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MAJOR ARTICLE

Association of the Kynurenine Pathway of Tryptophan Metabolism With Human Immunodeficiency Virus-Related Gut Microbiota Alterations and Visceral Adipose Tissue Accumulation

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Background. The aim of the study was to investigate the association between human immunodeficiency virus (HIV)-related gut microbiota changes, alterations in the kynurenine (Kyn) pathway of tryptophan (Trp) metabolism, and visceral adipose tissue in the context of HIV infection.

Methods. Three hundred eighty-three people with HIV (PWH) were included from the Copenhagen comorbidity in HIV infection (COCOMO) study. Gut microbiota composition was analyzed by 16S ribosomal ribonucleic acid sequencing. Plasma metabolites were analyzed by liquid chromatography-tandem mass spectrometry. Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) areas were measured by single-slice computed tomography (CT) scan (4th lumbar vertebra).

Results. The HIV-related gut microbiota alterations were associated with lower Trp (β −.01; 95% confidence interval [CI], −0.03 to −0.00) and higher Kyn-to-Trp ratio (β 0.03; 95% CI, 0.01–0.05), which in turn was associated with higher VAT-to-SAT ratio (β 0.50; 95% CI, 0.10–0.90) and larger VAT area (β 30.85; 95% CI, 4.43–57.28). In mediation analysis, the Kyn-to-Trp ratio mediated 10% (P = .023) of the association between the VAT-to-SAT ratio and HIV-related gut microbiota.

Conclusions. Our data suggest HIV-related gut microbiota compositional changes and gut microbial translocation as potential drivers of high Kyn-to-Trp ratio in PWH. In turn, increased activity in the Kyn pathway of Trp metabolism was associated with larger visceral adipose tissue area. Taken together, our findings suggest a possible role for this pathway in the gut-adipose tissue axis in the context of HIV infection.

Keywords. abdominal adipose tissue; gut microbiota; HIV infection; inflammation; kynurenine.

Despite the introduction of less metabolic harmful regimens of combination antiretroviral therapy (cART), abdominal adipose tissue accumulation remains a key feature of human immunodeficiency virus (HIV) infection [1]. Recent studies in both the general population [2] and people with HIV (PWH) [3] support the importance of gut microbiota in the pathogenesis of this phenotype, with the existence of a gut-adipose tissue axis recently being suggested [4].

Tryptophan (Trp) is an essential amino acid and represents the unique substrate for the synthesis of kynurenine (Kyn), which is subsequently metabolized to form either kynurenic acid (KA) or 3-hydroxy-kynurenine and, eventually, quinolinic acid (QA) [5]. Residual increased activity in the Kyn pathway of Trp metabolism and alterations in Kyn metabolites concentrations despite effective cART and viral suppression are well known hallmarks of HIV infection [6] and have been associated with abdominal adipose tissue accumulation and several non-acquired immune deficiency syndrome (AIDS)-associated comorbidities [7].

Recent results from our group suggested that specific compositional changes in the gut microbiota accompanies HIV infection and are associated with accumulation of visceral adipose tissue (VAT) [3]. A potential interplay between alterations in

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the gut microbiota and Trp metabolism has been extensively investigated [8, 9]. Increase of indoleamine 2,3-dioxygenase (IDO-1) activity is linked to gut mucosal barrier dysfunction, as a result of microbial translocation to the blood stream [10]. Gut bacteria populations have also been described to be capable of metabolizing Trp, thus affecting concentrations of systemic Kyn metabolites in the host [9]. Nonetheless, a complete understanding of the determinants behind this association remains elusive, especially in the context of HIV infection.

In the present study, we aimed to investigate the association of HIV-related compositional and functional changes in the gut microbiota with alterations in the Kyn pathway of Trp metabolism. Moreover, we investigated a possible association between this pathway and visceral adipose tissue accumulation, and we tested the possible association of Trp metabolism with the gut-adipose tissue axis.

