Contribution of zinc to reduce CD4⁺ risk factor for ‘severe’ infection relapse in aging: parallelism with HIV

Eugenio Mocchegiani, Mario Muzzioli, Remo Gaetti, Salvatore Vecchia, Claudio Viticchi, Giorgio Scalise

Abstract

Aging and HIV have parallelism in immunodeficiency status because of the appearance of infections or relapse leading to death in both conditions. HIV-RNA is predictor for HIV progression correlated with CD4⁺ depletion. CD4⁺ and plasma zinc levels (zincaemia) may be predictors for infections relapse in aging because of zinc relevance for normal immune efficiency against infections and for CD4⁺ growth. Moreover, zincaemia decreases in aging and infection. A total of 67 elderly subjects affected by infections resistant to antibiotic therapy were recruited. A total of 28 HIV+ subjects with HAART therapy were also used. CD4⁺ depletion (507 mm³) and zincaemia deficiency (76 μg/dl), as compared to CD4⁺ (700–1100 mm³) and zincaemia (85–100 μg/dl; age 40–75 years) normal ranges, are possible limits (Cox hazard regression) for severe infections relapse, such as chronic obstructive bronchitis and bronchopneumonia by bacteria or Candida complication, in aging. CD4⁺ and zincaemia values are within the lower limits of normal range in urinary tract infections. Zincaemia and HIV-RNA or CD4⁺ are inversely correlated (r = 0.57 and r = 0.72, respectively) in HIV+ HAART treated subjects. Consequently there is no appearance of opportunistic infections. Parallelism between aging and HIV may exist because of the resemblance in marked zinc deficiency and CD4⁺ depletion with high scores in relative risks for severe infections relapse. Supplementing zinc (12 mg Zn⁺⁺/day) for one month in infected elderly subjects and HAART therapy in HIV+ subjects reduces risk scores in CD4⁺ and zincaemia deficiencies for infections relapse, suggesting that the zinc beneficial effect may be independent.
either by HIV-virus or pathogen agents involved. While HAART may reduce the occurrence of opportunistic infections in HIV by means of also major zinc bioavailability, supplementing zinc can be recommended in elderly people as resistance to infections. Since zinc deficiency is correlated with CD4⁺ depletion, this latter may also be good diagnostic marker to detect ‘clear immunodeficiency’ in aging, as in HIV condition. © 1999 International Society for Immunopharmacology. Published by Elsevier Science Ltd. All rights reserved.

Keywords: Aging; HIV; Zinc; CD4⁺; HIV-RNA; Infection relapse; Risk factors

1. Introduction

Aging and HIV have parallelism in immunodeficiency status because of the appearance of infections or relapse leading to death in both conditions (Pawelec & Solana, 1997). Proteases inhibitors reduce opportunistic infections (Chaisson & Moore, 1997) because of HIV-RNA relevance for HIV progression as major predictor (Mellors, Rinaldo, Gupta, White, Todd & Kingsley, 1996), other than CD4⁺ depletion (Levy, 1989). CD4⁺ count dysregulation causes infections or infections recidive (Pawelec & Solana, 1997). No specific immunological limits under which risk of infection or infection relapse are still available in aging. Together with CD4⁺, zinc may be a predictor because: (i) zinc is important for immune efficiency against infections (Sugarman, 1983); (ii) zinc is predictor for death in comatose patients for high frequency of infectious episodes (Mocchegiani, Imberti, Testasecca, Zandri, Santarelli & Fabris, 1995a); (iii) zinc deficiency is a cofactor for infections in old age (Chandra, 1989). Finally zinc affects CD4⁺ maturation and differentiation (Beck, Prasad, Kaplan, Fitzgerald, & Brewer, 1997). Moreover zinc decreases in aging (Fabris, Mocchegiani, Amadio, Zannotti, Lierasto & Franceschi, 1984) and during infections (Mocchegiani Vecia, Ancarani, Scalise, & Fabris, 1995b; Sandstead, 1994; Shankar & Prasad, 1998), whereas CD4⁺ depletion occurs during infections (Pawelec & Solana, 1997). In turn, infections and infections relapse are constant events in aging (Fabris & Mocchegiani, 1995). Plasma zinc levels (zincaemia) and CD4⁺ are tested in infected elderly subjects from remission phase as possible limits and, as such, possible risk factors for infections relapse resistant to conventional antibiotic therapy (Lewis & Reeves, 1994). Peripheral T-cells are used to give more complete picture of generalized immunodeficiency in aging, as in canine bronchoalveolar infections (Dirscherl, Beisker, Kremmer, Mihalkov, Voss & Ziesenis, 1995). HIV model with HAART therapy was used to further study the possible parallelism between HIV and aging for infections relapse incidence. Because of zincaemia heterogeneity in aging (Fabris et al., 1984; Prasad, Fitzgerald, Hess, Kaplan, Pelen & Dardenne, 1993) and HIV (Fabris, Mocchegiani, Galli, Irato, Lazzarin & Moroni, 1988; Mocchegiani et al., 1995b), total thymulin (TT) (active zinc-bound ZnFTS + inactive zinc-unbound FTS) and active thymulin (ZnFTS) (AT) ratio, which is the unsaturated fraction of thymulin (FTS) by zinc ions (Fabris et al., 1984) is a good marker to detect real zinc deficiency because of the inverse strict correlation between zincaemia status and the ratio itself (Fabris et al., 1984). Thus, zincaemia was associated with TT/AT ratio. Supplementing zinc from remission phase was carried out in elderly subjects affected by pre-existing chronic
obstructive bronchitis. Relative risk factors were calculated from the remission phase (time 0) of infection to month 4 of observation. An HIV model was used as comparison.

