

Elevated homocysteine levels in human immunodeficiency virus-infected patients under antiretroviral therapy: A meta-analysis

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Abstract

AIM: To evaluate the association between the levels of homocysteine (Hcy), folate, vitamin B12 in human immunodeficiency virus (HIV)-infected patients who were treated with antiretroviral therapy (ART) or not treated with ART.

METHODS: The PubMed and Scielo databases were searched. Eligible studies regarding plasma Hcy level in HIV-infected patients were firstly identified. After careful analysis by two independent researches, the identified articles were included in the review according to two outcomes (1) Hcy, folate and vitamin B12 blood concentration in HIV-infected subjects *vs* health controls and; (2) Hcy blood concentration in HIV-infected subjects under ART *vs* not treated with ART. RevMan (version 5.2) was employed for data synthesis.

RESULTS: A total of 12 studies were included in outcome 1 (1649 participants, 932 cases and 717 controls). Outcome 1 meta-analysis demonstrated higher plasma Hcy (2.05 $\mu\text{mol/L}$; 95%CI: 0.10 to 4.00, $P < 0.01$) and decreased plasma folate concentrations (-2.74 ng/mL; 95%CI: -5.18 to -0.29, $P < 0.01$) in HIV-infected patients compared to healthy controls. No changes in vitamin B12 plasma concentration were observed between groups. All studies included in the outcome 2 meta-analysis (1167 participants; 404 HIV-infected exposed to ART and 757 HIV-infected non-ART patients) demonstrated higher mean Hcy concentration in subjects HIV-infected under ART compared to non-ART HIV subjects (4.13 $\mu\text{mol/L}$; 95%CI: 1.34 to 6.92, $P < 0.01$).

CONCLUSION: This meta-analysis demonstrated that the levels of Hcy and folate, but not vitamin B12, were associated with HIV infection. In addition, Hcy levels were higher in HIV-infected patients who were under ART compared to HIV-infected patients who

were not exposed to ART. Our results suggest that hyperhomocysteinemia should be included among the several important metabolic disturbances that are associated with ART in patients with HIV infection.

Key words: Antiretroviral therapy; Homocysteine; Folate; Vitamin B12; Human immunodeficiency virus; Acquired immune deficiency syndrome

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Core tip: Although antiretroviral therapy (ART) has changed dramatically the speciation of life of human immunodeficiency virus (HIV)-infected patients, it has increased the incidence of chronic diseases, especially cardiovascular diseases. Nowadays, elevated levels of homocysteine have been considered to be an independent risk factor for cardiovascular disease development. Our study demonstrated that the levels of Hcy and folate, were associated with HIV infection, especially for those exposed to ART.

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INTRODUCTION

The introduction of antiretroviral therapy (ART) has changed the spectrum of human immunodeficiency virus (HIV) infections, reducing the risk of opportunistic infections and substantially reducing mortality rates^[1]. Although ART has changed HIV infection from an acute to a chronic disease, this therapy has increased the incidence of cardiovascular disease (CVD) among HIV-infected subjects^[2], associated with the presentation of risk factors, such as dyslipidemia, insulin resistance, and lipodystrophy, among others. Development of these risk factors may be due to HIV infection itself or ART-associated toxicity^[3]. Epidemiological studies have demonstrated an increased incidence of myocardial infarction, atherosclerotic disease, and mortality in HIV-infected patients compared to noninfected individuals, especially when exposed to ART^[4-7].

Since McCully *et al.*^[8] firstly demonstrated elevated incidence of homocystinuria in patients with severe atherosclerosis and arterial thrombosis, elevated levels of homocysteine (Hcy) have been considered to be an independent risk factor for CVD development^[9,10]. Recently, several studies have demonstrated an association between hyperhomocysteinemia (HHcy) and a spectrum of diseases, including neurodegenerative diseases, diabetes, chronic kidney disease, and fatty liver disease^[11-15]. Much of this association has been

