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Caffeine and Insomnia in People Living With HIV From the Miami Adult Studies on HIV (MASH) Cohort

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Abstract

We explored the relationship between caffeine consumption, insomnia, and HIV disease progression (CD4+ T cell counts and HIV viral loads). Caffeine intake and insomnia levels were measured using the Modified Caffeine Consumption Questionnaire and the Pittsburgh Insomnia Rating Scale (PIRS) in 130 clinically stable participants who were living with HIV, taking antiretroviral therapy, and recruited from the Miami Adult Studies on HIV cohort. Linear regressions showed that caffeine consumption was significantly and adversely associated with distress score, quality-of-life score, and global PIRS score. Linear regression analyses also showed that global PIRS score was significantly associated with lower CD4+ T cell counts and higher HIV viral loads. Caffeine could have precipitated insomnia in susceptible people living with HIV, which could be detrimental to their disease progression states.

Keywords

caffeine; CD4+ T cell count; HIV viral load; insomnia; people living with HIV

Sleep quality is significantly lower in people living with HIV (PLWH), when compared to the general population (Womack et al., 2017). Among clinically stable PLWH, poor sleep quality and increased psychological distress scores have been associated with lower CD4+ T cell counts and higher HIV viral loads after adjusting for the effects of antiretroviral therapy (ART; Ramamoorthy et al., 2017). The Symptom Experience Dimension of the revised University of California San Francisco Symptom Management Conceptual Model showed that sleep quality was adversely affected by anxiety, lower general well-being, number of years living with HIV, and clinical depression (Nokes & Kendrew, 2001). A study of 146 clinically stable PLWH showed that stress levels were significantly associated with deteriorating sleep quality, after adjusting for covariates such as age, sex, ART, other medications, substance use, and income (Vosvick et al., 2004). In addition, better sleep quality was associated with improved cognitive performance on tasks of attention, frontal executive functions, and psychomotor/motor speeds in PLWH, after adjusting for medications, alcohol consumption, and drug use (Gamaldo et al., 2013). Gamaldo and colleagues (2013) also reported that more than one-third of the PLWH participants in their study were chronically and severely sleep deprived.

In a study that investigated the effects of caffeine on cognitive and psychomotor performance as well as sleep quality in HIV-uninfected participants, caffeine in doses of 250 mg/day significantly decreased initial critical flicker fusion threshold scores, signifying higher levels of neuronal excitability (Hindmarch et al., 2000). In a randomized double-blind study of 72 HIV-uninfected participants with various forms of anxiety disorders, oral administration of 480 mg/day of caffeine provoked acute stress responses (Nardi et al., 2009). General stress levels were substantially higher in subjects administered 480 mg/day of caffeine when compared to controls after adjusting for gender, age, education level, occupation, and anxiolytic medications. Four hundred eighty mg of caffeine precipitated panic attacks in 60.7% of the participants in the experimental arm of the study. The study concluded that higher doses of caffeine (480 mg/day) precipitated anxiety and panic attacks (Nardi et al., 2009). Caffeine intake also affected sleep quality, as reported in a study

conducted with 88 PLWH (Dreher, 2003). Subjects having high levels of caffeine consumption (>400 mg/day) reported poor sleep quality (Dreher, 2003). Within 1 month, subjects who reduced their baseline caffeine consumption by 90% or higher showed significant improvements in sleep quality after adjusting for co-variables such as sleep medications, other comorbidities, and substance use.

In summary, there is adequate evidence that caffeine consumption is associated with increased periods of insomnia, which could produce adverse effects on disease progression in PLWH. The specific aim of our study was to explore the relationship between caffeine consumption and insomnia levels among PLWH. We also looked for a relationship between insomnia and immunological and virologic markers of HIV disease progression (decreases in CD4+ T cell counts and increases in HIV viral loads).

