Ageing Research Reviews
3 (2004) 91–104

ageing
research
reviews

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Impact of nutritional status and nutrient supplements on immune responses and incidence of infection in older individuals

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Received 16 July 2003; accepted 5 August 2003

Abstract

With advancing age there is a progressive decline in immune responses although this is not inevitable. The impairment in immunocompetence is noticeable as early as 35–40 years in many individuals. At the same time, some persons even in the 80s may show a vigorous immune system comparable with that of the young adult. Nutrient deficiencies are frequent in older populations. A variety of nutrients are affected: zinc, iron, beta-carotene, Vitamins B6, B12, C, D and E, ad folic acid. The causal interaction between nutritional deficiencies and impaired immunity has been known in children; a similar relationship has been postulated in the elderly. In the last 25 years, many studies employing different designs have examined the role of diet, nutritional status, and nutrient supplements in the immune responses of older individuals. Some nutrients, for example zinc and Vitamin E, have been shown to increase selected immune responses but have not been beneficial in terms of reduction in infectious morbidity. A growing consensus indicates that the use of a multinutrient containing optimum amounts of essential trace elements and vitamins is likely to result in enhanced immune responses and reduction in the occurrence of common infections. These findings have considerable fundamental, clinical and public health significance.

Keywords: Infection; Immune system; Cell-mediated immunity; Antibody response; Trace elements; Vitamins

1. Introduction

Infections frequently plague the lives of older individuals and are important contributors to morbidity and mortality in this age group (Chandra, 1990, 1991, 2002b; Fox,

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1568-1637/$ – see front matter © 2003 Published by Elsevier Ireland Ltd.
doi:10.1016/j.arr.2003.08.004

1984; Niederman, 1991). There are many determinants of an increased risk of infection as we age; a decline in host resistance may be an important variable. Linked to this is the individual's nutritional status that influences the biological magnitude of immune responses.

Many types of immune responses tend to decline with advancing age. The earliest indication for this is seen in individuals around 35–40 years of age. This is most evident in longitudinal studies that have repeated observations on groups of young individuals followed up for several years. However, these changes in the immune system are not inevitable. Many persons in their 80s and 90s have vigorous immune responses comparable in magnitude with that observed in the young adult. Besides genetic factors that must play an important role, several environmental and life style factors influence the ability to respond to infectious and other external and internal challenges. These include diet and nutritional status, physical activity, stress and other less-defined factors (Chandra, 2001).

Changes in immune responses with age are detailed elsewhere in this issue and other reviews (Bender et al., 1986; Chandra, 1983a,b; 1989, 1990, 1991, 1995, 2002b, 2003c; Chandra and Newberne, 1977; Facchini et al., 1987; Hessen et al., 1991; High et al., 2001; Gardner et al., 1997; Kemp et al., 2002; Makindon and Kay, 1980; Murasko et al., 1991; De Weck, 1992). Briefly, various studies have documented a decline in delayed cutaneous hypersensitivity, reduced number of T cells and certain subsets such as CD4+ helper cells and naïve T lymphocytes, decreased proliferative response to mitogens and antigens, reduced antibody response to some vaccines, phagocyte dysfunction, impaired production of several cytokines, restricted heterogeneity and affinity of antibody produced, and changes in the complement system. The wide variability in lymphocyte response to mitogens has been noted and is a source of problems in analysis and comparison of data. There are no data on mucosal immunity in the elderly. As is true of many other fields of science, data on immunologic changes in the elderly are not consistent. A case in point is the number and activity, both total and per cell basis, of natural killer cells; both normal and reduced values have been reported (Krishnaraj and Blandford, 1987; Mitchell et al., 2003). Also, there is a lack of consensus on the type and functional significance of various immune tests.

At the same time, various physiological and psychological changes in the elderly lead to nutritional deficiencies involving energy intake and intake of proteins, vitamins, trace elements and minerals (Chandra, 1992b, 1999; Chandra et al., 1982, 1991; Hoffer, 1996; Munro and Schlierf, 1992; Roebothan and Chandra, 1994a; Rosenberg and Sastre, 2002; World Health Organization and Tufts University, 2002). This has been shown by dietary intake data, and by blood nutrient values. There are advantages and disadvantages of both. Blood nutrient concentrations have the advantage of bypassing the variable of bioavailability, increased losses and metabolism. There were limited normative reference data for blood nutrient levels but this has been corrected to some extent (Chandra, 1992a).