METHODS

Study Population

The Copenhagen comorbidity in HIV infection (COCOMO) study is a longitudinal study aiming to assess the burden of non-AIDS comorbidities in PWH [11]. Individuals were invited to participate in connection with their regular outpatient visits at the Department of Infectious Diseases Rigshospitalet and Hvidovre Hospital. All PWH >18 years old were invited, and a total of 1099 individuals were included, representing approximately 40% of PWH in the Copenhagen area. Procedures for recruitment and data collection have been described elsewhere [11].

All 1099 COCOMO participants were invited to collect a stool sample and 405 individuals did so. Plasma levels of Trp metabolism and abdominal computed tomography (CT) scan images were available in 1045 and 919 individuals, respectively. For the present study, inclusion criteria were having gut microbiota, Trp metabolism measurements, and abdominal CT scan images available. This resulted in 383 COCOMO participants included in this study.

All the individuals included in this study were also included in the prior publication regarding the association between the Kyn pathway of Trp metabolism and abdominal adipose tissue [7]. Ethical approval was obtained by the Regional Ethics Committee of Copenhagen (H-15017350). Written informed consent was obtained from all participants.

Data Collection

Structured questionnaires were used in COCOMO to collect information about demographics and lifestyle. Data regarding HIV infection were obtained from complete review of medical charts.

Microbiota Analyses

Procedures used for stool sample collection, processing, library preparation, sequencing, and bioinformatics have been described previously [3] and are briefly described below.

Stool Samples Collection and Processing

Stool samples were collected using a standardized sampling device and collection tubes with DNA Stabilizer (Stratec Molecular GmbH, Berlin, Germany). Samples were stored at −80°C until use. Stool DNA was extracted using the PSP Spin Stool DNA-Plus Kit (Stratec Molecular GmbH) following the manufacturer's protocol, slightly modified by adding a bead-beating step.

Library Preparation and Sequencing

The DNA libraries were prepared as described previously [12]. In brief, libraries were generated (1) from polymerase chain reaction (PCR) amplicons targeting the hypervariable regions V3 and V4 of the 16S rRNA gene and (2) using dual-indexed universal primers 319F (forward) and 806R (reverse) along with Phusion High-Fidelity PCR Master mix m/HF buffer (Thermo Fisher Scientific). Cleaning and normalization of PCR products were performed using the SequalPrep Normalization Plate Kit (Thermo Fisher Scientific). Quality control and quantification of pooled libraries were performed using Agilent Bioanalyzer (Agilent Technologies) and Kapa Library Quantification Kit (Kapa Biosystems, London, United Kingdom). Sequencing was performed at the Norwegian Sequencing Centre (Oslo, Norway), applying the v3 kit for Illumina MiSeq (Illumina, San Diego, CA) and 300 base pair paired-end reads.

Bioinformatics

Paired-end reads were filtered for Illumina Universal Adapters and PhiX, demultiplexed, quality trimmed, and merged using bbduk 38.25, je 1.2, cutadapt 1.18, and bbmerge. Denoising to amplicon sequence variants ([ASVs], ie, taxonomic units), taxonomic classification, and filtering of contaminants and rare ASVs were done with QIIME2 (version 2018.8). Alpha diversity and all further analyses were performed on a rarefied (subsampled) dataset with an ASV count of 6247 per sample.

Prediction of Gut Microbial Gene Content

Prediction of the functional profiles from the microbiome dataset was carried out using Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt2) pipeline [12]. Pathways were predicted using the MetaCyc database. Differentially present pathways between groups high and others (quinolinic-to-kynurenic acid ratio and kynurenine-to-tryptophan ratio, visceral adipose tissue [VAT], visceral-to-subcutaneous adipose tissue ratio [VAT-to-SAT ratio]) were analyzed with Welch test using STAMP (version 2.1.3) [13]. Differentially present pathways with multiple comparison (Storey correction) adjusted $P < .05$ were presented.