Methods

Study Design and Setting

We recruited a convenience sample of 130 participants from the Miami Adult Studies on HIV (MASH) cohort, which consisted of 803 PLWH followed for more than 10 years in the Miami Metropolitan area. Recruitment for our study took place from February to July 2014. Our study included a baseline and follow-up visit, although only baseline data were used for the cross-sectional analysis presented here. Participants received \$5 USD as partial reimbursement for their time and effort. The initial screening included detailed explanation of the study and voluntary written consent for participation, which was read and signed by the participants. In order to obtain a study sample of 128 participants as estimated in our sample size calculations, we screened a total of 150 subjects and enrolled 130 participants, having excluded 20 participants who reported comorbidities after screening visits. The sample size was calculated using beta estimates to detect association between caffeine intake and PIRS scores one standard deviation above the mean using a one-tailed test with probability of alpha error at .05 and statistical power levels at .80. Total sample size calculated from estimates was 128 participants with an actual power of .801. The inclusion criteria for our study were: (a) enrollment in the MASH cohort studies, and (b) currently on ART. Exclusion criteria were: (a) cardiovascular abnormalities or implanted pacemakers; (b) morbid medical conditions such as uncontrolled hypertension, anemia, chronic inflammatory diseases, or malabsorption syndromes; and (c) AIDS diagnosis and opportunistic infections. The Institutional Review Board at Florida International University approved the study protocol and research procedures.

Measures

Demographics, substance use, dietary intakes, and anthropometric measures

—Demographic and substance use characteristics were collected by the MASH cohort studies and included age, gender, race/ethnicity, education, and income, and substance use factors such as tobacco use, alcohol consumption, and illicit drug use. Dietary intakes included total calories, carbohydrates, proteins, and fat consumed per day. Anthropometric measures included waist-to-hip ratio and body mass index.

Caffeine Consumption Questionnaire—We used the Modified Caffeine Consumption Questionnaire developed by Preston, Talaga, and O'Neal (2004; http://www.millersville.edu/healthservices/files/Caffeine_Questionnaire.pdf). The questionnaire is easy to understand, compact, organized, and reported adequate compliance, validity, and reliability (Preston et al., 2004). The questionnaire has been field tested and validated in many large-scale studies and adequately reflected average daily caffeine consumption levels (Gurpegui et al., 2007; Jones & Lejuez, 2005). It includes 21 sources of caffeine, classified into three groups: beverages, over-the-counter medications, and prescription medications. It also includes total caffeine consumption per day by adding together the individual sources. We considered caffeine consumption as a continuous variable (Gurpegui et al., 2007; Jones & Lejuez, 2005).

Pittsburgh Insomnia Rating Scale (PIRS)—The PIRS is a 65-item self-report questionnaire that measures subjective levels of insomnia experienced over the past 7 days (Moul, Pilkonis, Miewald, Carey, & Buysse, 2002; <http://www.psychiatry.pitt.edu/node/8235>). The questionnaire consists of four components: distress score, sleep parameter score, quality-of-life score, and total insomnia score. The distress score equals the total of the first 46 questions each rated on a 0-3 scale, and higher scores indicate increased levels of subjective sleep distress symptoms experienced by the participant. Similarly, the sleep parameter score totals questions 47 to 56, each rated on a 0-3 scale, and higher scores signify poor sleep quality. The quality-of-life score sums questions 57 to 65, and higher scores signify poor quality of life. The global PIRS score sums all 65 questions and higher scores represent increased subjective reports of insomnia. The PIRS questionnaire showed excellent internal consistency, test-retest reliability, and discriminative validity in a mixed sample of 456 normal adult participants between 18 and 85 years of age in the original study (Moul et al., 2002). The original study also reported a Cronbach's alpha coefficient of .88, indicating high internal consistency, and an intra-class correlation of .89, indicating good test-retest reliability. The original study also reported a sensitivity of 83.4% and a specificity of 88.6% for the questionnaire (Moul et al., 2002). All PIRS components, as well as the global PIRS scores, were considered as continuous variables.

CD4+ T cell counts and HIV viral loads—CD4+ T cell counts and HIV viral loads were used to measure HIV disease progression. The MASH cohort studies collected and recorded the lab reports for CD4+ T cell counts (FACSCanto II Flow Cytometer, BD Biosciences, San Jose, CA) and HIV viral loads (RealTime HIV-1 PCR, Abbott Molecular, Des Plaines, IL), after appropriate medical release forms were signed by the participants. In our analyses, CD4+ T cell counts and HIV viral loads were considered as continuous variables and were transformed into CD4+ T cell square root and Log₁₀ HIV viral load to ensure normal distribution and better model fit criteria.