2. Subjects and methods

2.1. Elderly subjects

A total of 48 male and 19 female subjects (63–75 years, mean 69 ± 5.8) admitted to the hospital were recruited in remission phase (time 0) of infection (urinary tract, chronic obstructive bronchitis and bronchopneumonia by bacteria or candida complication). Old patients are divided according to infections. Group A with urinary tract infections (18 subjects, 5 male and 13 female, mean age 70 ± 5 years), group B with chronic obstructive bronchitis (36 subjects, 25 male and 11 female, mean age 67 ± 4 years) and group C with bronchopneumonia by bacteria or candida complication (13 subjects, 10 male and 3 female, mean age 68 ± 3.5 years). Elderly patients with previous infections associated with other pathological conditions were excluded. Conventional antibiotic therapy was used before remission phase. Length of conventional antibiotic treatment was of 12 ± 2.0 and 14 ± 2.7 days before time 0 (Data are the mean number of days of antibiotic treatment) for group A and for groups B and C, respectively, with conventional therapeutic dose dependent by infection severity. No other drugs were administered other than Vitamins B complex in order to maintain a good balance of vitamins B by intestinal bacterial flora, which can be destroyed by antibiotic therapy. Blood withdrawal (time 0) was performed in remission phase of infection. The daily diet was similar to healthy old controls. Double-blinded controlled trial with zinc at the dose of 12 mg Zn++/day (USDA, 1976) or placebo (starch containing capsule) was carried out for one month in 15 (13 male and 2 female, mean age 68 ± 3 years) and 14 (11 male and 3 female, mean age 66 ± 2 years) elderly people subjects, respectively, after one week from remission phase of infection (chronic obstructive bronchitis). Relative risk factors as well as possible infection relapse were evaluated from month 0 to 4 of observation. Supplementing zinc was carried out in chronic obstructive bronchitis because of more common infection relapse in aging (Pawelec & Solana, 1997) with consequent major subjects availability.

2.2. HIV+ subjects

A total of 21 male and 7 female intravenous drug-users HIV+ subjects (20–36 years, mean 28 ± 5.5) were recruited with CD4+ number between 250 and 400 mm³ (Stage III of disease) (Murray et al., 1985). Because of HIV-RNA as predictor for HIV progression (Mellors et al., 1996) with HAART to block virus replication (Sepkowitz, 1998), the medical ethic suggested to immediatly perform HAART when CD4+ ≤ 400–500 mm³ and HIV-RNA ≥ 10,000 copies/ml (Sepkowitz, 1998). No other drugs administered other than HAART [2 nucleoside analogues (AZT + 3TC) and 1 proteases inhibitor (IND or RIT)] at standard doses/day (Sepkowitz, 1998), with compliance of 92%. HIV-RNA, immunological and nutritional parameters were detected at months 0 and 4 after HAART therapy as well as possible opportunistic infections censoring. Relative risk factors were evaluated from month 0 to 4 of observation. The data of
relative risk factors were compared with HIV+ subjects (18 subjects) with CD4+ between 250 and 400 mm³ treated with only AZT because of no availability of other antiviral drugs in this retrospective study (Mocchegiani et al., 1995b). The daily diet was similar to young healthy controls. No vegetarian subjects were present. ELISA and Western blot confirmed HIV seropositivity.