Human Immunodeficiency Virus-Related Gut Microbiota Index

The computation of the HIV-related gut microbiota index, independent of sexual behavior and other relevant confounders, has

previously been described [3]. In brief, it consists of increased relative abundance of the bacterial class Gammaproteobacteria, the family *Desulfovibrionaceae*, as well as the genera *Eisenbergiella*, *Oscillibacter*, and a concurrent reduction in numerous Clostridia, including *Ruminococcaceae UCG-003*, *Romboutsia*, and several genera of the family Lachnospiraceae (*CAG-56*, *Butyrivibrio*, *Coprococcus-2*, *Lachnospiraceae UCG-001*, *Lachnospiraceae UCG-004*, *and GCA-900066575*) [3].

Kynurenine Pathway of Tryptophan Metabolism

Plasma samples were collected and stored at −80°C until use. Plasma was analyzed for Trp, Kyn, and Kyn metabolites by liquid chromatography-tandem mass spectrometry, as previously described [7]. These analyses were performed at BEVITAL (www.bevital.no). Plasma levels of lipopolysaccharide-binding protein (LBP) were measured in duplicate by enzyme immunoassays (EIAs) using commercially available antibodies (R&D Systems, Minneapolis, MN) in a 384 format using a combination of a SELMA (Jena, Germany) pipetting robot and a BioTek (Winooski, VT) dispenser/washer. Absorption was read at 450 nm with wavelength correction set to 540 nm using an EIA plate reader (Bio-Rad, Hercules, CA). Intra- and interassay coefficients of variation were <10%.

Visceral and Subcutaneous Adipose Tissue

The VAT and SAT were measured at the level of the 4th lumbar vertebra in a single slice using 320-multidetector scanner (Aquilion OneViSION Edition, Canon, Japan) in a single rotation (275 ms). A detailed description of the scanning protocol has been reported in [14].

Statistics

Associations of HIV-related gut microbiota index, Shannon diversity index, and LBP with metabolites of the Kyn pathway of Trp metabolism were tested using univariable linear regression models, with the metabolites as dependent variables. Likewise, association between metabolites of the Kyn pathway of Trp metabolism and VAT-to-SAT ratio, VAT and SAT, respectively, were tested using univariable linear regression models. The models including quinolinic-to-kynurenic acid ratio, QA, and KA were adjusted for Kyn concentrations.

The mediation effect (mean indirect effect) by kynurenine-to-tryptophan ratio on the association between HIV-related gut microbiota index and VAT-to-SAT ratio was investigated using the mediate function included in the R package "Psych". In these analyses, the dependent variable was VAT-to-SAT ratio, the independent variable was HIV-related gut microbiota index, and the mediating variable was kynurenine-to-tryptophan ratio. Statistical significance and confidence intervals (CIs) of the mean indirect effect were computed using bootstrapping method with 1000 iterations. All statistical analyses were performed using R statistical software version 4.0.5.

RESULTS

General Characteristics of the Population

A total of 383 individuals were included in the present study. Demographic and clinical characteristics of the population are presented in Table 1. In brief, the majority was of male sex (84%) with a median age of 52 (46.1–61.0) years. The vast majority was virally suppressed (95%) and currently on cART (98%), with a median duration of HIV infection of 15.5 years (7.4–23.1).

Association of Human Immunodeficiency Virus-Related Gut Microbiota Changes With the Kynurenine Pathway of Tryptophan Metabolism

An overview of the metabolites included in the Kyn pathway of Trp metabolism is presented in Supplementary Figure 1. The HIV-related microbiota index was associated with higher kynurenine-to-tryptophan ratio (β 0.03; 95% CI, 0.01–0.05) and lower Trp concentrations (β −.01; 95% CI, −0.03 to −0.00). These associations were mainly driven by increase in the family *Desulfovibrionaceae* and genus *Eisenbergiella* and reduction in the *Lachnospiraceae CAG 56* and *Coprococcus* 2 (Figure 1). Among the Kyn metabolites, HIV-related microbiota index was associated with higher quinolinic-to-kynurenic acid ratio (β 0.03; 95% CI, 0.00–0.06) and lower KA (−0.04; 95% CI, −0.06 to −0.01). Among the bacteria included in the HIV-related microbiota index, *Eisenbergiella* was associated with KA concentrations (β 0.42; 95% CI, 0.34–0.49).