Nutrition is a critical determinant of immunocompetence; protein-energy malnutrition and deficiencies of several vitamins and trace elements impair immune responses (Fig. 1). In children, epidemiological and clinical studies have confirmed the causal relationship between nutritional deficiencies, immune responses, and increased risk of gastrointestinal and respiratory infections (Chandra, 1972, 1986, 2003c; Fawzi and Stampfer, 2003; Erickson et al., 2000). In the elderly, such data are less than firm. However, several recent well-designed trials have shown that a good balanced diet together with appropriate nutrient

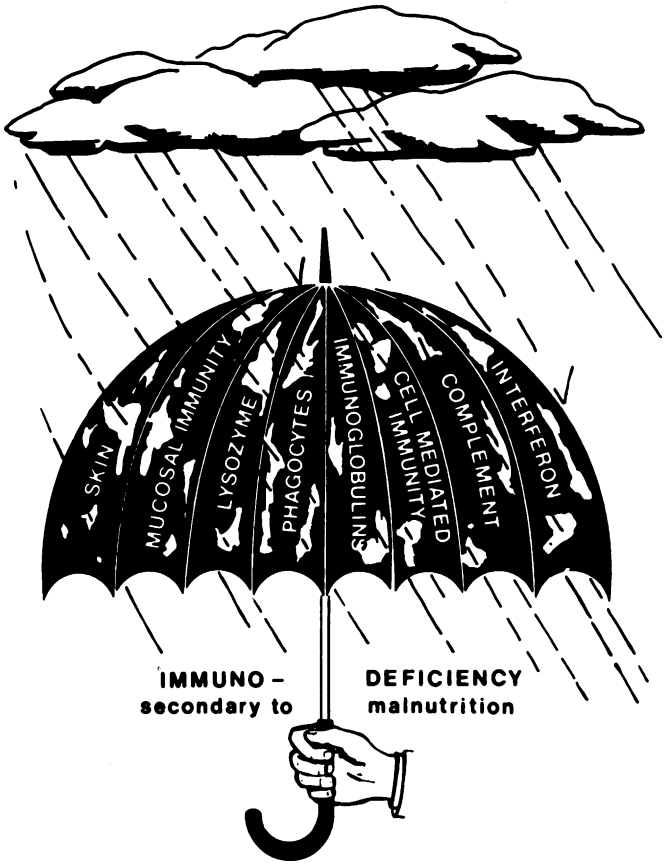

Fig. 1. In protein-energy malnutrition, most of the host defense mechanisms are breached, allowing microbes to invade and produce clinical infection which is more severe and prolonged (Copyright R.K. Chandra).

supplements result in enhanced immune responses and reduced incidence of common respiratory illnesses (Chandra, 2002c) and this is a cost-effective intervention (Chandra, 2002a, 2003a,d).

This topic has been discussed extensively and this selective review highlights important observations and relies on recent publications (Adolfsson and Meydani, 2002; Chandra, 1992b, 2002c, 2004; Mitchell et al., 2003).

2. Study design considerations

The design of studies that evaluate the effects of nutrient supplementation is very important, as is true of studies evaluating other compounds including pharmaceuticals. The important criteria of an acceptable good study are: randomized, prospective, double-blind, placebo-controlled, adequate sample size, choice of a range of objective intermediate proxy

Table 1
Summary of randomized controlled and intervention studies investigating the association between vitamin trace elements and mineral supplements and immune functions

