The Journal of Infectious Diseases

MAJOR ARTICLE

# Abdominal Adipose Tissue Is Associated With Alterations in Tryptophan-Kynurenine Metabolism and Markers of Systemic Inflammation in People With Human Immunodeficiency Virus

**Marco Gelpi,[1] Per Magne Ueland,[2] Marius Trøseid,[3] Amanda Mocroft,[4] Anne-Mette Lebech,[5] Henrik Ullum,[6] Øivind Midttun,[2] Jens Lundgren,[1,7] and Susanne D. Nielsen,[1] for the Copenhagen Comorbidity in HIV Infection (COCOMO) Study**

[1]Viro-immunology Research Unit, Department of Infectious Diseases 8632, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]Section for Pharmacology, Department of Clinical Science, University of Bergen, Bergen, Norway, [3]Section of Clinical Immunology and Infectious Diseases, University Hospital Rikshospitalet, Oslo, Norway, [4]HIV Epidemiology and Biostatistics Unit, Department of Infection and Population Health, University College London, London, United Kingdom, [5]Department of Infectious Diseases, Hvidovre Hospital, Copenhagen University Hospital, Copenhagen, Denmark, [6]Department of Clinical Immunology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, and [7]Centre of Excellence for Health, Immunity and Infections, Department of Infectious Diseases 8632, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;

**(See the Editorial commentary by Guaraldi and Milic, on pages 343–5.)**

***Background.*** While both adipose tissue accumulation and tryptophan metabolism alterations are features of human immunodeficiency virus (HIV) infection, their interplay is unclear. We investigated associations between abdominal adipose tissue, alterations in kynurenine pathway of tryptophan metabolism, and systemic inflammation in people with HIV (PWH).

***Methods.*** Eight hundred sixty-four PWH and 75 uninfected controls were included. Plasma samples were collected and analyzed for kynurenine metabolites, neopterin, high-sensitivity C-reactive protein (hs-CRP), and lipids. Regression models were used to test associations in PWH.

***Results.*** PWH had higher kynurenine-to-tryptophan ratio than uninfected individuals ($P < .001$). In PWH, increase in waist-to-hip ratio was associated with higher kynurenine-to-tryptophan ratio ($P = .009$) and quinolinic-to-kynurenic acid ratio ($P = .006$) and lower kynurenic acid concentration ($P = .019$). Quinolinic-to-kynurenic acid ratio was associated with higher hs-CRP ($P < .001$) and neopterin concentrations ($P < .001$), while kynurenic acid was associated with lower hs-CRP ($P = .025$) and neopterin concentrations ($P = .034$).

***Conclusions.*** In PWH, increase in abdominal adipose tissue was associated with increased quinolinic-to-kynurenic acid ratio, suggesting activation of proinflammatory pathway of kynurenine metabolism, with reduction of anti-inflammatory molecules and increase in systemic inflammation. Our results suggest dysregulation of kynurenine metabolism associated with abdominal fat accumulation to be a potential source of inflammation in HIV infection.

**Keywords.** kynurenine; abdominal adipose tissue; HIV infection; inflammation.

Despite the introduction of less metabolic harmful combination antiretroviral therapy (cART) regimens, abdominal accumulation of adipose tissue is still a distinct feature in people with human immunodeficiency virus (PWH) [1]. Furthermore, an important role for new-generation antiretroviral agents, especially integrase inhibitors, in weight gain has recently been proposed [2–5]. While the cardiometabolic consequences of central obesity are well described, its impact on markers of systemic inflammation is less clear [6]. However, recent studies have suggested adipose tissue to have a critical role in proinflammatory cell dynamics [7].