Table 1. Demographic and Clinical Characteristics of the Population

	PWH, n = 383
Age, median (IQR)	52 (46.1–61.0)
Sex, male, n (%)	322 (84.1)
Origin, n (%)	
	278 (73.7)
	48 (12.7)
	49 (13.0)
	2 (0.5)
CD4 nadir <200 cells, n (%)	148 (39.6)
History of AIDS-defining events, yes, n (%)	71 (18.6)
History of severe immunodeficiency, yes, n (%)	95 (25.5)
Viral load <50 copies/mL, yes, n (%)	364 (95.3)
Current cART treatment	375 (98.4)
Duration of HIV infection, years, median (IQR)	15.5 (7.4–23.1)
Kynurenine-to-tryptophan ratio, median (IQR)	25.3 (21.6–30.5)
Kyn, median (IQR)	1.6 (1.4–1.9)
Trp, median (IQR)	62.9 (55.0–70.5)
Quinolinic-to-kynurenic acid ratio, median (IQR)	78.1 (63.2–106.0)
QA, median (IQR)	386 (316.0–488.5)
KA, median (IQR)	49.1 (38.0–61.8)
VAT-SAT, median (IQR)	0.7 (0.4–1.1)

Abbreviations: AIDS, acquired immune deficiency syndrome; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; KA, kynurenic acid; Kyn, kynurenine; PWH, people with HIV; QA, quinolinic acid; SAT, subcutaneous adipose tissue; Trp, tryptophan; VAT, visceral adipose tissue.