attributed to the characteristics of Hcy, which is a potent toxic agent that may increase oxidative stress and promote neurotoxicity, endothelial dysfunction, and accelerate the atherosclerotic process^[16-19]. Hcy is an amino acid formed exclusively by demethylation of methionine^[10]. In Hcy synthesis, methionine is activated by ATP to form S-adenosylmethionine (SAM). SAM acts primarily as a universal methyl donor in the synthesis of methylated compounds such as neurotransmitters (epinephrine, norepinephrine), DNA, RNA, phosphatidylcholine and creatine^[11]. A subproduct of these methylation reactions is S-adenosylhomocysteine, which is hydrolyzed to adenosine and Hcy^[10]. Hcy can be remethylated to form methionine by the action of the enzyme methionine synthase which uses *N*^{5,10}-methylene-THF-reductase (MTHFR) as a methyl donor. Vitamins B12 and folate are co-factors in this reaction. The catabolism of methionine is performed by transsulfuration, with Hcy reacting with serine to form cystathionine in an irreversible reaction catalyzed by cystathione-β-synthase and dependent of vitamin B6^[16].

Owing to their involvement in the Hcy remethylation pathway, vitamin B12 and folate deficiencies have been associated with elevated Hcy concentrations^[20,21]. However, studies examining this association in HIV patients have reported conflicting results. Folate and vitamin B12 deficiencies have been reported in HIV-infected patients due to low intake and/or malabsorption^[22,23]. Remacha *et al.*^[23] demonstrated that HIV-infected subjects with low serum vitamin B12 and red blood cell folate concentrations had HHcy. In contrast, studies found no changes in folate and vitamin B12 levels during follow-up after ART^[24-26].

Given the inconsistency of the existing literature and the insufficient statistical power of primary studies, we conducted a meta-analysis to clarify the relationship between the levels of Hcy, folate, and vitamin B12 in HIV-infected patients. We also investigated the relationship between Hcy levels in HIV-infected patients who were treated with ART or not treated with ART.

MATERIALS AND METHODS

The PubMed and Scielo databases were searched for English- or Spanish-language articles, by using the following keywords: "homocysteine," "HIV-infected," and "AIDS". Any case-control, cross-sectional, or cohort study that assayed the blood concentrations of Hcy, vitamin B12, or folate in HIV-infected patients was analyzed. After careful analysis by two independent researchers, identified articles were included in the review if they satisfied the following criteria: (1) contained human clinical outcomes (rather than outcomes from animal experiments); (2) used a case-control, cross-sectional trial or cohort design; (3) contained quantitative information regarding Hcy, vitamin B12, or folate plasma or serum concentrations; and (4) included a healthy

