Original Article

Factors associated with serum retinol, α-tocopherol, carotenoids, and selenium in Hispanics with problems of HIV, chronic hepatitis C, and drug use

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Abstract The effects of hepatitis and drug use on nutritional problems in HIV infection have rarely been examined despite the importance of drug use in the global HIV pandemic. We examined the effects of HIV, hepatitis C, and drug use on serum micronutrients in 300 US Hispanic adults. Chronic hepatitis C infection was associated with lower serum retinol (−8.2 μg/dl, $P<0.0001$), α-tocopherol (−0.10 ln μg/dl, $P=0.024$), and carotenoids (−19.8 μg/dl, $P<0.0001$). HIV infection was associated with lower selenium (−6.1 μg/l, $P=0.028$). Elevated triglycerides in HIV infection were associated with higher serum retinol and α-tocopherol. Drug use was not independently associated with micronutrient alterations. We conclude that hepatitis C is an important determinant of low serum micronutrients, and should be considered in any nutritional assessment of HIV infected populations. As the safety of micronutrient supplementation is not established, policy for appropriate HIV clinical care should distinguish between populations with and without hepatitis coinfection.

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Introduction

In many parts of the world, intravenous drug use (IDU) is an important driver of the human immunodeficiency virus (HIV) epidemic, and the co-occurrence of hepatitis infection is common in these

populations. For example, 37 per cent of HIV infected US veterans have detectable antibodies to hepatitis C (HCV).[1] In Eastern Europe, where IDU is the predominant mode of HIV transmission,[2] HCV or hepatitis B (HBV) coinfection rates are over 30 per cent among high-risk populations, including female sex workers.[3,4] In Iran, where IDU accounts for two-thirds of HIV infections, HCV coinfection rates are estimated to be 74 per cent.[5] Thus, in some areas of the world, the majority of HIV-infected persons may be coinfected with HCV.

Nutritional and metabolic abnormalities have been frequently reported in both HIV and HCV infections. Serum micronutrient deficiencies were commonly observed in HIV-infected persons before the availability of effective antiretroviral therapy (ART).[6–14] Low serum micronutrients have also been reported in persons with chronic hepatitis infection.[15–17] In HIV infection, abnormal serum lipid profiles are seen, and have been related to HIV replication, low CD_4 cell counts,[18] and ART,[19] whereas low cholesterol is found in chronic HCV infection.[20] The metabolism of lipids and micronutrients, such as vitamin A, vitamin E, and carotenoids, are intimately linked.[21–23]Alterations in lipid levels resulting from either HIV or chronic HCV infection can impact serum micronutrient levels. In HIV/HCV coinfected persons, both HIV and HCV infections have the potential to influence micronutrient and lipid levels.

The role of HCV infection as a potential determinant of serum micronutrient levels in HIV infected drug-using populations is not well described as few studies have evaluated HCV infection. On the basis of the published literature, we suspected that hepatitis infection and drug use might confound the effect of HIV infection on serum micronutrient status. Therefore, our study was designed to separate the effects of hepatitis infection and drug use from the effects of HIV on serum micronutrient levels. We hypothesized that, because of its impact on metabolism, chronic HCV infection would be a significant risk factor for low serum micronutrients in persons with HIV infection. We examined serum vitamin A (retinol), vitamin E (α-tocopherol), carotenoids, and selenium because of their importance in immune function. We do not present the results of our measurements of serum zinc.

We have chosen to publish our data in a policy journal because the results of our study suggest that, in addressing the problem of micronutrient deficiencies in persons living with HIV/AIDS, we need

to make a distinction between those who are infected with HIV alone and those who are coinfected with HIV and HCV. We present detailed analyses to support our conclusion that chronic HCV infection has a profound influence on serum micronutrient status, and believe that our findings have important implications for policies on the nutritional assessment of persons living with HIV/AIDS and their appropriate clinical care, including recommendations for micronutrient supplementation. Although the potential benefits of micronutrient supplementation in HIV infection are best evaluated by randomized trials, a thorough understanding of the determinants of serum micronutrient deficiencies is important to ensure that trials are targeted appropriately. The benefits micronutrient supplementation may differ among subgroups, including those who are or not coinfected with HCV.