Statistical Analyses

SPSS version 23 for Windows (IBM Corp, Armonk, NY) was used for statistical analyses. Descriptive statistics were used to understand demographic characteristics, substance use, dietary intakes, anthropometric measures, caffeine consumption, and PIRS scores, and were expressed in terms of means, standard deviations, and percentages. Correlation analyses

were used to identify the associations between caffeine consumption, PIRS variables, and immunological and virologic markers of disease progression. Linear regression analyses were used to estimate the strength of association between caffeine consumption and individual components and global PIRS scores. Linear regression analyses were also used to estimate the strength of association between global PIRS scores and the markers of HIV disease progression. All assumptions of linear regression were followed prior to analyses. For both linear regression analyses, we initially used crude models and subsequently adjusted for the covariates. The covariates included in the analyses were age, gender, race/ethnicity, education, income; time from diagnosis of HIV, drug use, smoking status, alcohol use; and CD4+ T cell count and HIV viral load. Statistical significance was set at $p < .05$ for all analyses.

Results

Demographic and Substance Use Characteristics

A total of 130 participants were included in the study and 79 (60.8%) were men. The mean age was 47.89 ± 6.37 ($M \pm SD$) years. Most of the participants were African Americans (75.4%); Hispanics contributed 16.9%, Whites 5.4%, and other races 4.6%. About 24% of the participants had a college education, while 45.4% were high school graduates, and 30.8% had some form of primary education. All participants had incomes lower than the level of poverty, and the mean income was \$495.91 USD $\pm$ \$465.88 per month (Table 1). About 63% of the participants reported smoking within 6 weeks of their scheduled baseline visits, 57.9% reported alcohol use, and 48.2% tested positive for illicit drug use. Total daily calorie intake was 2015.10 ± 993.40 calories. The mean waist-to-hip ratio was 0.93 ± 0.07 and body mass index was 27.28 ± 5.66 kg/m².

Caffeine Consumption from Different Sources, Individual Components, Global PIRS Score, and Biologic Markers

The participants reported a mean total caffeine consumption of 337.63 ± 304.97 mg/day. Coffee constituted the largest source of caffeine, and mean consumption levels were 161.26 ± 194.95 mg/day. Caffeinated soft drinks constituted the second largest source of caffeine, and mean consumption levels were 63.23 ± 92.98 mg/day (Table 2). For all other sources of caffeine in the questionnaire, except those listed in Table 2, participants reported no-to-negligible levels of consumption. The mean global PIRS score was 75.82 ± 47.82 . The mean CD4+ T cell count was 500.82 ± 297.49 cells/mm³, and the mean HIV viral load was $32,324.30 \pm 82,965.10$ copies/mL (Table 2).

Correlation Between Caffeine Consumption, PIRS, and Biologic Markers

There were significant associations between caffeine consumption, individual components, and global PIRS scores (Table 3). Significant associations were also found between global PIRS scores and CD4+ T cell square roots ($r = 0.994$, $p < .05$) and Log₁₀ HIV viral loads ($r = -0.837$, $p < .05$).

Relationship Between Caffeine Intake and PIRS Scores

Linear regression analysis showed that caffeine consumption was significantly associated with distress score ($\beta = 1.506, p = .048$), quality-of-life score ($\beta = 1.784, p = .001$), and global PIRS score ($\beta = 1.776, p = .046$) after adjusting for covariates (Table 4).

Relationship Between Global PIRS Score and Biologic Markers

Linear regression analysis showed that global PIRS scores were significantly associated with lower CD4+ T cell counts ($\beta = -1.202, p = .015$) and higher HIV viral loads ($\beta = 1.949, p = .045$) after adjusting for covariates (Table 5).

Discussion

We found that caffeine consumption was associated with higher levels of insomnia. We also found that insomnia symptoms were adversely associated with HIV disease progression variables, including lower CD47plus; T cell count and higher HIV viral load.