Reference[a]	Supplement type/dose	Duration	Adherence	*N*[b]	Ages	Gender	Location	Results[c,d]
Multinutrients								
RCT; Chandra (1992a)	MN	12 months	Pill counts and interview every 2 weeks and upon completion of study	96 (86)	66–86	55 women, 41 men	Canada	↑T-lymphocyte number, NK cell number, NK activity ↑LPR to PHA, antibody response to influenza vaccine ↑IL-2 production, IL-2 receptor release ↓Number of days of infection, number of days of use of antibiotics
RCT; Bogden et al. (1994)	MN	l2 months	Pill counts at 6 and 12 months—95.9 ± 1.3% consumed	56	59–85	37 women, 19 men	USA	↑DTH
RCT; Pike and Chandra (1995)	MN	12 months	Interview every 3 months, morbidity forms, phone calls, pill counts	47 (35)	61–79	34 women, 13 men	Canada	↑NK number ↓CD4+ and CD3+ number in placebo no change in LPR, NK activity
PPT with control; Buzina-Suboticanec et al. (1998)	MN	10 weeks	Pills distributed daily by nurse	72 (70)	60–89	47 women, 25 men	Croatia	↑DTH No change in LPR, number of lymphocytes
RCT; Boardley and Fahlman (2000)	MN	10 weeks	Interviews and pill counts—98% consumed	31	65–89	31 women, 0 men	USA	No change in number of lymphocytes or LPR
RCT; McKay et al. (2000)	MN	8 weeks	Pill counts	(80)	50–87	26 women, 54 men	USA	No change in production of IL-2, 6, 10 or PGE_2
RCT; Jain (2002)	MN	12 months	Unknown	44 (41)	50–65	22 (21) women, 22 (20) men	Canada	↑T-lymphocyte number, antibody response to influenza vaccine ↑IL-2 production ↓Number of days of infection

Vitamin E								
RCT; Meydani et al. (1990)	800 mg/day	30 days	Pills given daily at research center	32	≥60	23 women, 9 men	USA	↑DTH, LPR to ConA, IL-2 production ↓PGE_2 production, PLP no change in IL-1 production
RCT; Meydani et al. (1997)	60, 200 or 800 mg/day	246 days	Measurement of serum Vitamin E at 0, 30 and 128 days, pill count at end of study ≥98% consumed	88 (72)	≥65	44 women, 44 men	USA	↑DTH for 200 mg/day group, antibody titer to Hepatitis B and tetanus, no change in antibody response to diphtheria, neutrophil activity
RCT; Pallast et al. (1999)	50 or 100 mg/day	6 months	Pill counts ≥83% (most ≥90%) consumed	161 (157)	65–80	79 (76) women, 82 (81) men	The Netherlands	No significant difference b/w placebo and control in cytokine production (IL-2, IFN-γ, IL-4) during LPR to PHA, and DTH Among individuals with low DTH at baseline ↑DTH with 100 mg supplementation
PPT; De la Fuente and Victor (2000)	200 mg/day	3 months	Unknown	25 12	>60 30–40	0 women, 37 men	Spain	↑Adherence of lymphocytes to nylon, LPR to PHA
Zinc								
RCT; Duchateau et al. (1981)	440 mg/day	1 month	Unknown	30	≥70	16 women, 14 men	Belgium	↑DTH, proportion of T lymphocytes ↑Antibody response to tetanus vaccine
RCT; Bogden et al. (1988, 1990)	15 or 100 mg/day	12 months	Pill counts 82.7% ± 1.4% consumed	158 (63)	60–89	40 women, 23 men	USA	No significant association of zinc with DTH or LPR ↑DTH sig. higher in control group consuming MV than those receiving zinc plus MV zinc at 100 mg/day may reduce positive effect of MV

Table 1 (*Continued*)