Tryptophan is an essential amino acid involved in protein and serotonin synthesis. Tryptophan also represents the unique substrate for the synthesis of kynurenine and kynurenine metabolites, collectively called kynurenines [8]. The first and rate-limiting step of this pathway is mainly catalyzed by the enzyme indoleamine 2,3-dioxygenase 1 (IDO-1). IDO-1 is expressed in several tissues, including adipose tissue, and its activity is induced by proinflammatory cytokines [8]. Kynurenine is then further metabolized by kynurenine aminotransferase and kynurenine monooxygenase, to form either kynurenic acid or, alternatively, 3-hydroxykynurenine and, eventually, quinolinic acid [8, 9] (Supplementary Figure 1). Within the adipose tissue, kynurenine monooxygenase has been described to be mainly expressed in resident macrophages, and not in primary adipocytes [10]. Accordingly, in presence of macrophage

Received 15 July 2019; editorial decision 5 August 2019; accepted 11 September 2019; published online October 23, 2019.

Correspondence: M. Gelpi, MD, Viro-immunology Research Unit, Department of Infectious Diseases 8632, Copenhagen University Hospital, Blegdamsvej 9B, DK-2100 Copenhagen Ø, Denmark (marco.gelpi@regionh.dk).

**The Journal of Infectious Diseases® 2020;221:419–27**



DOI: 10.1093/infdis/jiz465

activation, the catabolism of kynurenine shifts from adipocytes toward macrophages, leading to reduction in the production of kynurenic acid in favor of quinolinic acid (ie, increasing the quinolinic-to-kynurenic acid ratio) [10]. Kynurenic acid has been reported to have anti-inflammatory properties, to beneficially regulate energy homeostasis and lipid metabolism in the adipose tissue and has been proposed as a potential therapeutic agent in obesity in uninfected individuals [11–13].

While IDO-1 activity is known to be increased in PWH [14, 15], the possible impact of fat accumulation in human immunodeficiency virus (HIV) infection on the kynurenine pathway of tryptophan metabolism is unknown. The association of kynurenine metabolites with fat accumulation [16, 17] and cardiovascular disease (CVD) risk [18–20] has been the subject of increasing interest in uninfected individuals, but remains largely unexplored in PWH [21].

In the present study, we aimed to investigate the complex interplay between fat accumulation, alterations in the kynurenine pathway of tryptophan metabolism, and systemic inflammation, in the context of HIV infection. For this purpose, in PWH we (1) investigated possible associations between waist-to-hip ratio and kynurenine-to-tryptophan ratio, quinolinic-to-kynurenic acid ratio, and kynurenine metabolites; (2) investigated possible associations of quinolinic acid, kynurenic acid, and quinolinic-to-kynurenic acid ratio with markers of systemic inflammation; and (3) exploratively assessed possible associations between kynurenine metabolites and serum lipids, hypertension, and diabetes.

## METHODS

### Study Population

PWH were recruited from the Copenhagen Comorbidity in HIV infection (COCOMO) study. The COCOMO study is an ongoing longitudinal, observational study with the aim of assessing the burden of non-AIDS comorbidities in PWH. Of the 1099 participants in the COCOMO study, 864 PWH ≥40 years old and with available measurements of tryptophan, kynurenine, and kynurenine metabolites were included in the present study. Seventy-five uninfected controls from the background population were also included as a part of the COCOMO study.

Procedures for recruitment and data collection for COCOMO have been described elsewhere [22]. Ethical approval was obtained by the Regional Ethics Committee of Copenhagen (COCOMO: H-15017350). Written informed consent was obtained from all participants.

### Clinical and Biochemical Assessments

Structured questionnaires were used in COCOMO to collect information about demographics, physical activity, smoking, and lipid lowering therapy [22]. Data regarding HIV infection were obtained from complete review of medical charts [22].

All physical examinations were performed by trained clinic staff, as previously described [22]. According to Joint National Committee guidelines, hypertension was defined as antihypertensive treatment and/or as having ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic blood pressure values [23]. Diabetes was defined as minimum one of antidiabetic treatment, nonfasting venous plasma glucose ≥11.1 mmol/L, and hemoglobin A1c ≥48 mmol/mol.

Height, weight, hip, and waist measurements and body mass index (BMI) calculations were performed according to World Health Organization guidelines [24].

