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Metabolomics of sleep disorders in HIV: a narrative review

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Abstract

Purpose Sleep disturbances are prevalent among patients with human immunodeficiency virus (HIV), even those who are being treated on antiretroviral therapy. It is important to understand the metabolomic mechanisms underlying sleep disturbances among people living with HIV (PLWH).

Methods A review of recent literature was performed to explore the use of metabolomics in understanding sleep among PLWH.

Results We found only two studies that used metabolomics to explore sleep health among PLWH.

Conclusion This paper reviews common sleep disorders in HIV, the existing metabolomic studies that may explain the relationship, and implications for future research. The use of metabolomics in exploring sleep disorders among PLWH will help to elucidate mechanistic links to improve patient outcomes.

Keywords Sleep disorders · Sleep disturbances · Human immunodeficiency virus (HIV) · Metabolomics · Antiretroviral therapy · Inflammation

Introduction

Metabolomics is defined as the "comprehensive analysis of all metabolites and low molecular weight molecules in a biological specimen" [1]. It has been estimated that there is an excess of 40,000 (expected and detected) metabolites in the human body [2]. As metabolomics has the ability to integrate metabolic changes at the gene, transcript, and protein levels, all while accounting for environmental interactions [3], metabolomics analysis gives important insight into the metabolic underpinnings of chronic illnesses such as HIV. Metabolomics may be particularly useful in the study of disordered sleep, as poor sleep health is a comorbidity of great concern among PLWH [4–7].

The sleep-wake cycle is determined by a complex interplay between circadian clock and behavioral and environmental influences, which direct numerous metabolic pathways including carbohydrate, protein and amino acid, lipid, and adenine dinucleotide (NAD+) metabolism [8]. Chronic sleep restriction (5.5 h of sleep over 8 nights) has been associated with 16 biochemical changes with the biggest changes associated with amino acid and peptide, followed by lipid metabolism [9]. There is also a known association between amino acid metabolism and sleep timing. Habitually, late sleep timing is associated with higher levels of branched chain amino acids and systematic changes in several other amino acid pathways [10]. Chronic sleep deprivation and late sleep timing have also been found to be associated with alterations to fatty acid and lipid metabolism [10]. This review will provide an overview of sleep disorders in HIV and explore existing metabolomic studies in the context of HIV and sleep, mechanisms for the relationship, and future research directions.

Sleep disorders in adults with HIV

Poor sleep health is a comorbid condition of particular concern among PLWH. Up to 73% of the HIV-infected individuals in the United States experience sleep disturbances of some kind, as compared to only 10-35% of the general population [11–13]. Sleep disturbances are defined as difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening. Sleep disturbances (insomnia and daytime sleepiness) are among the most prevalent and distressing symptoms experienced by people diagnosed with HIV even when their disease is well managed [5, 13, 14]. Daytime sleepiness can

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lead to difficulties with concentrating, poor cognitive functioning, depressive symptoms, and reduced overall productivity [14]. Poor sleep quality contributes to HIV-related fatigue [15]. Poor sleep has been linked to disease progression, medication therapy, employment status, and a lack of good sleep promotion skills in HIV-infected people [16–19]. The consequences of poor sleep among PLWH are significant and have been associated with lower CD4+ T-lymphocyte counts which is a strong predictor of AIDS-related mortality, [20] and increased cardiovascular mortality [21], which is now one of the leading causes of death among PLWH [22].

Methods

Publications were identified via PubMed. Additional references that were included within the identified articles were also considered for inclusion in the review. Search terms included: sleep, HIV, and metabolites. Studies were chosen based on relevancy, being published in the last 10 years, and primary data collection methods.