The relationship between caffeine consumption and insomnia was expected, because caffeine consumption has been associated with poor sleep quality and worsening anxiety symptoms in studies of HIV-uninfected participants (Drake, Roehrs, Shambroom, & Roth, 2013; Lodato et al., 2013). Other studies have stated that PLWH had deteriorated sleep quality, increased periods of insomnia, post-morning sleepiness, cognitive impairments, increased anxiety symptoms, and tiredness (Lee et al., 2012; Taibi, 2013; Webel et al., 2013). However, studies associating caffeine consumption to these adverse effects have been rare in PLWH. A study on patients living with HIV reported adverse effects of caffeine consumption on sleep quality and general well-being (Dreher, 2003). This study, however, was limited due to its small sample size ($n = 88$) and very high mean caffeine consumption level (476 mg/day), which was about 2.4 times the average caffeine consumption in the United States (Dreher, 2003). Although many studies have associated caffeine intake with impaired sleep quality in HIV-uninfected populations, our study was among the few that have investigated the association between caffeine consumption and insomnia symptoms in a population of clinically stable PLWH (Gallego et al., 2004; Hudson, Portillo, & Lee, 2008; Lee, Portillo, & Miramontes, 2001).

Caffeine consumed orally is rapidly absorbed through the gastrointestinal tract and peak plasma concentrations are reached in 30-75 minutes (Mandel, 2002). Animal studies have demonstrated that the majority of caffeine consumed is used by brain cells (Dragicevic et al., 2012; Kaplan et al., 1997). Caffeine is converted to paraxanthine (80%), theobromine, theophylline, and many other xanthine alkaloids. Paraxanthine accumulates and inhibits the clearance of caffeine as well as its metabolites. In addition, these metabolites have the same biological actions as caffeine. Therefore, the half-life of any dose of caffeine ranges from 3 to 7 hours, depending on liver and kidney function levels (Martínez-López et al., 2014; Orrú et al., 2013). Caffeine is primarily an adenosine receptor blocker. The stimulant effect of caffeine is achieved through A1 and A2A adenosine receptor blockade in the central nervous system (Elmenhorst, Meyer, Matusch, Winz, & Bauer, 2012; Feduccia et al., 2012). A1 receptors are primarily located in the cerebrum, cerebellum, hippocampus, and thalamus,

whereas A2A receptors are located in the nucleus accumbens, striatum, and olfactory tubercle. Many of these centers are complexly related to the reticular activating system, thereby affecting sleep and its quality (Basheer, Strecker, Thakkar, & McCarley, 2004).

Irrespective of these physiological mechanisms, the body develops tolerance to the effects of caffeine on adenosine receptors. The effects of the same levels of caffeine could be different between habitual consumers and non- and occasional consumers. Therefore, studies that use caffeine pills and report the effects cannot be entirely validated unless abstinence from caffeine for a long time has been ascertained through blood or urine tests (Lovallo et al., 2005). This would compromise the feasibility of the study because more than 80% of the general population consumes caffeine. In addition, significant differences have been observed in the stimulating effects of caffeine between caffeine-naïve and habitual caffeine consumers, as well as in caffeine-non-naïve consumers before and after abstinence (James, 2004). Hence, we decided to analyze caffeine as a continuous variable instead of comparing between consumers and nonconsumers.

We found that caffeine intake was adversely associated with many parameters of the PIRS questionnaire, after adjusting for age, gender, race/ethnicity, education, income, and time from diagnosis of HIV, drug use, smoking status, alcohol use, and CD4+ T cell count and HIV viral load. Our analyses were adjusted for these variables because the literature reported their associations with poor sleep quality (Patel, Grandner, Xie, Branas, & Gooneratne, 2010; Roehrs, Burduvali, Bonahoom, Drake, & Roth, 2003). Our findings suggest that although the adverse effects of caffeine on insomnia symptoms were marginal, they could additionally complicate the adverse effects of medication side effects and cocaine and amphetamine use, which have stronger effects on sleep disturbances.