Materials and Methods

Participants: Between August 2002 and December 2006, we recruited to this study all qualified persons from a cohort of Hispanic adults participating in a study of nutrition and drug use. In this population of Hispanics, drug use is an important risk factor for HIV infection.[24] We recruited the cohort by street out-reach into one of four groups: HIV-infected drug users, HIV non-infected drug users, HIV-infected persons who do not use drugs, and healthy Hispanic adults who denied drug use. The exclusion criteria for the cohort were pregnant at recruitment, non-HIV-associated malignancies, refusal to consent to the release of medical records, a history of gender reassignment, and renal dialysis. The Institutional Review Board of the Tufts Medical Center approved the study and participants gave written informed consent.

Assessments: We asked the participants to come to the clinic in a fasting state, and the staff noted whether the participant reported eating within 5 hours of the visit. No participants were febrile. Using standardized interviews, Hispanic study staff collected information on medical history, including all current medications, alcohol, and drug use. The protocol defined current drug use as reported use of opiates, cocaine, or amphetamines within the past 6 months. We did not consider marijuana a drug of abuse. Past drug users were classified as non-drug users. The statistical programmer coded

self-reported alcohol use in several ways as current use of any alcohol (vs. no use); use of alcohol at an average frequency of at least once per day (vs. < once per day); or use of alcohol at an average frequency of at least three times per day (vs. < three times per day). We assessed smoking as current use (vs. never or past). The interviewers measured body mass index (BMI) from height and weight,[25] and body composition by bioelectric impedance analysis (RJL Systems Inc., Clinton, MI, USA) using the Lukaski equations.[26–28]

Micronutrient analyses: Clinic staff drew blood in trace element-free conditions, and stored it at −70 °C until processing. The laboratory staff measured serum vitamin A (retinol) and vitamin E (α-tocopherol) by reverse-phase high-performance liquid chromatography (ESA EZChrom Elite Chromatography Data System, ESA, Chelmsford, MA, USA);[29] carotenoids by spectrophotometry;[30] and selenium by graphite furnace atomic absorption spectrophotometry (AAanalyst 800, Perkin Elmer, Shelton, CT, USA). We defined low values as retinol $<30\,\mu$g/dl; α-tocopherol $<500\,\mu$g/dl; carotenoids $<29.5\,\mu$g/dl, which is the fifth percentile for the US general population level of serum carotenoids from the NHANES III survey 1988–1994; and selenium $<85\,\mu$g/l.[10]

Other blood assays: The laboratory of the Massachusetts Department of Public Health conducted the hepatitis tests. We defined chronic viral hepatitis as a positive serum test for HBV surface antigen (HBsAg Enzyme Immunoassay 3.0, Biorad Laboratories, Redmond, WA, USA) or HCV RNA (AMPLICOR Hepatitis C Virus test, Version 2.0 Roche Molecular Systems Inc., Branchburg, NJ, USA). As HBV infection was uncommon (<2 per cent), we excluded data from six participants with HBV infection to focus on HCV (total $n=300$). The Tufts Medical Center laboratories conducted the following assays: HIV status (Genetic Systems™ HIV1/HIV2 Plus O EIA, Biorad Laboratories, Redmond, WA, USA); high-sensitivity C-reactive protein (CRP; UniCel® DxC 800 Synchron® Clinical System and CRP High-Sensitivity Reagent (Beckman Coulter, Fullerton, CA, USA); CD4 lymphocyte counts using a specific monoclonal antibody and fluorescence-activated cell-sorting analysis and alanine amino transferase (ALT), total cholesterol and triglycerides (Synchron® Clinical System, Beckman Coulter, Fullerton, CA, USA). The virology laboratory measured HIV RNA (Roche Amplicor Monitor reverse transcriptase polymerase

chain reaction, Roche Molecular Systems, Somerville NJ, USA). We set undetectable viral load (< 400 copies per ml) to a value of 200 copies per ml.