2.3. Control groups

Seven men and eight women healthy young subjects (25 ± 3.4 years) admitted to the hospital for minor surgery served as controls. Five men and ten women healthy elderly subjects (67 ± 4.6 years) were recruited in accordance to immunogerontological ‘SENIEUR protocol’ (Ligthart et al., 1984). Vegetarian subjects were excluded. They were recruited and examined according to the guidelines of Helsinki declaration. The informed consent for blood withdrawals as well as for zinc trial was obtained.

2.4. Methods

HIV-RNA plasma detection was performed by means of RT-PCR amplification of specific primers (SK38, SK39) (Menzo, Bagnarelli, Giacca, Manzin, Varaldo & Clementi, 1992). TT/AT ratio were tested in the plasma by inhibiting azathioprine-sensitive rosettes assay (Fabris et al., 1984). Zincaemia was tested using A.A.S. (Fabris et al., 1984). CD4+ absolute number was counted with cytofluorimetry (Epics V, Culter, USA) using Leu3a FITC (Becton-Dickinson, USA). Differences were compared using ANOVA (two-way). Cox hazard regression (Matthews & Farewell, 1988) was used to test relative predictors (CD4+ and zincaemia) for infection risks and for possible limits under which infections risk may be high. Least-square method and analysis of covariance were used for correlations and to test significance among regression lines, respectively. Differences were significant when \( P \leq 0.05 \).

Table 1
Immunological and nutritional parameters in elderly subjects in remission phase of infection (time 0)\( ^a \)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Ratio T.T./A.T. (log₂)</th>
<th>Zincaemia (µg/dl)</th>
<th>CD 4+ (mm³)</th>
<th>No of infections/subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2.0 ± 0.3</td>
<td>83.3 ± 4.9</td>
<td>696 ± 58</td>
<td>18/18</td>
</tr>
<tr>
<td>B</td>
<td>2.5 ± 0.3*</td>
<td>75.3 ± 3.2**</td>
<td>457 ± 53*</td>
<td>13/13</td>
</tr>
<tr>
<td>C</td>
<td>2.4 ± 0.2*</td>
<td>76.8 ± 4.3**</td>
<td>460 ± 66*</td>
<td>36/36</td>
</tr>
<tr>
<td>D</td>
<td>1.6 ± 0.2</td>
<td>88.5 ± 5.8</td>
<td>877 ± 47</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>1.1 ± 0.2</td>
<td>120.0 ± 6.5</td>
<td>925 ± 68</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) *P < 0.01 and **P < 0.05 when compared to group D.

\( ^b \) A = Elderly subjects (n = 18) with pre-existing infections (urinary tract); B = Elderly subjects (n = 13) with pre-existing infections (bronchopneumonia by bacteria or Candida complication); C = Elderly subjects (n = 36) with pre-existing infections (Chronic obstructive bronchitis); D = Elderly age-matched healthy controls (n = 15) (age 60–73 years); E = Young healthy controls (n = 15) (age 20–30 years).
3. Results

3.1. Elderly subjects

TT/AT ratio > 2 (Groups B and C) is associated with more marked zinc deficiency as compared to TT/AT ratio (=1.6) and zincaemia values of old healthy controls (P < 0.01) (Table 1). The anamnestic analysis at time 0 (remission phase) shows that urinary infections (18/18 patients), bronchopneumonia [by bacteria (8/13 patients) or by Candida complication (5/13 patients)] and chronic obstructive bronchitis (36/36 patients) are pre-existing infections. CD4⁺ count is reduced (groups B and C) (P < 0.01), whereas no difference in group A as compared to old healthy controls (Table 1). CD4⁺ (437 ± 49 mm³) and zincaemia (74 ± 3.4 µg/dl) values in old patients affected by bronchopneumonia by Candida complication are not different as compared to those ones by bronchopneumonia by bacteria complication (CD4⁺ = 478 ± 62 mm³; zincaemia = 76 ± 3.8 µg/dl). No differences in CD4⁺ and zincaemia exist between old patients affected by chronic obstructive bronchitis and by bronchopneumonia (Table 1), as well as between male and female (data not shown). CD4⁺ and zincaemia values for urinary tract infections are included within the normal range (Table 1). Suplementing zinc for one month from remission phase (time 0) in elderly subjects affected by chronic obstructive bronchitis increases CD4⁺ cell number (from 462 ± 48 time 0 to 690 ± 41 time 1 month; P < 0.01) with significant reduction of infections relapses (2 relapses/15 patients = 13.3%) as compared to placebo group (6 relapses/14 patients = 42.8%) (P < 0.01) at month 4 of observation. CD4⁺ depletion and zinc deficiency in placebo group are relative risk factors for infections relapse with significant scores as compared to old zinc-treated group (Table 2). Moreover, taking into account CD4⁺ and zincaemia normal ranges (700–1100 mm³; 20–75 years; 85–100 µg/dl; 40–75 years, respectively) from our laboratory, CD4⁺ (507 mm³) (range 454–530) and zincaemia (76 µg/dl) (range 75–91) may be possible limits at borderline for chronic obstructive bronchitis infections relapse. When the data of zincaemia from old infected patients before and after zinc supplementation and respective healthy controls are plotted against the corresponding values of CD4⁺, significant positive inverse correlation is found (r = 0.81 P < 0.01).