We also found that higher levels of insomnia were associated with lower levels of CD4+ T cell counts and higher HIV viral loads after adjusting for the co-variables associated with HIV disease progression (Lyles et al., 2000; Schneider, Chersich, Neuman, & Parry, 2012). Similar findings were reported in another PLWH study, where poor sleep quality and worsening psychological distress scores were associated with lower CD4+ T cell counts and higher HIV viral loads (Motivala et al., 2003). Nevertheless, comparability with our study is limited, because they used a sample of PLWH beginning to show symptoms of AIDS, whereas our participants were clinically stable PLWH receiving ART and free from AIDS, opportunistic infections, and other major comorbidities. The deleterious effects of poor sleep quality on HIV disease progression would have been more prominent in PLWH who were beginning to show symptoms of AIDS, compared to our stable participants receiving ART, because recovery of immune function and controlled viral loads were attained only with ART (Lyles et al., 2000). Our study findings were unique because we explored the adverse effects of caffeine on insomnia in the absence of advanced HIV disease progression states.

Limitations

We enrolled a convenience sample of 130 PLWH, thus the results may not be generalizable. The study was a cross-sectional analysis, and although we found associations, causal relationships could not be established. The survey instruments used in the study did not measure outcomes within the same time frame because PIRS measured insomnia levels

during the past week and the Modified Caffeine Consumption Questionnaire measured caffeine consumption during the past 24 hours. In addition, the instruments were self-reported and susceptible to memory and recall biases. Furthermore, our study had very few subjects who abstained from caffeine and we did not have an adequately sized non-caffeine-consuming comparison group to eliminate the effects of confounding factors influencing the relationship between independent and dependent variables in the study.

Conclusions

Large-scale studies should be done with controlled dietary and lifestyle factors to overcome the limitations of our study. Although our findings showed that caffeine intake was adversely associated with insomnia symptoms, and insomnia symptoms were, in turn, adversely associated with HIV disease progression, the causality of these findings should be confirmed by experimental studies.

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Key Considerations

- Health professionals managing people living with HIV (PLWH) should assess caffeine consumption levels and sleep quality as a part of routine clinical assessments.
- Health professionals managing PLWH should educate patients about the adverse effects of caffeine on sleep quality and insomnia, which, in turn, could affect HIV disease progression.
- Health professionals managing PLWH should be educated and trained about the importance of regulating caffeine consumption in this population.

Table 1
Characteristics of Participants (*n* = 130)

Characteristics	Total
Age in years (<i>M</i> ± <i>SD</i>)	47.89 ± 6.37
Gender, <i>n</i> (%)	
Male	79 (60.8)
Female	51 (39.2)
Race and ethnicity, <i>n</i> (%)	
White	7 (5.4)
Hispanic	22 (16.9)
Black	98 (75.4)
Other	3 (2.3)
Education in years, <i>n</i> (%)	
<12	40 (30.8)
12	59 (45.4)
>12	31 (23.8)
Income in USD per month (<i>M</i> ± <i>SD</i>)	495.91 ± 465.88
Smoking cigarettes, <i>n</i> (%)	80 (63.5)
Alcohol use, <i>n</i> (%)	73 (57.9)
Total drug use, <i>n</i> (%)	53 (48.2)
Marijuana, <i>n</i> (%)	44 (33.8)
Cocaine, <i>n</i> (%)	41 (31.5)
Other drugs, <i>n</i> (%)	10 (9.1)
Total calorie intake in Cal/day (<i>M</i> ± <i>SD</i>)	2015.10 ± 993.40
Total carbohydrate intake in g/day (<i>M</i> ± <i>SD</i>)	250.49 ± 132.61
Total protein intake in g/day (<i>M</i> ± <i>SD</i>)	85.03 ± 48.01
Total fat intake in g/day (<i>M</i> ± <i>SD</i>)	72.18 ± 46.41
Waist to hip ratio (<i>M</i> ± <i>SD</i>)	0.93 ± 0.07
Body mass index in kg/m ² (<i>M</i> ± <i>SD</i>)	27.28 ± 5.66
Pulse rate in bpm (<i>M</i> ± <i>SD</i>)	95.13 ± 13.45
Systolic blood pressure in mm Hg (<i>M</i> ± <i>SD</i>)	103.64 ± 26.92
Diastolic blood pressure in mm Hg (<i>M</i> ± <i>SD</i>)	76.93 ± 27.25

Note. *SD* = standard deviation; USD = U.S. dollars; Cal/ day = calories/day; g/day = grams/day; kg/m² = kilograms/meter squared; mm Hg = millimeter of mercury.