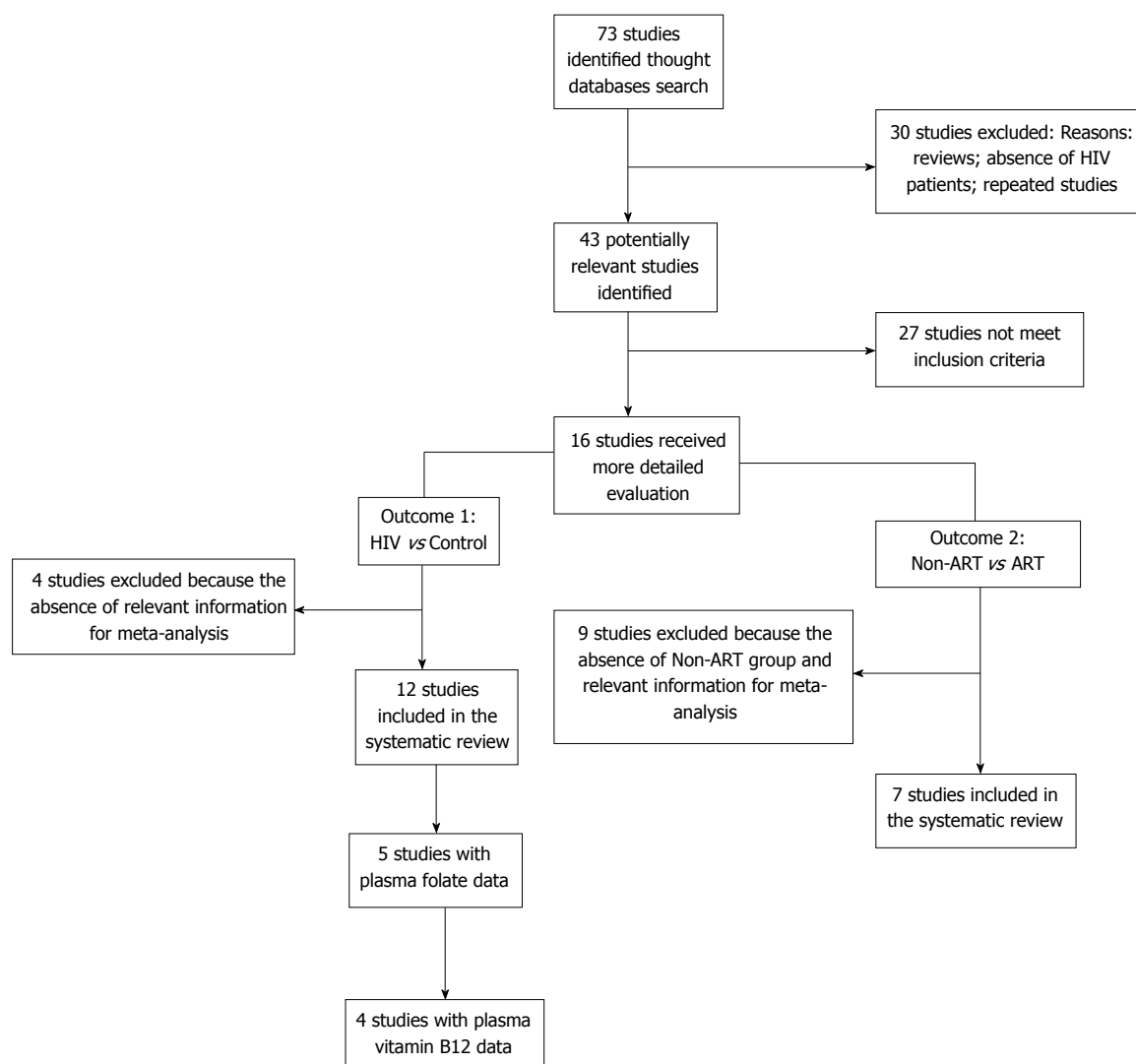


Figure 1 PRISMA flow diagram of the study selection process. After careful discussion between the 3 reviewers, two outcomes were identified and included in the meta-analysis. HIV: Human immunodeficiency virus; ART: Antiretroviral therapy.

control group. Relevant articles that were cited in the publications were reviewed and included in the meta-analysis if they satisfied the inclusion criteria.

The search was conducted considering two main outcomes: (1) Hcy blood concentrations in HIV-infected subjects compared to healthy controls; and (2) Hcy blood concentrations in HIV-infected individuals who were treated by ART compared to HIV-infected individuals who were not treated by ART (HIV-infected ART vs non-ART groups, Figure 1). A subgroup of outcome 1 was created to determine the vitamin B12 and folate plasma concentrations in HIV-infected individuals compared to healthy controls. The selection process is described in Figure 1.

For all articles included in the meta-analyses for the two outcomes, the following data were extracted: authors and year of publication; country where the study was conducted; study design; number of subjects in the study; plasma/serum concentrations of Hcy, vitamin B12, percent of each group with HHcy; and folate in HIV-infected and control subjects. Inclusion of studies in

the meta-analyses was discussed by the 3 authors. All meta-analysis procedures were conducted as described by Stroup *et al*^[27].

Statistical analysis

Effects of HIV infection on the Hcy blood concentration were quantified by performing meta-analyses for the two outcomes described above with the RevMan software package (version 5.0). In outcome 1, two subgroup analyses were performed to assess the impact of HIV on the folate and vitamin B12 plasma concentrations. RevMan was used to calculate the weighted mean difference. The 95%CI was employed for presenting the statistical results for continuous outcomes. Weighted percentages were based on the sample sizes of respective studies. Differences with a P value < 0.05 were considered to be statistically significant. Study heterogeneity was evaluated by the I^2 statistic. All meta-analyses were considered to be of high heterogeneity ($I^2 > 75\%$), and the random-effects model was used^[28]. All data were analyses with