Nonfasting venous blood was collected and analyzed for high-sensitivity C-reactive protein (hs-CRP), total cholesterol, low- and high-density lipoprotein (LDL and HDL, respectively), and triglycerides. Blood samples were analyzed at Herlev University Hospital, Copenhagen [22].

Plasma samples were collected and stored at –80°C until use. Plasma was analyzed for tryptophan, kynurenine, kynurenine metabolites, and neopterin concentrations by liquid chromatography–tandem mass spectrometry as previously described [25]. These analyses were performed at BEVITAL (www.bevital.no).

The ratio between kynurenine and tryptophan was used as a measure of IDO-1 activity and the quinolinic-to-kynurenic acid ratio as a measure of the macrophage dependent kynurenine metabolism (Supplementary Figure 1). Plasma concentration of neopterin was used as a marker of macrophage activation. In the interest of clarity, kynurenine-to-tryptophan ratio and quinolinic-to-kynurenic acid ratio were multiplied for a factor of 1000 and 10, respectively.

### Statistical Analyses

Continuous variables were reported as median and interquartile range and categorical variables as frequency and percentage. PWH and uninfected controls were compared with *t* tests or Mann–Whitney *U* test for continuous data with normal or nonnormal distribution, respectively, and $\chi^2$ and Fisher tests for categorical data.

In PWH, multivariable linear regression models were used to assess the association of waist-to-hip ratio and kynurenine-to-tryptophan ratio and kynurenine metabolites. Covariates included in the base model were age, sex, smoking status, origin, and BMI. Kynurenine concentration was also added to the model when using quinolinic acid, kynurenic acid, and quinolinic-to-kynurenic acid ratio as dependent variables.

The associations of quinolinic acid, kynurenic acid, and quinolinic-to-kynurenic acid ratio with markers of systemic inflammation and macrophage activation were also explored. In these models, hs-CRP and neopterin concentrations were used as dependent variables. Confounders included in the models were age, sex, smoking status, origin, BMI, and kynurenine concentration.

In sensitivity analyses, the base model was further adjusted for renal function (estimated glomerular filtration rate [eGFR])

and physical activity (inactive, moderately inactive, moderately active, and very active).

In exploratory analyses, when assessing the association between lipids and kynurenine metabolites in PWH, the base model was further adjusted for current lipid-lowering therapy. In these analyses, due to lack of a clear predefined hypothesis, *P* values were also adjusted for multiple testing (Bonferroni–Holm method). Finally, associations between hypertension, diabetes, and kynurenine metabolites were explored using logistic regression models adjusted for age, sex, smoking status, origin, and BMI.

In regression analyses, the concentrations of kynurenine metabolites were log-transformed to better fit the models and estimates are presented as changes in percentage to facilitate the interpretation of the results.

All statistical analyses were performed using R statistical software, version 3.4.1 (Foundation for Statistical Computing, Vienna, Austria). The following packages were used (in alphabetical order): "compareGroups," "ggplot2," "jtools," and "Publish."

## RESULTS

### Demographic Characteristics

Eight hundred sixty-four PWH and 75 uninfected controls from the COCOMO study were included. Characteristics of the participants are shown in Table 1.

### Kynurenine Metabolism and Immune Activation in PWH and Uninfected Controls

PWH had higher kynurenine-to-tryptophan ratio and kynurenine concentration compared to uninfected controls (25.5 vs 22.2, $P < .001$ and 1.6 vs 1.4 μmol/L, $P < .001$, respectively). No difference in tryptophan concentration, quinolinic-to-kynurenic acid ratio, quinolinic acid, kynurenic acid, or 3-hydroxyanthranilic acid concentrations was found between PWH and controls after adjusting for confounders (Table 2).