Assessment of dietary intake and supplement use: We measured nutrient intake with a food frequency questionnaire (FFQ) previously validated in this population.[31,32] The nutrition staff calculated the nutrient profiles with the Nutrient Data System, version 4.06 (NDS, University of Minnesota, Minneapolis, MN, USA). The interviewers asked study participants about the use of vitamin and food supplements.

Statistical Analyses: In Tables 1 and 2, we used the *F*-test, χ^2-test or Fisher's exact test where appropriate to test the between-group differences at $\alpha = 0.05$). To give a 'cleaner' comparison group in the analyses shown in Table 2, we excluded data from 45 HIV/HCV uninfected drug users. Serum vitamin E was transformed using the natural logarithm. We treated the following variables as potential predictors of serum micronutrients: HIV and HCV infections, current drug use, dietary intake, vitamin supplement use, age, gender, alcohol use, smoking, BMI, cholesterol, and CRP. As we had an *a priori* interest in all the variables, we report the full models in Table 3 to allow readers to compare the predictors of each micronutrient. We examined triglycerides as a predictor of serum micronutrients in a subset ($n = 255$) with available triglyceride data. There were too few data to assess men and women separately. We conducted the multivariate modeling, using the general linear model procedure in SAS version 9.0 (SAS Institute, Cary, NC, USA), and evaluated influential observations using Cook's distance.

Results

Table 1 shows the characteristics of the 300 study participants, stratified by infection status. There were significant between-group differences in age, smoking, alcohol use, ALT, BMI, and cholesterol. Supplement use was more common among the HIV-infected groups. Selenium intake from food was lowest in the HIV-infected group.

Among all participants with HIV infection, the unadjusted prevalence of low micronutrients was 13 per cent (18/141) for vitamin A, 11 per cent (15/141) for vitamin E, 10 per cent (14/141)

Table 1: Participant characteristics in relation to infection with HIV and/or chronic HCV infection (s.d.)

	Group 1: HIV and HCV	*Group 2: HIV alone*	*Group 3: HCV alone*	*Group 4: Uninfected controls*	P-*value*[a]
Number	79	62	50	109	—
Male (%)[b]	64 (81)	34 (54)	44 (88)	59 (54)	—
Age, years	42 (7)	40 (9)	37 (9)	37 (11)	0.010
Smoker (%)	61 (77)	31 (50)	49 (98)	63 (58)	<0.0001
Alcohol ⩾ 1 drink per day	2 (2.5)	0 (0)	7 (14)	5 (5)	0.006
BMI, $kg\,m^{-2}$	26.8 (3.7)	28.1 (8.0)	26.1 (4.4)	29.1 (6.0)	0.006
Fat-free mass, kg in men	60 (7.4)	57 (7.5)	59 (7.4)	60 (9)	0.20
Fat-free mass, kg in women	43 (5)	44 (10)	46 (5)	46 (7)	0.52
Body fat, % in men	23 (7)	21 (9)	23 (8)	25 (8)	0.056
Body fat, % in women	36 (6)	38 (11)	32 (8)	36 (10)	0.54
Diabetes (%)[c]	4 (5)	7 (11)	1 (2)	2 (2)	0.24
Estimated years with HCV	23 (10)	NA	16 (11)	NA	0.0013
ALT, U/l	44 (29, 68)	26 (20, 33)	41 (29, 80)	21 (18, 32)	<0.0001
C-reactive protein, mg/l[d]	2.1 (0.6, 4.5)	2.5 (0.9, 6.0)	3.0 (0.8, 5.2)	2.1 (0.8, 4.9)	0.63
Cholesterol, mg/dl	158 (44)	179 (44)	163 (36)	185 (161, 220)	<0.0001
Vitamin A from food, μg/day[d]	975 (632, 1415)	925 (545, 1341)	927 (612, 1475)	981 (623, 1687)	0.76
Vitamin E from food, IU/day[d]	12 (8, 17)	10 (7, 15)	11 (6, 17)	12 (8, 17)	0.19
Carotenoids from food, μg/day[d]	11583 (7402, 17767)	9062 (6093, 17856)	10093 (6544, 13570)	11912 (7463, 18815)	0.10
Selenium from food, μg/day[d]	119 (79, 166)	86 (69, 120)	109 (88, 151)	121 (84, 178)	0.034
Supplement use (%)	32 (41)	27 (44)	13 (26)	30 (28)	0.058
HIV$^+$*only*					
Years with HIV	11 (5)	9 (4)	NA	NA	0.0027
AIDS (%)	23 (29)	11 (18)	NA	NA	0.12
CD4 count, cells/μl	376 (253)	438 (280)	NA	NA	0.17
CD4 < 200 cells/μl (%)	19 (24)	12 (20)	NA	NA	0.54
Viral load ($\log_{10}$ U)	3.3 (1.2)	3.3 (1.2)	NA	NA	0.89
HAART use (%)	41 (52)	40 (63)	—	—	0.13