Reference[a]	Supplement type/dose	Duration	Adherence	*N*[b]	Ages	Gender	Location	Results[c,d]
PPT; Cossack, 1989	60 mg/day	4 months	Blood measures of zinc at 1 and 4.5 month	8 (8)	65–79	0 women, 8 men	Denmark	↑DTH, erythrocyte nucleoside phosphorylase activity no change in total lymphocyte count
COD; Prasad et al. (1993)	(Cross-over study) 30 mg/day	6 months	Plasma, platelet and immune cell measures of zinc at 0 and 6 months	13	50–80	6 women, 7 men	USA	↑IL-1 production ↑Plasma thymulin activity (a thymic hormone) ↑Lymphocyte ecto-5′-nucleotidase (zinc dependent enzyme, assessed in 6 participants)
RCT; Fortes et al. (1997, 1998)	25 mg/day	3 months	Pill counts every 10–15 days, ≥85% consumed	136 (118)	≥65	89 women, 29 men	Rome	↑ CD4+ DR+, cytotoxic T lymphocytes ↓ PLP
RCT; Provinciali et al. (1998)	400 mg/day	60 days	Unknown	384	64–100	287 women, 97 men	Italy	No difference in antibody response to influenza vaccine
Vitamin A								
RCT; Murphy et al. (1992)	One does treatment: 200000 IU control: 1000 IU	3 months of observation	given by research assistant	120 (109)	>60	76 women, 33 men	UK	No difference in number of infections or days of antibiotic use
RCT; Fortes et al. (1998)	800 μg/day	3 months	Pill counts every 10 to 15 days ≥85% consumed	136 (118)	≥65	89 women	Rome	↓ CD3+, CD4+ T cells no change in LPR
β-Cartotene								
RCT; Watson et al. (1991)	15, 30, 45 or 60 mg/day	2 months	Pill counts every 30 days, “medication consumption reports completed by subject”	20	≥50	10 women, 10 men	USA	↑ CD8+ T cells (15 mg/day) ↑ CD4+ T cells, NK cells (≥30 mg/day) ↑ IL-2 receptors, transferrin (≥30 mg/day)

RCT; Santos et al. (1996)	50 mg every other day	10–12 years	Self-reported questionnaire-≥87% consumed all pills	73 (59)	51–86	0 women, 59 men	USA	↑ NK cell activity in those age 65–84 years no change in NK number, IL-2 production, PGE_2 levels, DTH, LPR, prostaglandian E_2 production, lymphocyte subset number
RCT; Santos et al. (1997)	90 mg/day	3 week	Unknown	25 (23)	60–80	25 women, 0 men	USA	No change in DTH, LPR, IL-2 production, prostaglandian E2 production, or lymphocyte subset number

Reproduced from Mitchell et al., (2003).

[a] RCT: randomized controlled trial, PPT: pretest/post-test, COD: crossover design.

[b] Number in parentheses indicates the number of participants who completed the study and were used for follow-up measures. *For studies with only one number, no information was given about retention of participants*.

[c] LPR: lymphocyte proliferative response, PHA: phytohemagglutinin, ConA: concanavalin A, PWM: pokeweed mitogen, DTH: delayed type hypersensitivity, PLP: plasma lipid peroxide, LPS: lypopolysaccharide, MN: multinutrient.

[d] Statistically significant changes are labeled with arrows.

functional indicators of immunity and disease susceptibility, adequate length of trial, collection of verifiable data on illnesses, proper statistical analysis and interpretation, and logical clinical and public health recommendations based on the data obtained. Unfortunately not many studies fulfill these criteria (see Table 1) and thus a reliance on the data therein is less than satisfactory.

3. Individual nutrients

Publication bias and other reasons probably explain why most studies in the literature report benefit from the use of many nutrients given singly. It is non-physiological, however, to administer supplements containing one or a limited number of nutrients because of the adverse effects on absorption and utilization of other nutrients (Chandra, 1996, 1997). For example, modest excess of zinc leads to problems in the absorption of iron and of copper. Excessive intake of zinc impairs immune responses, both lymphocyte functions and phagocyte functions (Chandra, 1984). Similarly, iron supplements may lead to subclinical zinc deficiency. There is also the practical consideration of the public health application of such data. For example, several studies, even by the same group of investigators, found beneficial, largely in vitro, effects from the use of Vitamin B6 (Talbott et al., 1987), beta-carotene (Santos et al., 1996), and Vitamin E (Meydani et al., 1997). In some instances, a few tests showed an enhancement with the use of beta-carotene, whereas other tests were unaffected (Santos et al., 1996, 1997). Although such data are useful to gather fundamental scientific information, there is difficulty in translating it into practical advice for the elderly. Which of these nutrients would you advocate to be provided to a person or even a population group, given that nutrient deficiencies are often subclinical and are difficult and expensive to document even by dietary intake data and blood nutrient levels? Similar difficulties in interpretation of data among children has led to a failure to lay down public health policies particularly in developing countries where multiple nutrient deficiencies are rampant and the problem is of immense magnitude and importance.