**Table 1. Characteristics of Study Participants**

| Characteristics | PWH (n = 864) | Controls (n = 75) |
|---|---|---|
| Age, median (IQR) | 52.0 (47.0–60.4) | 59.8 (51.6–67.1) |
| Sex, male | 731 (84.6) | 53 (70.7) |
| BMI, kg/m$^2$, median (IQR) | 24.6 (22.4–27.3) | … |
| Origin | | |
| Scandinavian | 640 (75.3) | … |
| Other European Union country | 99 (11.6) | … |
| Middle Eastern | 10 (1.2) | … |
| Other | 101 (11.9) | … |
| HIV transmission mode | | |
| Heterosexual | 203 (23.7) | … |
| IDU | 12 (1.4) | … |
| MSM | 586 (68.5) | … |
| Other | 54 (6.3) | … |
| Current CD4 count, cells/μL, median (IQR) | 670 (510–880) | … |
| CD4 nadir <200 cells/μL | 378 (44.7) | … |
| Current viral load <50 copies/mL | 815 (95.1) | … |
| Taking cART | 846 (98.4) | … |
| Cumulative cART duration, y, median (IQR) | 13.3 (6.5–18.0) | … |
| Smoking status | | |
| Current smoker | 238 (28.2) | … |
| Ex-smoker | 325 (38.6) | … |
| Never smoker | 280 (33.2) | … |
| Waist-to-hip ratio, median (IQR) | 0.9 (0.9–1.0) | … |
| Total cholesterol, mmol/L, median (IQR) | 4.9 (4.2–5.7) | … |
| LDL, mmol/L, median (IQR) | 2.8 (2.2–3.4) | … |
| HDL, mmol/L, median (IQR) | 1.1 (0.9–1.5) | … |
| TG, mmol/L, median (IQR) | 1.8 (1.2–2.7) | … |
| Anti-dyslipidemic treatment | 133 (16.4) | … |
| eGFR, mL/min/1.73 m$^2$, median (IQR) | 87.8 (76.8–97.5) | … |
| Hypertension | 382 (48.0) | … |
| Diabetes | 42 (5.1) | … |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; cART, combination antiretroviral therapy; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IDU, intravenous drug use; IQR, interquartile range; LDL, low-density lipoprotein; MSM, men who have sex with men; PWH, people with human immunodeficiency virus; TG, triglycerides.

**Table 2. Differences in Kynurenines and Inflammatory Markers Between People With Human Immunodeficiency Virus and Uninfected Controls**

| Variable | PWH (n = 864) | Controls (n = 75) | *P* Value | Adjusted *P* Value[a] |
|---|---|---|---|---|
| Kynurenine-to-tryptophan ratio | 25.5 (21.6–30.5) | 22.2 (19.7–24.7) | < .001 | < .001 |
| Kynurenine, µmol/L | 1.6 (1.4–1.9) | 1.4 (1.2–1.6) | < .001 | < .001 |
| Tryptophan, µmol/L | 62.3 (55.4–70.9) | 63.0 (57.9–68.9) | .369 | .439 |
| Quinolinic-to-kynurenic acid ratio | 80.7 (65.7–106.0) | 83.6 (63.6–99.8) | .856 | .716[b] |
| Quinolinic acid, nmol/L | 388.0 (312.0–484.0) | 351.5 (275.0–437.8) | .009 | .364[b] |
| Kynurenic acid, nmol/L | 48.0 (37.3–60.2) | 42.9 (37.1–49.5) | .020 | .847[b] |
| 3-Hydroxyanthranilic acid, nmol/L | 44.7 (34.8–59.7) | 35.3 (29.5–48.2) | < .001 | .141[b] |
| Neopterin, nmol/L | 16.7(13.4–21.4) | 13.9 (12.1–17.0) | < .001 | < .001 |
| hs-CRP, mg/dL | 1.2 (0.6–2.5) | 0.9 (0.5–1.7) | .010 | <. 001 |

Data are presented as median (interquartile range) unless otherwise indicated.

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; PWH, people with human immunodeficiency virus.

[a] *P* value after adjusting for human immunodeficiency virus status, age, and sex.

[b] These *P* values have been further adjusted for kynurenine concentrations.

PWH had higher hs-CRP and neopterin concentrations both before and after adjusting for confounders (Table 2).

