormonal, and clinical outcome parameters in burns. *J. Am. Diet. Assoc.* **93**, 1261 – 1268.

Kimura M, Tanaka S, Isoda F, Sekigawa K, Yamakawa T & Sekihara H (1998): T lymphopenia in obese diabetic (*db*/*db*) mice is nonselective and thymus independent. *Life Sci.* **62**, 1243 – 1250.

Marti A, Marcos A & Martínez JA (2001): Obesity and immune function relationships. *Obes. Rev.* **2**, 131 – 140.

Matarese G (2000): Leptin and the immune system: how nutritional status influences the immune response. *Eur. Cytokine Network* **11**, 7 – 14.

Moriguchi S, Kato M, Sakai K, Yamamoto S & Shimizu E (1998): Decreased mitogen response of splenic lymphocytes in obese Zucker rats is associated with the decreased expression of glucose transporter 1 (GLUT-1). *Am. J. Clin. Nutr.* **67**, 1124 – 1129.

Nieman DC, Nehlsen-Cannarella SL, Henson DA, Butterworth DE, Fagoaga OR, Warren BJ & Rainwater MK (1996): Immune response to obesity and moderate weight loss. *Int. J. Obes. Relat. Metab. Disord.* **20**, 353 – 360.

Nieman DC, Henson DA, Nehlsen-Cannarella SL, Ekkens M, Utter AC, Butterworth DE & Fagoaga OR (1999): Influence of obesity on immune function. *J. Am. Diet. Assoc.* **99**, 294 – 299.

Ochoa MC, Lamas O, Martínez JA & Marti A (2001): Efectos de los ácidos grasos ω-3 sobre la función inmne. *An. Real Acad. Farm.* **67**, 473 – 487.

Plotkin BJ, Paulson D, Chelich A, Jurak D, Cole J, Kasimos J, Burdick JR & Casteel N (1996): Immune responsiveness in a rat model for type II diabetes (Zucker rat, *fa*/*fa*): susceptibility to *Candida albicans* infection and leucocyte function. *J. Med. Microbiol.* **44**, 277 – 283.

Raymond NC, Dysken M, Bettin K, Eckert ED, Crow SJ, Markus K & Pomeroy C (2000): Cytokine production in patients with anorexia nervosa, bulimia nervosa, and obesity. *Int. J. Eat. Disord* **28**, 293 – 302.

Samad F, Uysal KT, Wiesbrock SM, Pandey M, Hotamisligil GS & Loskutoff DJ (1999): Tumor necrosis factor α is a key component in the obesity-linked elevation of plasminogen activator inhibitor 1. *Proc. Natl. Acad. Sci.* **96**, 6902 – 6907.

Samartín S & Chandra RK (2001): Obesity, overnutrition and the immune system. *Nutr. Res.* **21**, 243 – 262.

Tanaka S, Inoue S, Isoda F, Waseda M, Ishihara M, Yamakawa T, Sugiyama A, Takamura Y & Okuda K (1993): Impaired immunity in obesity: suppressed but reversible lymphocyte responsiveness. *Int. J. Obes. Relat. Metab. Disord.* **17**, 631 – 636.

Tanaka S, Isoda F, Yamakawa T, Ishihara M & Sekihara H (1998): T lymphopenia in genetically obese rats. *Clin. Immunol. Immunopathol.* **96**, 219 – 225.

Tanaka S, Isoda F, Ishihara Y, Kimura M & Yamakawa T (2001): T lymphopaenia in relation to body mass index and TNF-α in human obesity: adequate weight reduction can be corrective. *Clin. Endocrinol.* **54**, 347 – 354.

Visser M, Bouter LM, McQuillan GM, Wener MH & Harris TB (1999): Elevated C-reactive protein levels in overweight and obese adults. *JAMA* **282**, 2131 – 2135.

Wing EJ, Stanko RT, Winkelstein A & Adibi SA (1983): Fasting-enhance immune effector mechanisms in obese subjects. *Am. J. Med.* **75**, 91 – 96.

Yaqoob P (1998): Monounsaturated fats and immune function. *Proc. Nutr. Soc.* **57**, 511 – 520.