Unfortunately, most trials of supplements with one nutrient or a limited number of nutrients have had little rationale for choosing the dose(s) employed. There is little doubt that there is an upper threshold for every nutrient, above which adverse effects are to be expected (Chandra, 1991, 2003b). Thus, an inverted U shape describes the relationship between nutrient status on the one hand and immunologic response and illness on the other. The best, and perhaps the only, method to determine the optimum amount of a nutrient for good immunity and less risk of infections is to undertake dose–response curves. For example, in the case of zinc, an intake of 25 mg provides the highest lymphocyte response to phytohemagglutinin, interleukin-2 production, NK cell activity and antibody response to influenza virus vaccine, and less infections. Of this amount, approximately 11 mg is provided by the average diet. Thus, based on such data the optimum amount of zinc in a supplement meant to improve immune responses should contain 14 mg of zinc. Similar information has been collected for other essential trace elements and vitamins (Chandra, 1992a); the combination of vitamins and trace elements was then used in randomized clinical trials (Chandra, 1992a, 2002, 2003d; Jain, 2002; Liu et al., 2004).

Table 2
Selective immunological data from a randomized controlled trial of multivitamin-trace element supplementation in elderly individuals

Variable	Placebo[a]	Supplement[a]	
CD3+ T cells (%)	52.8 (4.2)	66.1 (1.0)	Significant
CD4+ helper T cells (%)	42.1 (3.3)	48.9 (2.7)	Significant
CD8+ cytotoxic/suppressor T cells (%)	22.1 (2.7)	21.7 (2.8)	NS
B cells (%)	9.8 (1.6)	11.2 (1.6)	NS
NK cells (%)	9.3 (1.6)	12.7 (1.6)	Significant
Lymphocyte response to mitogen cpm	52978 (5688)	87601 (9345)	Significant
Interleukin-2 (U/ml)	3.6 (0.8)	12.8 (1.2)	Significant
Natural killer cell activity (%)	27 (3)	41 (5)	Significant
Antibody response to influenza virus vaccine, log reciprocal	2.1 (0.4)	3.2 (0.5)	Significant

NS: not significant; cpm: counts per minute; data from Chandra (1992a).
[a] Data at 12 months of the trial. There were no significant difference between the two groups at base-line. Figures represent means (standard deviation).

Data on various supplementation studies are summarized in Table 1 (Mitchell et al., 2003). Selected results of our study in the elderly are shown in Table 2.

Vitamin A supplements have been linked to reduction in morbidity and mortality in young children in developing countries but trials among the elderly have failed to show a consistent benefit. It should be pointed out that large single doses of Vitamin A may have adverse effects, including a transient reduction in lymphocyte response to mitogens and number of T cells and CD4+ helper lymphocytes, and an increase in incidence of infection. In addition, Vitamin A even in modest doses can impair liver function, and lead to fractures, particularly in the elderly (Chandra, 2003b).

Beta-carotene is a precursor of Vitamin A and is less likely to produce serious side-effects even in large doses. The data on beta-carotene usage and immune responses are not consistent. Some putatively positive studies had very small number of subjects; a total of 10 individuals in one study with two persons in each group (Watson et al., 1991), making statistical analysis and conclusion impossible (Bryant and Prasad, 1991). In another study with 13 men in an older age group, beta-carotene supplementation was associated with higher NK cell activity but no change in DTH, lymphocyte proliferation, IL-2 production and lymphocyte subsets (Santos et al., 1996, 1997).

There are limited data on Vitamin C (Kennes et al., 1983), and Vitamin B6 (Talbott et al., 1987), with one study each showing an increase in lymphocyte response to mitogens in the supplemented group.

Vitamin E has been at the center of heightened interest in the last decade (Chandra, 1997; Meydani et al., 1997; Pallast et al., 1999; Graat et al., 2002). In particular, this nutrient has been suggested to provide the best antioxidant effect needed in the elderly and is postulated to act through its effect on eicosanoid production. There is some evidence that modest amounts of Vitamin E supplements improve selected measures of immune function (Meydani et al., 1997). However, not all aspects of immunocompetence benefit and the most optimum dose is not known. Large doses impair immune responses (Prasad, 1980). One trial suggested 200 mg of vitamin daily to give the best benefits in terms of delayed-type hypersensitivity

(DTH) to seven antigens and antibody response to hepatitis B vaccine (Meydani et al., 1997), whereas another recent study found detrimental clinical effects from the use of the same dose of Vitamin E; Vitamin E users had more frequent and more prolonged respiratory infections that resulted in more visits to doctors and hospitals (Graat et al., 2002). It may well be that a more modest dose, around 40 mg in the supplement in addition to the diet, would provide the best immunological benefit. (Chandra, 1992a).