ALT, alanine amino transferase; BMI, body mass index; HAART, highly active antiretroviral therapy; HCV, hepatitis C; NA, not applicable.
[a]*P*-value for difference in proportions by χ^2 or Fisher's exact test or *F*-test for continuous variables.
[b]ND: statistical testing not done as differences were a function of the recruitment strategies.
[c]Data do not include 64 healthy control participants.
[d]Median (25th and 75th percentiles).
Values in brackets are SD or % or 25^{th}, 75^{th} percentiles.

Table 2: Micronutrient status in relation to infection with HIV and/or chronic HCV

	HIV and HCV	*HIV alone*	*HCV alone*	*Healthy*[a]	P-*value*[b]
Number in group	79	62	50	64	—
Retinol, μg/dl[c]	41 (31, 51)	51 (43, 60)	38 (30, 45)	44 (42, 54)	—
Retinol < 30 μg/dl (%)	17 (22)	1 (3)	13 (26)	2 (3)	<0.0001
α-tocopherol, μg/dl[c,d]	832 (549, 1025)	906 (739, 1293)	610 (560, 820)	743 (605, 921)	—
α-tocopherol < 500 μg/dl (%)[d]	12 (15)	3 (5)	8 (16)	5 (8)	0.12
Carotenoids, μg/dl [c,d]	59 (39, 87)	88 (67, 121)	65 (45, 91)	104 (76, 135)	—
Carotenoids < 29.5[e,d] μg/dl (%)	11 (14)	3 (5)	5 (10)	0 (0)	0.0042
Selenium, μg/l[c]	95 (84, 109)	102 (95, 111)	101 (91, 118)	109 (98, 124)	—
Selenium < 85 μg/l (%)	22 (28)	4 (6)	9 (18)	6 (9)	0.0024

HCV, hepatitis C; HIV, human immunodeficiency virus.
[a]HIV-uninfected drug users without chronic hepatitis were not included (n=45).
[b]Fisher's exact test for differences in proportions (— indicates that statistical tests were not done).
[c]Median (25th and 75th percentiles).
[d]α-tocopherol and carotenoid values were not adjusted for lipids.
[e]29.5 μg/dl is the 5th percentile for the US general population level of serum carotenoids from NHANES III survey 1988–1994.
Values in brackets are % or 25th, 75th percentiles.