Table 2
Relative risk factors for chronic obstructive bronchitis relapse in elderly subjects treated with zinc and for opportunistic infections in HIV⁺ subjects treated with AZT (retrospective study) or HAART

<table>
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<tbody>
<tr>
<td></td>
<td>Placebo (n = 14)</td>
<td></td>
<td></td>
<td>Zinc treatment (n = 15)</td>
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<tr>
<td>CD4⁺</td>
<td>0.82</td>
<td>2.27</td>
<td>P &lt; 0.01</td>
<td>0.36</td>
<td>1.44</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>zincaemia</td>
<td>0.71</td>
<td>2.03</td>
<td>P &lt; 0.01</td>
<td>0.41</td>
<td>1.51</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>HIV⁺ (AZT treatment) (n = 18)</td>
<td></td>
<td></td>
<td></td>
<td>HIV⁺ (HAART treatment) (n = 28)</td>
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<td></td>
</tr>
<tr>
<td>CD4⁺</td>
<td>0.78</td>
<td>2.18</td>
<td>P &lt; 0.01</td>
<td>0.51</td>
<td>1.67</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>zincaemia</td>
<td>0.85</td>
<td>2.34</td>
<td>P &lt; 0.01</td>
<td>0.48</td>
<td>1.62</td>
<td>P &gt; 0.05</td>
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3.2. 

TT/AT ratio > 2 is associated with more marked zinc deficiency at time 0 as compared to day 120 of observation (Table 3). CD4+ and body weight (Δ%) are reduced at time 0 as compared to young healthy controls (P < 0.001) (Tables 3 and 1). HAART increases zincaemia, body weight and CD4+ and reduces HIV-RNA (copies/ml) as compared to time 0 (P < 0.01) (Table 3). This reduction is also > 1 log10. HAART avoids CD4+ depletion and zinc deficiency as relative risk factors for opportunistic infections, as compared to AZT HIV+ treated subjects (Table 3). HAART induces no appearance of opportunistic infections during the period of observation as compared to AZT treated group (Stage III of disease) of the retrospective study (0 infections vs 13 opportunistic infections among whom, three by Candida) (Mocchegiani et al., 1995b). No difference between male and female and between drug-users and heterosexuals is found (data not shown). Significant inverse correlations exist between zincaemia and HIV-RNA (r = 0.57; P < 0.05), between CD4+ and HIV-RNA (r = 0.72, P < 0.01) and between zincaemia and body weight (r = 0.76, P < 0.01) in HAART treated HIV+ subjects.

4. Discussion

CD4+ depletion and marked zinc deficiency are cross-linked in elderly subjects for infections relapse, such as bronchopneumonia and chronic obstructive bronchitis, resistant to conventional antibiotic therapy. HAART induces no appearance of opportunistic infections because of increased CD4+ and zincaemia values, which are both inversely correlated with HIV-RNA. HAART reduces also CD4+ and zincaemia relative risk factors for opportunistic infection incidence. Supplementing zinc in elderly infected subjects restores CD4+ cell number with significant infections relapse reduction, as it occurs in HIV+ HAART treated subjects. Thus marked zinc deficiency and CD4+ depletion may be considered as probable predictors for infections relapse in aging with HIV parallelism.