Table 1 Characteristics of studies included in the outcome 1

Ref.	Country	Sample size (Control/HIV)	Study design	Hcy ($\mu\text{mol/L}$)		HHcy	Folate (ng/mL)/Vitamin B12 (pg/mL)	
				Control	HIV		Control	HIV
Castagna <i>et al</i> ^[29]	Italy	20/14	CS and CC of some patients	10.8 \pm 3.8	6.0 \pm 2.2	-	-	-
Muller <i>et al</i> ^[30]	Norway	15/21	CS	9.2 \pm 7.3	9.0 \pm 5.0	-	-	-
Naisbitt <i>et al</i> ^[31]	England	33/33	CS	11.9 \pm 4.7	14.5 \pm 5.6	-	-	-
Bernasconi <i>et al</i> ^[32]	Swaziland	80/73	COS	7.6 \pm 3.6	8.7 \pm 4.1	5% control; 12.3% HIV	-	-
Vilaseca <i>et al</i> ^[33]	Spain	170/69	COS	6.2 (4.0-10.4) ²	9.9 (5.5-23.3) ²	50.7% HIV	Folate 19.1 \pm 7.5/ B12 455 \pm 160 ¹	Folate 12.6 \pm 6.7/ B12 481 \pm 181 ¹
de Larrañaga <i>et al</i> ^[34]	Argentina	31/128	CS	9.0 (7.2-13.0) ²	9.0 (6.5-12.7) ²	12.9% control; 16.4% HIV	Folate 2.5 (2.1-3.1) ² /B12 309 (268-477) ²	Folate 3.6 (2.5-5.6) ² /B12 337.4 (222-493) ²
Remacha <i>et al</i> ^[23]	Spain	128/235	CS	7.5 \pm 7.8	14.3 \pm 12.9	6.2% control;	-	B12 368.6 \pm 219
Raiszadeh <i>et al</i> ^[35]	United States	127/249	COS	7.2 \pm 2.7	7.4 \pm 2.7	13.4% control; 16.90%	-	-
Vigano <i>et al</i> ^[36]	Italy	19/23	CS	9.0 \pm 5.0	11.0 \pm 8.0	-	Folate 6.9 \pm 1.7	Folate 4.7 \pm 1.5
Abdollahi and Shoar ^[37]	Iran	58/58	CC	12.6 \pm 1.1	27.1 \pm 10.2	91.4% HIV	-	-
Borges-Santos <i>et al</i> ^[38]	Brazil	20/12	CC	13.9 \pm 5.5	9.8 \pm 1.6	-	Folate 7.5 (6.3-9.0) ² /B12 288 \pm 130	Folate 1.9 (1.4-6.6) ² /B12 367 \pm 139
Deminice <i>et al</i> ^[39]	Brazil	10/23	CS	6.6 \pm 1.5	9.4 \pm 2.7	0% controls; 30.4% HIV	Folate 11.7 \pm 3.4/ B12 713.1 \pm 110.1	Folate 7.0 \pm 2/B12 514.6 \pm 99.3

¹Folate and vitamin B12 determined in 56 controls and 69 HIV-infected patients only. Values in Hcy, folate and vitamin B12 are expressed as mean \pm DP; ²Values expressed as range (25th-75th percentiles). CC: Case-control; CS: Cross-sectional; COS: Cohort study; Hcy: Homocysteine; HHcy: Hyperhomocysteinemia; HIV: Human immunodeficiency virus.

a biostatistician support.

RESULTS

Outcome 1

The initial search was independently executed by two reviewers, resulting in the selection of 73 articles. Reviews, repeated studies, and studies conducted in the absence of a control group identified 43 relevant studies. Screening by title and abstract was conducted in accordance with inclusion criteria. After extensive discussions between the authors, 16 articles were identified and included in the meta-analyses. Studies were included in either outcome 1 or 2, as described in Figure 1.

Twelve studies were included in the meta-analysis for outcome 1. Table 1 describes the characteristics of the 12 studies included in outcome 1. Four of the 16 selected studies were excluded because of the absence of a control group^[40,41,42,43]. These studies included 1649 participants (932 HIV-infected patients and 717 healthy controls). Nine of the 12 studies reported that the mean Hcy concentration was greater in HIV-infected individuals compared to controls. Only five^[33,34,36,38,39] and four^[33,36,38,39] of the included studies described quantitative folate and vitamin B12 data, respectively (Table 1).

A meta-analysis performed on outcome 1 indicated that the plasma Hcy levels in HIV-infected patients were 2.05 $\mu\text{mol/L}$ higher than the plasma Hcy levels in uninfected controls (95%CI: 0.13-4.01, $P < 0.01$;

Figure 2).

Subgroup analyses on folate and vitamin B12 plasma concentrations between test groups (Figure 3) demonstrated plasma folate levels were -2.74 ng/mL decreased in HIV-infected patients compared to uninfected controls (95%CI: -5.18 - -0.29, $P < 0.01$), but no significant difference in the B12 concentration between the two groups. Funnel plot analysis did not show evidence of substantial publication bias for the association between Hcy level and HIV infection.