Iron deficiency is quite common among the elderly. A link between dietary iron intake and immunocompetence (Roebothan and Chandra, 1994b, 1996) has been shown and further trials using iron supplements are needed.

Zinc is crucial for optimum immunocompetence. Its importance in infants and children is recognized (Chandra, 1992b, 2004; Erickson et al., 2000). Data in the elderly are conflicting (Bogden et al., 1988, 1990, 1994; Kemp et al., 2002). Some studies show a modest benefit in terms of DTH response. It is interesting to note that zinc enhances lymphocyte proliferation response to mitogens, whereas the response to antigens is not enhanced, perhaps implying the mitogen-like role of zinc rather than indicating any zinc deficiency that benefits from zinc supplements. Other data show that higher amounts of zinc are detrimental to the overall immune response (Chandra, 1984) and may abrogate the benefit obtained with a multinutrient.

A few studies have looked at the effect of a limited number of nutrients with variable results (Chavance et al., 1993; Giordon et al., 1999) or attempted a correlation between blood levels and dietary intake with immune tests. (Payette et al., 1990; Ravaglia et al., 2000)

4. Multinutrients

It is logical to examine the role of multinutrients containing vitamins and trace elements in enhancing immune responses in the elderly; multiple nutrient deficiencies occur in more than one-third of persons above 50 years in North America and Europe and it is impractical and very expensive to estimate dietary nutrient intake and perform blood nutrient levels on individuals who may go to or be referred to a physician or nutritionist for advice. Thus it is logical to consider giving a multivitamin-trace element supplement to all individuals at and above the imaginary threshold of mid-life, i.e. 45–50 years (Chandra, 1997). The ideal supplement should contain optimum amounts of all essential vitamins and trace elements determined by suitable dose–response curves (vide supra). The amounts of all ingredients should not produce adverse side-effects even after prolonged use of many years.

The results of various studies conducted with multinutrients have been summarized by Mitchell et al. (see Table 1). In general, such a supplement is associated with an improvement in several measures of immune function. In addition, there was a reduction in the incidence of respiratory illnesses. Clinical benefit is particularly noted among those showing evidence of nutrient deficiencies at the onset and in those with an at-risk primary disease such as diabetes mellitus type II (Chandra, 1992a, 2004; Barringer et al., 2003). In a very large study of 763 nursing home residents, the regular use of the multinutrient supplement (Chandra, 1992a) for 19 months was associated with reduced number of episodes of infection (Liu et al., 2004). Some studies that have noted no significant benefit have dealt with an extraordinarily

healthy and well nourished population and used a supplement that contained only 25–50% of the RDA values of trace elements; the rationale for such reduced amounts was not clear. Not all studies have shown a positive benefit, immunological or clinical; this may well be explained with the choice of the multinutrient especially the amounts of various vitamins and trace elements contained in it, small number of subjects, short duration of the study, and choice of tests that are not consistently altered in the elderly. The statement of Mitchell et al in this regard is worth quoting in their entirety. "Overall, the results of studies . . . are consistent in their conclusions that multinutrient supplementation has a significant positive association with a number of immune measures, especially among individuals with an inadequate nutritional status. Multinutrient supplementation may be the most practical approach when considering an elderly population as most elderly do not have a deficiency in a single nutrient but may have a reduced intake of a number of nutrients and it would not be practical to identify and supplement each nutrient deficiency".

5. Complete nutritional supplement

In many individuals, particularly those with very advanced age and a primary disease that interferes with adequate nutrition, a few studies have looked at the use of a high energy feeding formula that contained a variety of nutrients including proteins, carbohydrates, fatty acids, vitamins and trace elements. There was an increase in antibody response to influenza virus vaccine (Chandra and Puri, 1985) and in DTH response (Chandra et al., 1982). More work in this area is required. Morbidity data were not collected.

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