Table 3: Results of multivariate analyses of predictors of serum micronutrients

Micronutrient	*Retinol (μg/dl)*	*α-tocopherol (ln μg/dl)*	*Carotenoids (μg/dl)*	*Selenium (μg/l)*
	Estimate (s.e.m.)	*Estimate (s.e.m.)*	*Estimate (s.e.m.)*	*Estimate (s.e.m.)*
Intercept[a]	40.5 (1.8)**	6.5 (0.045)**	96.0 (4.7)**	110 (3.1)**
Male	6.0 (1.7)**	0.11 (0.043)*	12.0 (4.4)***	4.7 (2.9)
Age, years	−0.014 (0.081)	0.0055 (0.0020)***	0.22 (0.21)	−0.057 (0.14)
HIV	7.2 (1.6)**	0.20 (0.040)**	−4.5 (4.2)	−6.1 (2.8)*
HCV	−8.2 (1.9)**	−0.10 (0.045)*	−19.8 (4.7)**	−4.9 (3.1)
Drug use	−2.5 (1.8)	0.036 (0.044)	−7.3 (4.5)	−1.7 (3.0)
BMI, kg m^{-2}	0.080 (0.14)	0.00056 (0.0033)	−0.48 (0.34)	−0.0083 (0.23)
Diabetes	−0.86 (3.5)	0.0052 (0.087)	−4.6 (9.0)	−4.1 (6.0)
Alcohol, >1 drink per day	7.6 (3.5)*	−0.012 (0.087)	5.6 (9.0)	−1.2 (6.0)
Smoker	1.4 (1.8)	−0.0034 (0.044)	−6.9 (4.6)	−4.4 (3.0)
Diet[b]	1.2 (1.1)	−0.033 (0.028)	8.4 (2.6)***	0.59 (2.2)
Supplement use	1.8 (1.6)	0.17 (0.039)**	1.9 (4.0)	−0.23 (2.7)
CRP (ln mg/l)	−2.2 (0.60)**	−0.0091 (0.015)	−4.8 (1.5)***	−1.4 (1.0)
Cholesterol, mg/dl	0.088 (0.018)**	0.0048 (0.00045)**	0.39 (0.046)**	0.037 (0.031)

BMI, body mass index; CRP, C-reactive protein; HCV, hepatitis C; HIV, human immunodeficiency virus.

[a]Intercept is interpreted as the average serum micronutrient level in female, HIV-uninfected, **HCV**-uninfected, non-smokers, non-drug users, without diabetes who do not use vitamins and have the average age, BMI, dietary intake of the micronutrient and the average CRP and cholesterol level of the cohort.

[b]Source of the micronutrient from food as reported by food frequency questionnaire.*$P<0.05$, **$P<0.001$, ***$P<0.01$.

Values in brackets are s.c.m.

for carotenoids, and 18 per cent (26/141) for selenium. In contrast, when we stratified the results by infection status, the prevalence of low values among participants with HIV monoinfection did not differ remarkably from healthy controls, whereas low values were common in those with HCV infection (Table 2).

The factors associated with the individual serum micronutrients in multivariate analyses are shown in Table 3. Infection with HIV was associated with a higher serum vitamin A and vitamin E, but lower selenium compared with uninfected controls. Chronic HCV infection was associated with lower serum vitamin A, vitamin E, and carotenoids. There was no evidence of an interaction effect between HIV and HCV for any micronutrient. Alcohol (more than one serving per day) was associated with higher vitamin A. Supplement use, but not food, was associated with higher serum vitamin E, whereas serum carotenoids were influenced by dietary carotenoids, but not by supplements. Accounting for fasting state did not alter the conclusions. Treatment with ART, CD4 cell count, and HIV viral load were not predictors of micronutrient status in HIV-infected participants.

When we replaced the term for cholesterol in the models shown in Table 3 with a term for triglycerides, triglycerides were significantly associated with vitamin A (6.8 μg/dl, s.e.m. = 1.4, $P < 0.0001$), and HIV infection was no longer associated with higher vitamin A (3.0 μg/dl, s.e.m. = 1.9, $P = 0.11$). Similarly, triglycerides were significantly associated with vitamin E (0.0017 ln μg/dl, s.e.m. = 0.00016, $P < 0.0001$), but the association of HIV infection with higher vitamin E was no longer significant in the model that included a term for triglycerides (0.052 ln μg/dl, s.e.m. = 0.046, $P = 0.26$). Carotenoids and selenium were not significantly associated with triglycerides.

Discussion

Our study shows that chronic HCV coinfection is an important determinant of lower serum vitamin A, vitamin E, and carotenoids, independently of acute phase reaction, in persons with clinically stable HIV infection. Though it has long been recognized that hepatic disease leads to low serum vitamin A,[15–17,33] this effect has not been well described in the context of HIV infection.