CD4+ number is similar in young and old subjects (Cakman Rohwer, Schutz, Kirchner, & Rink, 1996). FasL-apoptosis by bacteria endotoxins may cause CD4+ dysregulation with consequent increased bacteria infections relapse (Pawlec & Solana, 1997; Castro, Bremer,

Table 3

<table>
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<tr>
<th>CD4+, zincaemia and HIV-RNA in HIV+ subjects treated with HAART from day 0–120 of observationa</th>
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<tr>
<td>Ratio TT/AT (log−2)</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>t0</td>
</tr>
<tr>
<td>t120</td>
</tr>
</tbody>
</table>

a *P < 0.01 and **P < 0.05 when compared to time 0. No opportunistic infections occur in HIV+ HAART treated subjects during the period of observation.

b The body weight was calculated as individual variance (Δ%) of the body weight from day 0–120 for each patient. The significance of Δ% = χ2 test.
Indeed, CD4+ depletion is significant in presence of pre-existing infections (bronchopneumonia and chronic obstructive bronchitis). Such a depletion may be more related to previous infections rather than to conventional antibiotic therapy effect because of the blood withdrawals in remission phase and because of the non-influence of antibiotics (independently by doses used or pathogen agent involved) on altered CD4+ subsets in peripheral blood by adult infected subjects (Kawakami et al., 1997), confirming also, at least, the antibiotic therapy poor efficacy in elderly infected subjects (Lewis & Reeves, 1994). Zincaemia and CD4+ decrease during infections (Pawelec & Solana, 1997; Fabris et al., 1988; Mocchegiani et al., 1995b; Sandstead, 1994), which often are, in turn, age-associated diseases (Fabris & Mocchegiani, 1995). Because of no availability of specific immunological limits under which infection relapse risk may be high in old age, zincaemia and CD4+ may be taken into account because: (i) zinc is important for immune efficiency against infections by virus, fungi and bacteria (Sugarman, 1983); (ii) zinc deficiency is a predictor of death in comatose patients suffering by numerous infectious episodes (Mocchegiani et al., 1995a); (iii) zinc deficiency is a cofactor for infection in aging (Chandra, 1989); (iv) zinc shows an age-related decrease (Fabris et al., 1984) and it is essential for CD4+ maturation and growth (Beck, Prasad, Kaplan, Fitzgerald & Brewer, 1997). Following that, zinc deficiency and CD4+ decrement may be cross-linked with possible limits under which infections relapse risk may be high. Because of no immune differences between chronic obstructive bronchitis and bronchopneumonia, such limits may be the same and both are reduced as compared to CD4+ (Hannet, Erkeller-Yuksel, Lydyard, Denesys, & DeBruyere, 1992) and zincaemia normal ranges (Fabris et al., 1984). CD4+ and zincaemia limits are within the lower limits of normal ranges in urinary tract infections. Thereby, these latter may be considered as ‘moderate’, whereas the others as ‘severe’ (Laurence, 1993). Without excluding other T-subsets dysregulations, such as ‘memory’ and ‘naive’ T-cells, in aging (Sansoni et al., 1993) and in infections (Pawelec & Solana, 1997), because of significant inverse correlation between CD4+ and zincaemia in remissed elderly infected subjects, the determination of CD4+ may also be good diagnostic marker to detect ‘clear immunodeficiency’ in aging, because of good CD4+ number maintenance (700 mm3) for good health (successful of aging) in centenarians (Sansoni et al., 1993).