Table 2
Mean Caffeine Consumption, PIRS Scores, and Immunological and Virologic Markers of
Participants (*n* = 130)

Caffeine intake from different sources in mg/day (M ± SD)	
Coffee	161.26 ± 194.95
De-caffeinated coffee	0.83 ± 9.21
Espresso	14.40 ± 64.35
Tea	34.70 ± 64.32
Green tea	7.34 ± 62.93
Energy drinks	46.32 ± 134.42
Hot cocoa	1.03 ± 5.00
Caffeinated soft drinks	63.23 ± 92.98
Chocolate candy bars	3.69 ± 13.81
Anacin	0.24 ± 2.80
Appetite control pills	4.61 ± 39.10
Total	337.63 ± 304.97
Individual components and global PIRS score	
Distress score	51.89 ± 33.40
Sleep parameter score	12.77 ± 8.24
Quality of life score	11.16 ± 7.32
Global PIRS score	75.82 ± 47.82
Immunological and virologic markers	
CD4+ T cell count	500.82 ± 297.49 cells/mm ³
HIV Viral load	32324.30 ± 82965.10 copies/mL

Note. *SD* = standard deviation; PIRS = Pittsburgh Insomnia Rating Scale.

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Table 3
Correlation Between Caffeine Consumption Levels, PIRS Scores, and Immunological and Virologic Markers ($n = 130$)

	1	2	3	4	5	6	7
1. Caffeine intake levels	–						
2. Distress score	.805**	–					
3. Sleep parameter score	.800**	.904**	–				
4. Quality of life score	.749**	.902**	.915**	–			
5. Global PIRS score	.815**	.992**	.944**	.941**	–		
6. CD4+ T cell square root	0.569	0.488	0.112	0.291	0.994*	–	
7. Log ₁₀ HIV viral load	–0.752	–0.624	–0.269	–0.454	–0.837*	–.463**	–

Note. PIRS = Pittsburgh Insomnia Rating Scale.

* $p < .05$;

** $p < .01$.

Table 4
Linear Regression Analysis of the Effect of Caffeine Consumption on PIRS Scores ($n = 130$)

PIRS Variables	Unadjusted			Adjusted ^a		
	Beta	SE	p-Value	Beta	SE	p-Value
Distress score	1.088	1.006	.239	1.506	1.103	.048
Sleep parameter score	1.022	1.001	.599	1.89	1.096	.586
Quality of life score	1.018	1.001	.002	1.784	1.226	.001
Global PIRS score	1.128	1.057	.048	1.776	1.12	.046

Note. PIRS = Pittsburgh Insomnia Rating Scale; SE = Standard error.

^aModel controlled for age (continuous), gender (male and female), race/ethnicity (White, Hispanic, Black, and Other), education (<12 years, 12 years, and >12 years), income (continuous), time from diagnosis of HIV (continuous), drug use (yes and no), smoking status (yes and no), alcohol use (yes and no), and CD4+ T cell count (continuous), and HIV viral load (continuous).

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Table 5
Linear Regression Analysis of the Effect of Global PIRS on Immunological and Virologic Markers of Disease Progression (*n* = 130)

Immunological and Virologic Markers	Unadjusted			Adjusted ^a		
	Beta	SE	p-Value	Beta	SE	p-Value
CD4+ T cell square root	−0.913	0.128	.316	−1.202	0.649	.015
Log ₁₀ viral load	1.659	0.735	.698	1.949	0.933	.045

Note. PIRS = Pittsburgh Insomnia Rating Scale; SE = Standard error.

^aModel controlled for time from diagnosis of HIV (continuous), drug use (*yes* and *no*), smoking status (*yes* and *no*), and alcohol use (*yes* and *no*).