Results

Sleep and inflammation

Sleep and the immune system share regulator molecules called cytokines [23]. HIV and other viral infections trigger the production of both anti- and pro-inflammatory cytokines which affect both the immune response and metabolism [24]. Cytokines are involved in both physiological sleep and the disrupted sleep that occurs in response to infection or chronic inflammation [23]. It is posited that sleep influences the immune system through the action of cytokines that are regulated during sleep [23]. Sleep loss results in increased secretion of pro-inflammatory cytokines interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) [25] and has been associated with a decrease in natural killer cell, T lymphocyte cell, and monocyte function [26]. HIV infection and its comorbidities such as encephalitis have been found to alter cytokine levels [27]. As sleep disturbances are linked to changes in inflammation, sleep-regulating hormones, and cytokine levels, it will be important to clarify the metabolomic mechanisms underlying these changes to guide novel treatments for sleep disturbances among PLWH.

Psychosocial factors and sleep disturbances

Stressful life events are strong predictors of the intensity of HIV-related fatigue and impaired function [28]. A recent study found HIV infection to not be systematically associated with greater sleep disturbances among women. This suggests that HIV-related sleep disturbances may be secondary to concomitant psychosocial factors [29]. Women living with HIV who report symptoms of insomnia are more likely to be depressed [30]. Symptoms of HIV likely to be associated with sleep, and particularly with insomnia, include pain, anxiety, fatigue and depressive symptoms [13, 30]. Thus, the consequences of insomnia (fatigue, mood disturbances, etc.) are also compounded by the HIV infection [6]. Accordingly, research studies should consider and control for common HIV symptoms that might contribute to sleep disorders in order to better discern the underlying mechanisms associated with this relationship among this population.

Antiretroviral therapy and sleep disturbances

Sleep disturbances are a known side effect of certain combination antiretroviral therapies (cART), specifically non-nucleoside reverse transcriptase inhibitors (NNRTI) [31]. In particular, PLWH taking efavirenz were observed to have longer sleep latencies and shorter duration of deep sleep in the first weeks of treatment [32]. A study by Shikuma et al. showed that the discontinuation of efavirenz after 12 weeks of therapy did not reverse sleep abnormalities [33]. Recent findings from Payne et al. suggest that although withdrawal from efavirenz did result in improved self-reported sleep quality among PLWH, it will not readily result in significant changes in neurocognitive function [34]. Another study found that men with HIV treated with cART for at least 6 months were less likely to be diagnosed with obstructive sleep apnea [35]. Case studies have observed OSA accompanying HIV-associated lipodystrophy and fat redistribution after antiretroviral therapy [36, 37].

Lack of studies exploring metabolomics, sleep, and HIV

Only two studies have explored metabolomics, sleep, and HIV [38, 20]. One prior study involving 139 subjects explored self-reported sleep disturbance, CD4 count, and 24 h urinary dopamine levels in ethnic minority women living with HIV [20]. They found that increased sleep disturbance was correlated with significantly reduced CD4 count and significantly decreased levels of dopamine. Poorer overall sleep quality was minimally associated with lower CD4 count and was not associated with dopamine. This study was limited by its cross-sectional design and subjective measure of sleep disturbance. These results suggest the possibility that metabolic differences may drive sleep disturbances and poorer outcomes in PLWH.

A study by Zhao et al., 2019, [38] illustrated that elevated ceramide levels were more closely associated with PLWH than those living without HIV when exploring the link to carotid atherosclerosis. Moreover, results showed that increased

Table 1

Author and year	Metabolite/biomarker	Population	Comments
Seay et al. 2013	CD4 and 24 h urinary dopamine	139 ethnic minority women living with HIV	Increased self-reported sleep disturbance was correlated with significantly reduced CD4 count and decreased levels of dopamine
Zhao et al. 2019	Ceramides (C16:0 and C24:1)	398 women (73% HIV+) and 339 men (68% HIV+)	C16:0 and C24:1 correlated with specific markers of immune activation and inflammation associated with progression of carotid artery atherosclerosis

ceramide levels were linked with cART use among participants living with HIV. Specifically, C16:0 (palmitoyl ceramide) and C24:1 (lignoceric ceramide) were found to be closely associated with specific monocyte activation, inflammation markers, and surface markers of CD4+ T cell activation. This study suggests that specific ceramides (C16:0 and C24:1 ceramides) correlating with specific markers of immune activation and inflammation are significantly associated with progression of carotid artery atherosclerosis. Prior findings from Pak et al., 2018 [39] showed that lower levels of ceramide species, mainly C16, C18:1 (N- Stearoylsphingosine), and C14 (N-myristoylsphingosine) were associated with sleepiness in subjects with suspected sleep apnea. Thus, it is possible that ceramides linked to inflammation are also linked to sleep disorders. These results will need to be replicated in a population of PLWH. See Table 1 for details. A total of two studies (Zhao et al., 2019, [38]; Seay et al., 2013 [20] were selected that met our search criteria (Table 1).