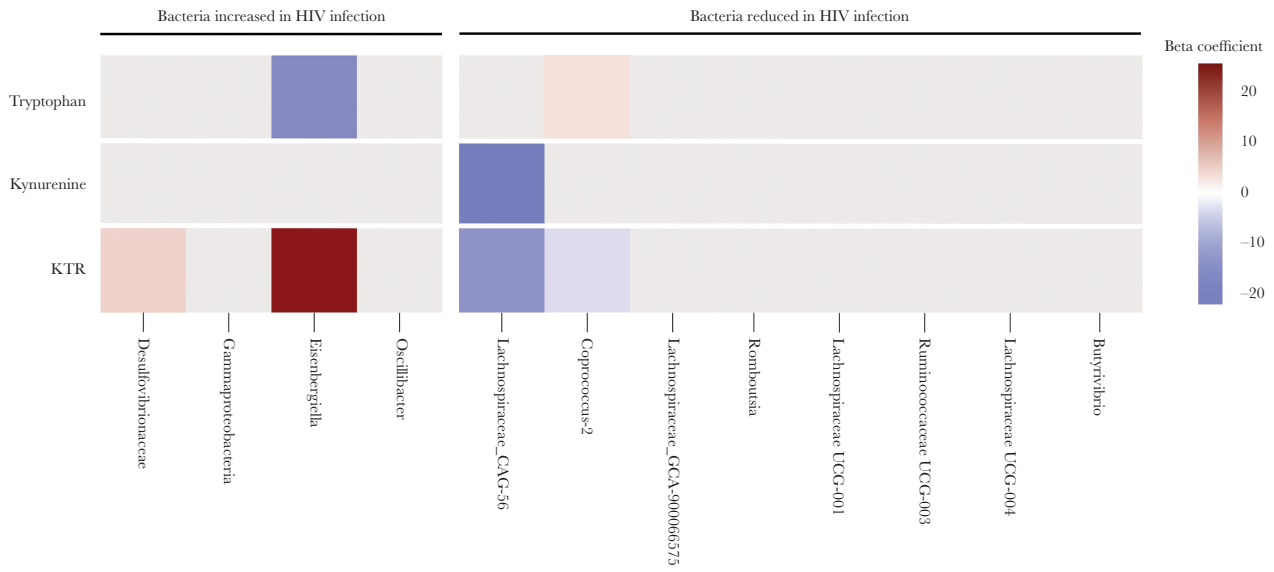

Figure 1. Association between bacteria included in the human immunodeficiency virus (HIV)-related microbiota index and the kynurenine-to-tryptophan ratio, kynurenine, and tryptophan in linear regression models. Only significant ($P < .05$) positive (red) and negative (blue) beta coefficients are shown. The computation of the HIV-related gut microbiota index is presented in Clin Infect Dis 2020 Nov 5; 71(8) [3]. KTR, kynurenine-to-tryptophan ratio.

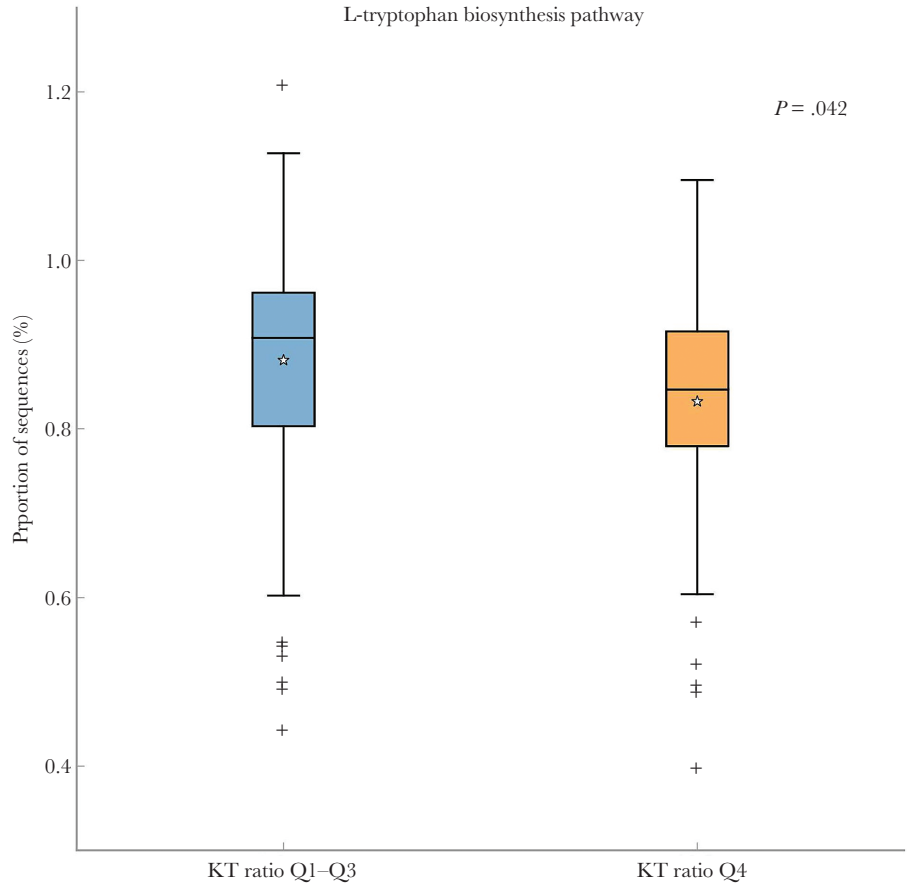

Figure 2. Difference in mean proportions of predicted bacterial L-tryptophan biosynthesis between people with human immunodeficiency virus with low and high kynurenine-to-tryptophan ratio levels (highest quartile). KT, kynurenine-to-tryptophan; Q1-3, 1st to 3rd quartiles; Q4, 4th quartile.