Outcome 2

Nine of the 16 studies selected were excluded from outcome 2 because of the absence of an HIV-infected non-ART group^[29,30-33,36-39] (Figure 1). Table 2 describes the characteristics of the 7 studies included in outcome 2. These studies included 1167 participants (404 patients in the HIV-infected ART group and 757 patients in the HIV-infected non-ART group). All studies included in the meta-analysis for outcome 2 described a higher mean Hcy concentration in the HIV-infected ART group compared to the HIV-infected non-ART group (4.13 $\mu\text{mol/L}$; 95%CI: 1.34-6.92, $P < 0.01$; Figure 4).

DISCUSSION

Overall, we found that HIV infection and ART were significantly associated with elevated plasma Hcy levels. The pooled mean Hcy concentration was greater in HIV-infected subjects compared to healthy controls. Hcy blood concentrations were elevated among HIV-infected

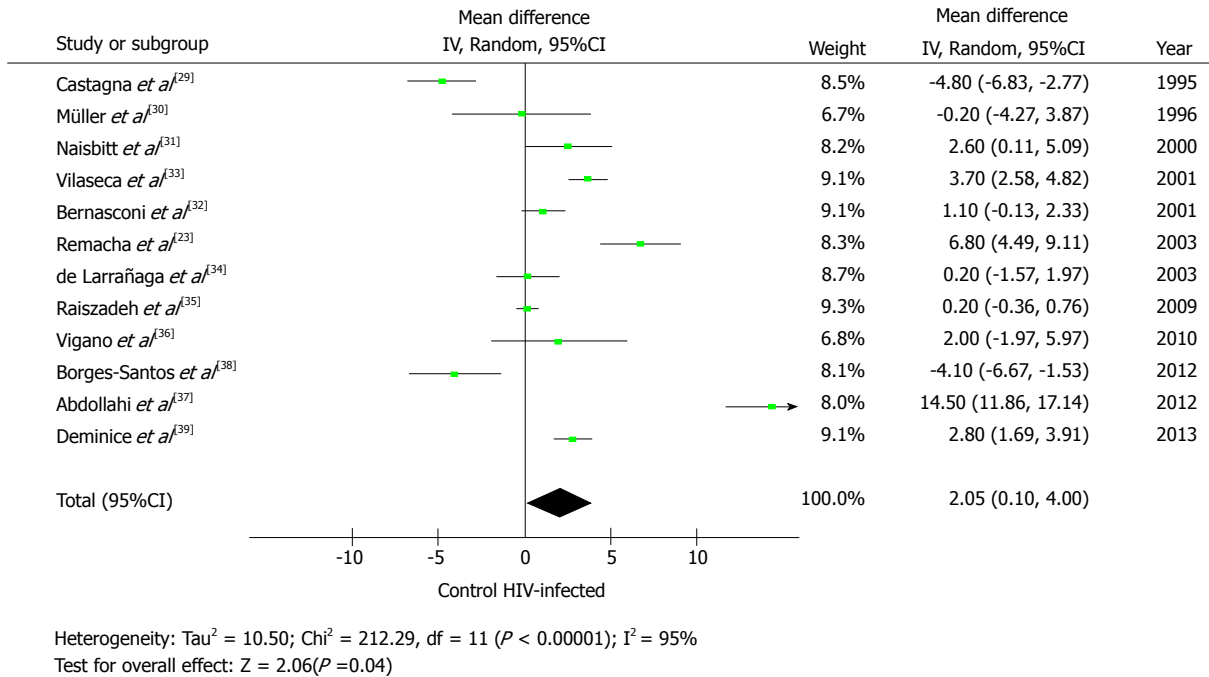


Figure 2 Meta-analysis of blood homocysteine concentration in human immunodeficiency virus-infected subjects compared with healthy controls. Calculation based on random effects model. Results are expressed as weighted mean difference of homocysteine ($\mu\text{mol/L}$) and 95%CI. HIV: Human immunodeficiency virus.