Conclusion

Overall, there is a need to clarify the mechanistic link between HIV and sleep disorders as they may share metabolic pathways. A review of the literature on the mechanistic link of metabolomics and sleep disorders in HIV has shown a lack of studies examining this association, with searches only yielding 2 studies. A study by Seay et al. found that sleep disturbance is independently related to immune status and dopamine levels in ethnic minority women living with HIV. Another study by Zhao et al. found that ceramides C16:0 and C24:1 were positively associated with inflammation and immune activation markers in PLWH. It is interesting to note that a study by Pak et al. showed that lower ceramides C16, C18:1, and C14 were associated with sleepiness in subjects with suspected sleep apnea. This suggests that ceramides warrant further exploration in this population in the context of sleep disturbance. Although the direction of the associations appears different in the two studies (the ceramides were increased among PLWH and decreased in sleepy suspected sleep apneic subjects), evaluating this link in a population of PLWH with sleep disturbances will help in elucidating an accurate hypothesis about the role of ceramides in PLWH with sleep disturbances. It will be important to assess metabolites as they relate to sleepiness symptoms and sleep duration subjectively and objectively among PLWH. Additionally, the role of cART (particularly NNRTI use) and alterations in plasma levels of ceramides and other metabolites and clarifying the relationship to inflammation and sleep will be important for future studies. Understanding the role of metabolomics and sleep disorders in HIV will help to identify potential targets and elucidate a mechanistic link to improve patient outcomes in this susceptible population. If we can determine a metabolomic link underlying the mechanism of sleep disorders in HIV, such as the role of ceramides, then we can improve sleep disorders by targeting specific metabolic pathways which could improve both symptoms and disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval Not applicable for this review.

Informed consent Not applicable for this review.

References

1. Clish CB (2015) Metabolomics: an emerging but powerful tool for precision medicine. Molecular Case Studies 1(1):a000588
2. Wishart DS, Jewison T, Guo AC, Wilson M, Knox C, Liu Y, Djoumbou Y, Mandal R, Aziat F, Dong E (2012) HMDB 3.0—the human metabolome database in 2013. Nucleic Acids Res 41(D1):D801–D807
3. Raamsdonk LM, Teusink B, Broadhurst D, Zhang N, Hayes A, Walsh MC, Berden JA, Brindle KM, Kell DB, Rowland JJ (2001) A functional genomics strategy that uses metabolome data to reveal the phenotype of silent mutations. Nat Biotechnol 19(1):45–50