Studies of HIV-infected persons with a low representation of drug users (<10 per cent) have shown a low prevalence of serum micronutrient deficiencies.[11–14] Studies with a greater representation of drug users (>20 per cent) consistently show deficiencies, with rates of vitamin A deficiency varying from 15 to 80 per cent.[6–10] Baum and Shor-Posner[34] compared micronutrient deficiencies in HIV-infected drug users and homosexual men. Deficiencies in vitamin A, vitamin E, and selenium were more common in drug users, at 55 per cent, 47 per cent, and 7 per cent, respectively, compared with homosexual men in whom the corresponding rates of deficiency were 10, 18, and 11 per cent. Our data show that the high rate of micronutrient deficiencies seen in drug users is associated with chronic HCV infection rather than with dietary deficiencies, drug use, or HIV infection.

The depressive effect of HCV infection on serum micronutrients is of concern because a block in micronutrient metabolism in the liver may lead to functional deficiencies. Carney and Russell.[35] found in patients with hepatic and gastrointestinal disease that 71 per cent of patients with serum vitamin A < 30 μg/dl had night blindness, a level of deficiency consistent with immune dysfunction Overall, 41 (14 per cent) of our participants had serum vitamin A below 30 μg/dl. Low serum vitamin A has been associated with a 5–6-fold increased risk of mortality in HIV-infected drug users.[6] However, it is not clear that micronutrient supplementation would result in an appropriate serum response in the presence of chronic HCV infection, or whether hepatic disease might block micronutrient metabolism. In the presence of liver damage, supplementation may even be harmful.[33] There is a need to clarify the safety and efficacy of micronutrient supplementation in the presence of chronic HCV infection.

When we included known predictors of serum micronutrients in multivariate models, HIV was associated with higher serum vitamins A and E. Tang *et al*[36] found that HIV-infected drug users had significantly higher vitamin E compared with HIV-uninfected drug users, an effect the investigators attributed to protease inhibitor therapy. Protease inhibitor therapy is associated with elevated triglycerides.[19]In our study, higher vitamin E in HIV infection was explained by higher triglycerides, but not by ART. Because the metabolism of vitamins E and A, and lipids are interrelated,[20–22] lipid elevations induced by ART may elevate serum micronutrient levels.

Among the micronutrients examined here, we found HIV infection to be independently associated only with lower selenium. Baum *et al*[10] showed that selenium $<85\ \mu g/l$ was associated with a high risk of mortality in HIV patients. A randomized controlled trial of selenium supplementation found that HIV patients who had a positive serum response to selenium supplementation had a better controlled HIV viral load and improved CD4 cell counts compared with placebo-treated patients.[37] These data suggest a clinically important relationship of selenium to HIV disease progression that warrants further investigation, including studies to establish whether selenium can be of benefit to HIV/HCV coinfected persons.

In this study, drug use was not a predictor of alterations in serum micronutrients once HCV infection was accounted for. Alcohol use was associated with significantly higher serum vitamin A. Alcohol has been associated with higher vitamin E and selenium in an earlier population-based study, [38] and thus, is not always associated with poor micronutrient status.

We recruited participants from the community, and therefore, our estimates are likely a good reflection of the target population. Because the diet of Hispanics differs from that of other racial/ethnic groups, the estimates of specific nutrient deficiencies may not be generalizable. The results pertaining to the effects of chronic HCV infection on serum micronutrients, however, should be widely generalizable. In the United States, ART has been available for over a decade, and the food supply is increasingly fortified with micronutrients. For these reasons, we have not compared our study to those conducted in areas of the world where access to ART is limited and malnutrition is common.

Weakness of our study includes the lack of information on the stage of liver disease. We may have misclassified self-reported lifestyle habits, which would underestimate associations. As we used an FFQ to measure dietary intake, we were unable to quantify specific micronutrient intakes.

In conclusion, our results show that HCV coinfection is an important determinant of micronutrient deficiencies in the context of HIV infection. Our data further suggest that the presence of HCV coinfection may confound the nutritional assessment of HIV-infected individuals. The extent to which this has affected our general understanding of the problem of micronutrient deficiencies in HIV infection is unknown.

Our results have implications for policies related to the nutritional requirements of persons living with HIV/AIDS. Recommendations for nutritional assessment should include an evaluation of HCV infection status in areas of the world where HIV/HCV coinfection is common. Dietary supplementation should be approached with caution until there is a better understanding of how HCV infection alters the metabolism of micronutrients, and how these alterations impact the progression of HIV and HCV infections.

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