The parallelism between aging and HIV may exist because, other than similar T-cell dysregulations (Ullum, Lepri, Victor, Skinhoj, Phillips & Pedersen, 1997), strong CD4+ depletion associated with marked zinc-deficiency causes the appearance of ‘severe’ opportunistic infections, including Candida aesophagea, in HIV+ subjects (Murray et al., 1985; Mocchegiani et al., 1995b). The pathogen agent involved is quite different between HIV and aging. Because of the lack of difference in CD4+ depletion between bronchopneumonia by Candida and bacteria complication while, one hand possible different immune responses by different pathogen agents may be avoided (Belkaid et al., 1994); on the other hand, the parallelism with HIV in CD4+ depletion for ‘severe’ infections may be further supported. Indeed supplementing zinc reduces infections relapse with low scores in CD4+ and zincaemia relative risk factors in elderly infected subjects, as it occurs in HIV+ zinc-treated subjects (Mocchegiani et al., 1995b). This suggests that zinc may induce resistance against infections (Shankar & Prasad, 1998). On the other hand resistance to respiratory and urinary infections in institutionalized elderly subjects (Girodon et al., 1997) and in Down’s syndrome (Licastro et
al., 1994) is observed during supplementing zinc. In addition, benefit of physiological zinc against gram-negative infections has been reported (Wellinghausen et al., 1996). A further evidence of zinc deficiency relevance for infections incidence comes from the AZT poor efficacy, as compared to HAART (Hazura & Kuo, 1997), in HIV condition. Indeed, HAART increases CD4⁺ cells number and zincaemia values, which are both inversely correlated with HIV-RNA, and, consequently, there is no appearance of opportunistic infections. The disappearance of CD4⁺ depletion and zinc deficiency as possible relative risk factors for opportunistic infections exclusively during HAART therapy (Table 2), is in line with this interpretation. The HAART effect may also occur by means of major zinc bioavailability due to decreased acute inflammation (Chandra, 1992) or to better zinc intestinal absorption, as shown by body weight increments. Because of the absence of zinc in HAART drugs (Vecchia, unpublished observation), these findings together with the effect of zinc supplementation in elderly subjects (in the present study) and in HIV⁺ subjects (Mocchegiani et al., 1995b), while one hand suggest the real efficacy of HAART, on the other hand pin-point zinc as beneficial against ‘severe’ infections, whose effect may be independent either by HIV-virus or by other pathogen agents involved. Moreover, such an effect may be more addressed to the extracellular matrix because of the disappearance of Candida aesophagea relapse in HIV⁺ zinc-treated subjects (Mocchegiani et al., 1995b). While HAART reduces infections occurrence in HIV by means of also major zinc bioavailability, this latter may be acquired by zinc supplementation in aging. Other micronutrients or vitamins deficits have been suggested as infection predictors (Chandra, 1989). Without excluding that, Vitamin A supplementation has been found deleterious on immune response in elderly people, whereas zinc prevents infections (Fortes et al., 1998)—further supporting, this latter, the relevance of zinc deficiency in infected elderly patients during the remission phase. Intestinal malabsorption (Lee, Prasad, Hydrick-Adair, Brewer, & Johnson, 1993) or inflammation (Chandra, 1992) may cause zinc loss in aging. Whatever causes, low zinc bioavailability is associated with CD4⁺ depletion, despite zinc content into young and old human lymphocytes has been found similar (Bunker, Hinks, Lawson, & Clayton, 1984), whereas it is different for others (Prasad et al., 1993). The free quota of zinc available is more relevant because zinc into lymphocytes (Yurkow & Makhijani, 1998) is more bound with zinc-binding metallothioneins, which are increased in aging (Mocchegiani, Muzzioli, Cipriano & Giacconi, 1998) and in infections (Sobocinski, Canterbury, Mapes, & Dinterman, 1995). Since Atomic Absorption Spectrophotometry (AAS) detects zinc-bound and zinc-unbound, the measure of zinc into lymphocytes may, therefore, result controversial and, at least, also misleading. Other zinc deficiency markers, such as ecto-5 nucleotidase, are useful (Prasad et al., 1993). However, TT/AT ratio purchases peculiar role to test real zinc deficiency because TT/AT ratio detects zinc ions bioavailability due to strict inverse correlation between zincaemia status and ratio itself. Moreover TT/AT ratio > 2 (log₂) is always associated with more marked zinc deficiency, as compared to TT/AT ratio = 1 (log₂) in presence of normal plasma zinc values (Fabris et al., 1984). Thus the low zinc ions bioavailability is evident in aging leading to CD4⁺ depletion and to the appearance of infections relapses. Thereby, the cross-linking between zinc deficiency and CD4⁺ depletion in aging may be probable relative risk factor avoided by supplementing zinc.

In conclusion, present data, despite obtained in limited number of subjects, may suggest parallelism between aging and HIV because of the resemblance in CD4⁺ depletion and zinc
deficiency as relative risk factors for ‘severe’ infections relapse. Because of CD4+ apoptosis involvement in both conditions (Castro et al., 1998; Algeciras, Dockrell, Lynch, & Paya, 1998), and, in turn, apoptosis may be directly (Sunderman, 1995) or indirectly (Shankar & Prasad, 1998) prevented by zinc, the resemblance may be further supported. New concepts on cause/s of ‘immunosenescence’ (Pawlec & Solana, 1997) may be thereby added with an emphasis on zinc.

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References