4. Wibbeler T, Reichelt D, Husstedt I-W, Evers S (2012) Sleepiness and sleep quality in patients with HIV infection. J Psychosom Res 72(6):439–442
5. Taibi DM, Price C, Voss J (2013) A pilot study of sleep quality and rest–activity patterns in persons living with HIV. J Assoc Nurses AIDS Care 24(5):411–421
6. Salahuddin N, Barroso J, Leserman J, Harmon JL, Pence BW (2009) Daytime sleepiness, nighttime sleep quality, stressful life events, and HIV-related fatigue. J Assoc Nurses AIDS Care 20(1):6–13
7. Redman K, Karstaedt A, Scheuermaier K (2018) Increased CD4 counts, pain and depression are correlates of lower sleep quality in treated HIV positive patients with low baseline CD4 counts. Brain Behav Immun 69:548–555
8. Bailey SM, Udoh US, Young ME (2014) Circadian regulation of metabolism. J Endocrinol 222 (2):R75-R96
9. Bell LN, Kilkus JM, Booth JN III, Bromley LE, Imperial JG, Penev PD (2013) Effects of sleep restriction on the human plasma metabolome. Physiol Behav 122:25–31
10. Xiao Q, Derkach A, Moore SC, Zheng W, Shu X-O, Gu F, Caporaso NE, Sampson JN, Matthews CE (2017) Habitual sleep and human plasma metabolomics. Metabolomics 13(5):63
11. Rubinstein ML, Selwyn PA (1998) High prevalence of insomnia in an outpatient population with HIV infection. Acquired Immunodeficiency Syndromes and Human Retrovirology 19:260–265
12. Wu J, Wu H, Lu C, Guo L, Li P (2015) Self-reported sleep disturbances in HIV-infected people: a meta-analysis of prevalence and moderators. Sleep Med 16(8):901–907. https://doi.org/10.1016/j.sleep.2015.03.027
13. Crum-Cianflone NF, Roediger MP, Moore DJ, Hale B, Weintrob A, Ganesan A, Eberly LE, Johnson E, Agan BK, Letendre S (2012) Prevalence and factors associated with sleep disturbances among early-treated HIV-infected persons. Clin Infect Dis 54(10):1485–1494. https://doi.org/10.1093/cid/cis192
14. Lee KA, Gay C, Portillo CJ, Coggins T, Davis H, Pullinger CR, Aouizerat BE (2012) Types of sleep problems in adults living with HIV/AIDS. J Clin Sleep Med 8(01):67–75
15. Lee KA, Gay C, Portillo CJ, Coggins T, Davis H, Pullinger CR, Aouizerat BE (2009) Symptom experience in HIV-infected adults: a function of demographic and clinical characteristics. J Pain Symptom Manag 38(6):882–893
16. Kenedi CA, Goforth HW (2011) A systematic review of the psychiatric side-effects of efavirenz. AIDS Behav 15(8):1803–1818
17. Omonuwa TS, Goforth HW, Preud'homme X, Krystal AD (2009) The pharmacologic management of insomnia in patients with HIV. J Clin Sleep Med 5(03):251–262
18. Saberi P, Neilands TB, Johnson MO (2011) Quality of sleep: associations with antiretroviral nonadherence. AIDS Patient Care STDs 25(9):517–524
19. Gutierrez J, Tedaldi EM, Armon C, Patel V, Hart R, Buchacz K (2019) Sleep disturbances in HIV-infected patients associated with depression and high risk of obstructive sleep apnea. SAGE Open Medicine 7:205031211984226
20. Seay JS, McIntosh R, Fekete EM, Fletcher MA, Kumar M, Schneiderman N, Antoni MH (2013) Self-reported sleep disturbance is associated with lower CD4 count and 24-h urinary dopamine levels in ethnic minority women living with HIV. Psychoneuroendocrinology 38(11):2647–2653. https://doi.org/10.1016/j.psyneuen.2013.06.022
21. Grandner MA (2014) Addressing sleep disturbances: An opportunity to prevent cardiometabolic disease?. International Review of Psychiatry 26 (2):155–176
22. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, Kowalska JD, de Wi St, Law M, el Sadr W, Kirk O, Friis-Moller N, Monforte Ad, Phillips AN, Sabin CA, Lundgren JD (2014) Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. The Lancet 384 (9939):241–248
23. Cardinali DP, Esquifino AI (2012) Sleep and the immune system. Curr Immunol Rev 8(1):50–62
24. Ahmed D, Roy D, Cassol E (2018) Examining relationships between metabolism and persistent inflammation in HIV patients on antiretroviral therapy. Mediat Inflamm 2018