Predicted Bacterial Tryptophan (Trp) Metabolism in Relation to Circulating Trp Metabolites

To predict a potential impact of bacterial Trp metabolism on circulating Trp metabolites, we applied the PICRUSt2 pipeline and the metaCyc database on the microbiota data. Functional predictions identified 9 differentially present metaCyc pathways separating the upper quartile of plasma kynurenine-to-tryptophan ratio (Q4) from Q1 to Q3 (Supplementary Figure 2). Individuals with high kynurenine-to-tryptophan ratio had lower expression of L-Trp biosynthesis pathway (corrected P = .042) (Figure 2). The other differentially present pathways between the kynurenine-to-tryptophan ratio groups are listed in Supplementary Figure 2.

Increased Activity in the Kynurenine Pathway as a Possible Mediator of the Association Between Human Immunodeficiency Virus-Related Gut Microbiota and Visceral-to-Subcutaneous Adipose Tissue Ratio

Kynurenine-to-tryptophan ratio was associated with higher VAT-to-SAT ratio (β 0.50; 95% CI, 0.10–0.90) and larger VAT area (β 30.85; 95% CI, 4.43–57.28). The QA was associated with larger VAT area (β 36.47; 95% CI, 6.15–66.80). No association between KA and quinolinic-to-kynurenic acid ratio with indices of abdominal adipose distribution was found.

In mediation analysis, the total and direct association of HIV-related microbiota index on VAT-to-SAT ratio were 0.11 (standard error [SE] = 0.04, P = .008) and 0.10 (SE = 0.04, P = .023), respectively. This resulted in a mean bootstrapped indirect (mediated) association of HIV-related microbiota on VAT-to-SAT ratio through kynurenine-to-tryptophan ratio estimated to be 0.01 (SE = 0.01, P < .001), suggesting that approximately 90% of the association between microbiota and VAT-to-SAT ratio is mediated by other factors than kynurenine-to-tryptophan ratio. In line with this, no association between predicted bacterial Trp metabolism and HIV-related gut microbiota index or VAT-to-SAT ratio were found (data now shown).

The LBP levels were associated with higher levels of kynurenine-to-tryptophan ratio (β 0.08; 95% CI, 0.02–0.15) and quinolinic-to-kynurenic acid ratio (β 0.21; 95% CI, 0.12–0.30). Finally, we assessed a potential association between LBP levels and indices of abdominal adipose tissue distribution. The LBP levels were associated with larger VAT (β 24.85; 95% CI, 10.22–39.48) and SAT (β 34.79; 95% CI, 17.50–52.08) area but not with VAT-to-SAT ratio (β 0.10; 95% CI, −0.12 to 0.33). At last, interferon (IFN)-gamma concentrations were associated with higher levels of kynurenine-to-tryptophan ratio (β 0.01; 95% CI, 0.00–0.01; P = .043).

DISCUSSION

In the present study, HIV-related gut microbiota alterations were associated with increased activity in the Kyn pathway of Trp metabolism, which, in turn, was associated with indices of abdominal adipose tissue accumulation at visceral level. Our results suggest a role for this metabolic pathway in the gut microbiota-adipose tissue axis.

A close interplay between gut microbiota and Trp metabolism has been proposed in both the general population [15] and PWH [9]. Previous studies suggested bacterial metabolism of Trp in the gut, as well as translocation of bacterial products in the systemic circulation, as potential determinants of this association [9]. In the present study, the predicted differences in microbial Trp metabolism related to kynurenine-to-tryptophan ratio as well as changes in LBP suggest that both factors may be involved, with the latter factor (microbial translocation) as the major determinant of the association between Trp metabolism and gut microbiota in the context of HIV infection. Of note, we found LBP to be associated with both increased IDO-1 activity and a shift from the production of KA to QA.