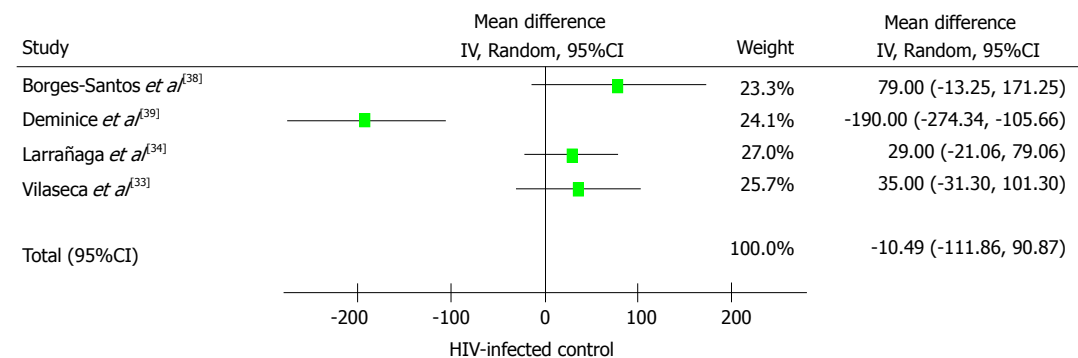
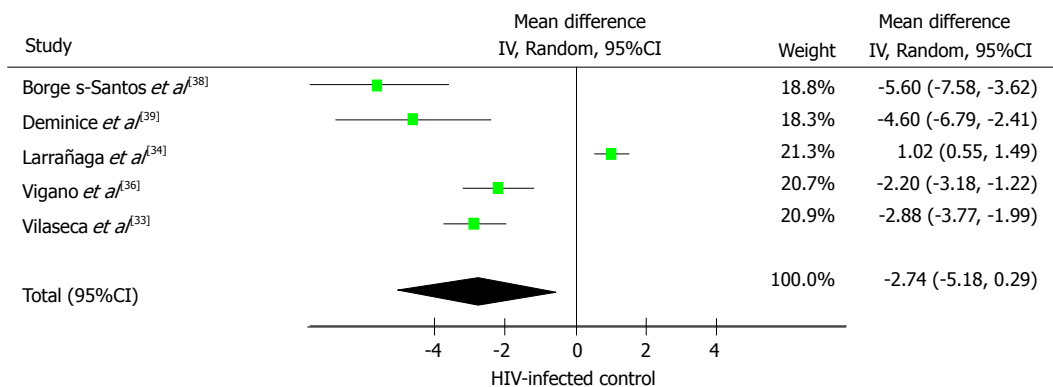
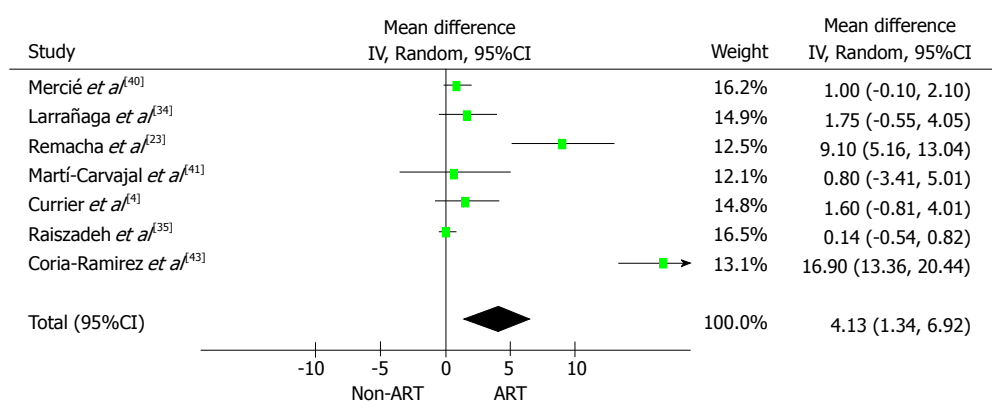


Figure 3 Meta-analysis of serum folate and vitamin B12 levels in human immunodeficiency virus-infected subjects compared with healthy controls. Calculation based on random effects model. Results are expressed as weighted mean difference of folate (pg/mL) and vitamin B12 (pg/mL) and 95%CI.