25. Vgontzas AN, Zoumakis E, Bixler EO, Lin H-M, Follett H, Kales A, Chrousos GP (2004) Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. The Journal of Clinical Endocrinology & Metabolism 89(5):2119–2126
26. Irwin M (2002) Effects of sleep and sleep loss on immunity and cytokines. Brain Behav Immun 16(5):503–512
27. Wilk A, Urbanska K, Yang S, Ying Wang J, Amini S, Del Valle L, Peruzzi F, Meggs L, Reiss K (2011) Insulin-like growth factor-I–forkhead box O transcription factor 3a counteracts high glucose/tumor necrosis factor-α-mediated neuronal damage: implications for human immunodeficiency virus encephalitis. J Neurosci Res 89(2):183–198
28. Leserman J, Barroso J, Pence B, Salahuddin N, Harmon J (2008) Trauma, stressful life events and depression predict HIV-related fatigue. AIDS Care 20(10):1258–1265
29. Burgess HJ, Weber KM, Burke-Miller J, McClellan L, Daubert E, Bond C, Morack R, Cohen M, French A (2019) 0849 sleep disturbance in women with and without HIV: the role of psychosocial factors. Sleep 42 (Supplement_1):A340-A341
30. Jean-Louis G, Weber KM, Aouizerat BE, Levine AM, Maki PM, Liu C, Anastos KM, Milam J, Althoff KN, Wilson TE (2012) Insomnia symptoms and HIV infection among participants in the Women's interagency HIV study. Sleep 35(1):131–137. https://doi.org/10.5665/sleep.1602
31. Oshinaike O, Akinbami A, Ojelabi O, Dada A, Dosunmu A, John Olabode S (2014) Quality of sleep in an HIV population on antiretroviral therapy at an urban tertiary Centre in Lagos, Nigeria. Neurology Research International 2014:6. https://doi.org/10.1155/2014/298703
32. Gallego L, Barreiro P, del Rio R, Gonzalez de Requena D, Rodriguez-Albarino A, Gonzalez-Lahoz J, Soriano V (2004) Analyzing sleep abnormalities in HIV-infected patients treated with Efavirenz. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 38(3):430–432. https://doi.org/10.1086/380791
33. Shikuma CM, Kohorn L, Paul R, Chow DC, Kallianpur KJ, Walker M, Souza S, Gangcuangco LMA, Nakamoto BK, Pien FD, Duerler T, Castro L, Nagamine L, Soll B (2018) Sleep and neuropsychological performance in HIV+ subjects on efavirenz-based therapy and response to switch in therapy. HIV Clinical Trials 19(4):139–147. https://doi.org/10.1080/15284336.2018.1511348
34. Payne B, Chadwick T, Blamire A, Anderson K, Parikh J, Qian J, Hynes A, Wilkinson J, Price D, team EoStLRiICFiEtPs (2017) Does efavirenz replacement improve neurological function in treated HIV infection? HIV medicine 18(9):690–695
35. Chen Y-C, Lin C-Y, Li C-Y, Zhang Y, Ko W-C, Ko N-Y (2019) Obstructive sleep apnea among HIV-infected men in the highly active antiretroviral therapy era: a nation-wide longitudinal cohort study in Taiwan, 2000-2011. Sleep Med. https://doi.org/10.1016/j.sleep.2019.07.011
36. Dorey-Stein Z, Amorosa VK, Kostman JR, Shannon RP (2008) Severe weight gain, lipodystrophy, dyslipidemia, and obstructive sleep apnea in a human immunodeficiency virus-infected patient following highly active antiretroviral therapy. Journal of the cardiometabolic syndrome 3(2):111–114
37. Schulz R, Lohmeyer J, Seeger W (2003) Obstructive sleep apnea due to HIV-associated lipodystrophy. Clin Infect Dis 37(10):1398–1399

38. Zhao W, Wang X, Deik AA, Hanna DB, Wang T, Haberlen SA, Shah SJ, Lazar JM, Hodis HN, Landay AL, Yu B, Gustafson D, Anastos K, Post WS, Clish CB, Kaplan RC, Qi Q (2019) Elevated plasma Ceramides are associated with antiretroviral therapy use and progression of carotid artery atherosclerosis in HIV infection. Circulation 139 (17):2003-2011. Doi:doi:https://doi.org/10.1161/CIRCULATIONAHA.118.037487

39. Pak VM, Dai F, Keenan BT, Gooneratne NS, Pack AI (2018) Lower plasma choline levels are associated with sleepiness symptoms. Sleep Med 44:89–96. https://doi.org/10.1016/j.sleep.2017.10.004