Our data suggest that compositional changes in gut microbiota may also play a role in this association. In particular, HIV-related gut microbiota alterations were associated with higher activity of the Kyn pathway of Trp metabolism. This association was mainly driven by the family *Desulfovibrionaceae* and the genus *Eisenbergiella*. The *Desulfovibrionaceae* family consists of sulfur-reducing bacteria that produce hydrogen sulfide, a molecule with known toxic effects on the gut epithelium [16]. Accordingly, increase in *Desulfovibrionaceae* has been linked with both local and systemic inflammation, as well as with disruption of the mucosal gut barrier [16]. It is interesting to note that HIV-related gut microbiota changes were also associated with a shift from the production of KA to QA. Although the nature of QA as a systemic proinflammatory and oxidative stress compound is well described [17], a recent study suggested KA to directly affect the gut, exerting mucosal protective and anti-inflammatory effect [18, 19]. Furthermore, bacterial Trp metabolism in the gut was associated with kynurenine-to-tryptophan ratio in plasma, but not with HIV-related dysbiosis or VAT-to-SAT ratio. Taken together, these results may support the hypothesis that mucosal dysfunction and bacterial translocation secondary to HIV-related gut microbiota alterations, rather than increased bacterial Trp metabolism, may play a central role in the association between gut microbiota and Trp metabolism in the context of HIV infection. However, whether this association is direct or mediated by proinflammatory endogenous cytokines (eg, IFN-gamma) remains to be determined.

The Kyn pathway of Trp metabolism has previously been associated with accumulation of adipose tissue at abdominal level, both in the general population [15, 20] and in PWH [7]. Nonetheless, a possible difference in role for visceral and subcutaneous adipose tissue in this association has not yet been investigated. In the present study, kynurenine-to-tryptophan ratio and QA were associated with accumulation of adipose tissue at visceral but not subcutaneous level. A similar pattern of associations has previously been described between HIV-related gut

microbiota index and abdominal adipose tissue distribution, with the HIV-related dysbiosis being associated with larger visceral, but not subcutaneous, adipose tissue area [3]. Thus, we hypothesized the existence of a self-enhancing gut-visceral adipose tissue axis at least partly driven by the Kyn pathway of Trp metabolism in PWH. Accordingly, activation of this metabolic pathway was found to significantly mediate approximately 10% of the association between HIV-related gut microbiota alterations and accumulation of adipose tissue at visceral, but not subcutaneous, adipose tissue. Consequently, 90% of the association between gut microbiota and visceral adipose tissue would be mediated by other factors than Kyn pathway of Trp metabolism, such as energy harvest, *lipopolysaccharide* activity, inflammation, and microbiota-related metabolites. One may speculate that, in the context of HIV infection, chronic low-grade systemic inflammation, compositional changes in gut microbiota, and gut mucosal disruption support conversion of Trp into Kyn and its metabolites, which are known to be associated with adipose tissue deposition and metabolic derangements. The proinflammatory milieu characteristic of visceral adipose tissue accumulation in the context of HIV infection may then skew the metabolism of Kyn towards the production of QA rather than KA [7], contributing further to the disruption of the gut mucosal barrier and thus promoting a self-enhancing axis. In addition, high cortisol levels known to be associated with obesity [21] may also play an important role by further activating the conversion of Trp into Kyn through the activation of the hepatic enzyme tryptophan 2,3-dioxygenase (as reviewed in [22]).

The present study has some limitations. Due to the cross-sectional design, no conclusion on causality can be drawn. Furthermore, for the same reason, the direction of the association between gut microbiota composition and tryptophan metabolism cannot be determined in the present study. Furthermore, the lack of uninfected controls prevented us from investigating a possible effect modification by HIV infection on the investigated associations. Although LBP was used as a marker of microbial translocation, other factors such as systemic inflammation and macrophage activation may alter its concentrations.

CONCLUSIONS

In the present study, HIV-related gut microbiota alterations were associated with increased activity in the Kyn pathway of Trp metabolism, which, in turn, was associated with indices of abdominal adipose tissue at visceral level. Taken together, our findings suggest a possible role for this pathway in the gut-adipose tissue axis in the context of HIV infection. Additional studies are warranted to investigate the translatability of our findings in different clinical conditions.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Disclaimer. The study was designed, conducted, analyzed, and written by the authors without involvement of any commercial party.

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