Table 2 Characteristics of studies included in the outcome 2

Ref.	Country	Sample size (Control/HIV)	Study design	Hcy ($\mu\text{mol/L}$)		HHcy	ART
				ART	Non-ART		
Mercié <i>et al</i> ^[42]	France	78/304	COS	12.5 \pm 4.8	11.5 \pm 4.3	-	-
de Larrañaga <i>et al</i> ^[24]	Argentina	31/128	CS	9.7 \pm 7.1	8.0 \pm 6.1	-	-
Remacha <i>et al</i> ^[23]	Spain	128/235	CS	17.3 \pm 13	8.2 \pm 7.8	-	Patients under ART (taking > 3 antiretroviral drugs)
Martí-Carvajal <i>et al</i> ^[41]	Venezuela	14/40	CS	10 \pm 7.5	9.2 \pm 6.7	48.6% non-ART; 45.5% ART	-
Currier <i>et al</i> ^[42]	United States	40/41	COS	9.6 \pm 5	8.0 \pm 6.1	-	Patients on ART including a PI continuously for 2 yr
Raiszadeh <i>et al</i> ^[35]	United States	127/249	COS	7.5 \pm 2.8	7.3 \pm 2.4	-	-
Coria-Ramirez <i>et al</i> ^[43]	Mexico	69/69	CC	24.8 \pm 14.6	7.9 \pm 3.4	7.3% non-ART; 79.9% ART	Patients who began ART and maintained the treatment for 6 mo

CC: Case-control; CS: Cross-sectional; COS: Cohort study; Hcy: Homocysteine; HHcy: Hyperhomocysteinemia; PI: Protease inhibitors; ART: Antiretroviral therapy.



Heterogeneity: $\tau^2 = 12.18$; $\chi^2 = 100.52$, $df = 6$ ($P < 0.00001$); $I^2 = 94\%$

Test for overall effect: $Z = 2.90$ ($P = 0.004$)

Figure 4 Meta-analysis of blood homocysteine concentration in human immunodeficiency virus-infected exposed and non-exposed to antiretroviral therapy. Calculation based on random effects model. Results are expressed as weighted mean difference of homocysteine ($\mu\text{mol/L}$) and 95%CI. ART: Antiretroviral therapy.

patients who were exposed to ART compared to patients who were not exposed to ART. In addition, HIV-infected patients presented decreased plasma levels of folate, but not vitamin B12. These findings provide consistent evidence that Hcy and folate levels are associated with HIV infection, especially when patients are also receiving ART.

Studies in rodents and *in vitro* have demonstrated that HHcy may be associated with decreased nitric oxide bioavailability and endothelial dysfunction^[44], altered cellular methylation, formation of Hcy adducts (e.g., Hcy-thiolactone), and oxidative stress. These perturbations are linked to cell toxicity^[16], in addition to atherosclerosis and thrombotic processes^[17-19]. In humans, a total Hcy level of 14.3 $\mu\text{mol/L}$ or greater was independently associated with a relative risk of mortality (54% for all-cause mortality and 52% for cardiovascular mortality)^[21,45]. Humphrey *et al*^[46] demonstrated that each increase of 5 $\mu\text{mol/L}$ in Hcy levels increased the risk of cardiovascular events by approximately 20%. However, previous studies have provided conflicting results regarding circulating Hcy levels in HIV-infected patients.

In nine of the 12 studies included in the meta-analysis of outcome 1, the mean Hcy concentrations were greater in HIV-infected subjects compared to levels in healthy controls. Our meta-analysis demonstrated that the plasma Hcy levels in HIV-infected patients were 2.05 $\mu\text{mol/L}$ higher compared to levels in healthy controls. This observation is particularly relevant considering the heterogeneity of patients included in those studies with regard to the disease stage, ART status, comorbidities, and gender, among others. Considering the relationship between the Hcy level and ART status, we observed that the Hcy levels were higher by an average of 4.13 $\mu\text{mol/L}$ in HIV-infected subjects who were exposed to ART compared to HIV-infected patients who were not exposed to ART.

ART is a causal factor of increased cardiovascular risk in HIV-infected subjects. ART promotes different metabolic disturbances, including hepatic and neurotoxicities, lipodystrophy syndrome, hyperlactatemia, hyperlipidemia, and insulin resistance^[47,48]. The present study demonstrates that HHcy can be included on this list. Different classes of antiretroviral drugs and time exposed to the treatment may generate different ART-

associated adverse metabolic effects^[47,49]. However, a lack of data in the revised papers prevents us from determining the contributions of different drug classes and durations of ART on Hcy levels (Table 2).

Although the precise mechanisms by which HIV infection and ART affect Hcy metabolism are not known, the vitamin B12 and folate levels have been shown to affect Hcy levels in HIV-infected patients^[23,50]. Specifically, Hcy levels are inversely related to the daily intake of folate and vitamin B12 in general population^[20,21]. That is because Hcy remethylation to methionine by methionine synthase requires folate^[10]. However, this association appears to be different in the context of HIV infection. Remacha *et al.*^[23] identified HHcy in 100% and 51.5% of HIV-infected patients who had erythrocyte folate concentrations below the 2.5th and 10th percentiles, respectively. In our results, decreased levels of plasma folate, but not vitamin B12, were associated with elevated Hcy levels in HIV-infected subjects. Deminice *et al.*^[39] demonstrated that folate intake was higher in HIV-infected patients compared to healthy controls. Coria-Ramirez *et al.*^[43] noted that nutritional abnormalities, such as decreased vitamin B12 and folate intake, were not responsible for the high incidence of HHcy observed in HIV-infected patients. Taken together, these findings suggest that disturbances in Hcy metabolism and the Hcy levels observed in HIV-infected patients may not be due to nutritional status. Instead, it may be that HIV and/or ART complications are linked to disturbances in Hcy metabolism. One possibility is that ART impairs the metabolism of Hcy, such as its remethylation or transsulfuration because both pathways may be affected^[43]. However, to the best of our knowledge, here are no studies demonstrating ART modify Hcy metabolism enzymes. It is probably because liver biopsies are an invasive procedure with a relatively high risk of complications. Animal models could enable studies on ART and Hcy metabolism however; few studies have tested ART in animal models.

This study has some limitations that need to be considered. First, only a few of the included studies analyzed HIV-infected patients in the context of Hcy metabolism. This fact contributed to the lack of clinical homogeneity among subjects of the included studies. Most of the studies did not consider the nature or duration of the ART that was administered. Most studies excluded the effects of comorbidities and diseases that may have affected Hcy levels (*e.g.*, kidney disease). Second, many studies did not include information regarding vitamin levels, or assessed folate plasma levels of determining folate status. Plasma folate levels may not be the best parameter for assessing folate deficiency or intake^[43,51,52]. Erythrocyte folate or serum methylmalonic acid levels are better indicators of folate status, because they reflect folate turnover over the preceding 2 to 3 mo^[23,43]. Lamarre *et al.*^[52] recently showed that formate levels provide important information regarding folate metabolism, and that increased Hcy levels can be caused by defects in the

remethylation and transsulfuration pathways. Finally, some studies have demonstrated an association of the MTHFR polymorphisms and HHcy in different cases and diseases. However, this association was not considered in our included studies.

In conclusion, the levels of Hcy and folate, but not vitamin B12, were associated with HIV infection. Hcy levels were higher in HIV-infected patients who were exposed to ART compared to HIV-infected patients who were not exposed to ART. Finally, HHcy can be included among the several important metabolic disturbances that are associated with ART in patients with HIV infection.

COMMENTS

Background

Although antiretroviral therapy (ART) has changed dramatically the speciation of life of human immuno deficiency virus (HIV)-infected patients, it has increased the incidence of metabolic disorders as dyslipidemia, insulin resistance, lipodystrophy and others. Elevated homocysteine (Hcy) levels have been considered to be an independent risk factor for cardiovascular disease development. However, few studies have been considered Hcy levels in HIV-infected patients.

Research frontiers

Elevated Hcy levels have been considered to be an independent risk factor for cardiovascular disease development. Recently, several studies have demonstrated an association between hyperhomocysteinemia (HHcy) and a spectrum of diseases, including neurodegenerative diseases, diabetes, chronic kidney disease, and fatty liver disease. However, few researchers have focused in study Hcy levels HIV-infected patients.

Innovations and breakthroughs

The data demonstrated that the levels of Hcy and folate, were associated with HIV infection, especially for those exposed to ART. That is the first meta analysis carried out in search of a relationship between plasma homocysteine levels and HIV infection.

Applications

HHcy is associated to ART can be included among the several important metabolic disturbances that are associated with ART in patients with HIV infection.

Terminology

Hcy is an S-containing amino acid formed exclusively by demethylation of methionine. Hcy has gained attention in medical field because its instability and toxicity, especially in elevated concentrations.

Peer-review

The topic of manuscript is interesting and valuable. The logical thinking is reasonable and convincing. The reference collection and analysis process described in detailed, it is easy to follow.

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