### Association of Waist-to-Hip Ratio With Kynurenine Metabolites and Systemic Inflammation in PWH

In PWH, a 0.5-unit increase in waist-to-hip ratio was associated with 31% higher kynurenine-to-tryptophan ratio, and 44% higher quinolinic-to-kynurenic acid ratio, increments that were reduced to 19% and 33%, respectively, after adjusting for confounders ($P < .01$ for all; Table 3). A 0.5-unit increase in waist-to-hip ratio was associated with higher concentrations of hs-CRP and neopterin, and lower kynurenic acid concentration (Table 3).

In sensitivity analyses, all the above associations were not modified by further adjusting the models for renal function (eGFR) and physical activity (data not shown).

### Association of Quinolinic Acid and Kynurenic Acid With Markers of Systemic Inflammation in PWH

In PWH, quinolinic-to-kynurenic acid ratio and quinolinic acid concentration were associated with higher hs-CRP (adjusted β coefficient [aβ] = 0.44 [95% CI, 0.25–0.64], and aβ = .79 [95% CI, 0.45–1.13], respectively; $P < .001$ for all) and higher neopterin concentrations (aβ = .23 [95% CI, 0.18–0.29] and aβ = .55 [95% CI, 0.46–0.64], respectively; $P < .001$ for all) (Figure 1). In contrast, kynurenic acid concentration was associated with lower hs-CRP (aβ = – .28 [95% CI, –0.52 to –0.03]; $P = .025$) and neopterin concentrations (aβ = – .07 [95% CI, –0.14 to –0.01]; $P = .034$) (Figure 1).

In sensitivity analyses, all the above associations were maintained after further adjusting the models for waist-to-hip ratio or renal function (eGFR) (data not shown).

### Association of Kynurenine Metabolism With Lipid Levels, Hypertension, Diabetes, and Duration of cART in PWH

In PWH, increase in kynurenine-to-tryptophan ratio, kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and quinolinic acid were associated with lower cholesterol and LDL plasma levels after adjusting for confounders (age, sex, BMI, smoking status, origin, and anti-dyslipidemia treatment) (Figure 2). Increase in kynurenine-to-tryptophan ratio, kynurenine, and quinolinic acid were also associated with lower HDL levels and increases in 3-hydroxykynurenine and tryptophan were associated with lower and higher levels of triglycerides, respectively (Figure 2). After adjusting for multiple testing, 3-hydroxyanthranilic acid, 3-hydroxykynurenine, kynurenine, and quinolinic acid

**Table 3. Percentage Change in Kynurenine-to-Tryptophan Ratio, Quinolinic-to-Kynurenic Acid Ratio, Kynurenic Acid, Quinolinic Acid, High-Sensitivity C-Reactive Protein, and Neopterin per 0.5-Unit Increase in Waist-to-Hip Ratio in People With Human Immunodeficiency Virus**

| | PWH | | | |
|---|---|---|---|---|
| Outcome | Crude β Coefficient (95% CI) | *P* Value | Adjusted β Coefficient (95% CI) | *P* Value |
| Kynurenine-to-tryptophan ratio | 31 (17–46) | < .001 | 19 (5–37) | .009 |
| Quinolinic-to-kynurenic acid ratio | 44 (22–69) | < .001 | 33 (8–66) | .006 |
| Kynurenic acid | 11 (–21 – 42) | .505 | –18 (–31 – –3) | .019 |
| Quinolinic acid | 52 (30–76) | < .001 | 9 (–3 – 34) | .151 |
| hs-CRP | 431 (232–749) | < .001 | 232 (80–504) | < .001 |
| Neopterin | 19 (1–37) | .033 | 15 (–6 – 40) | .160 |

Confounders included in multivariable models were age, sex, smoking, origin, body mass index, and kynurenine (only when quinolinic-to-kynurenic acid ratio, kynurenic acid, and quinolinic acid included as dependent variables).

Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; PWH, people with human immunodeficiency virus.

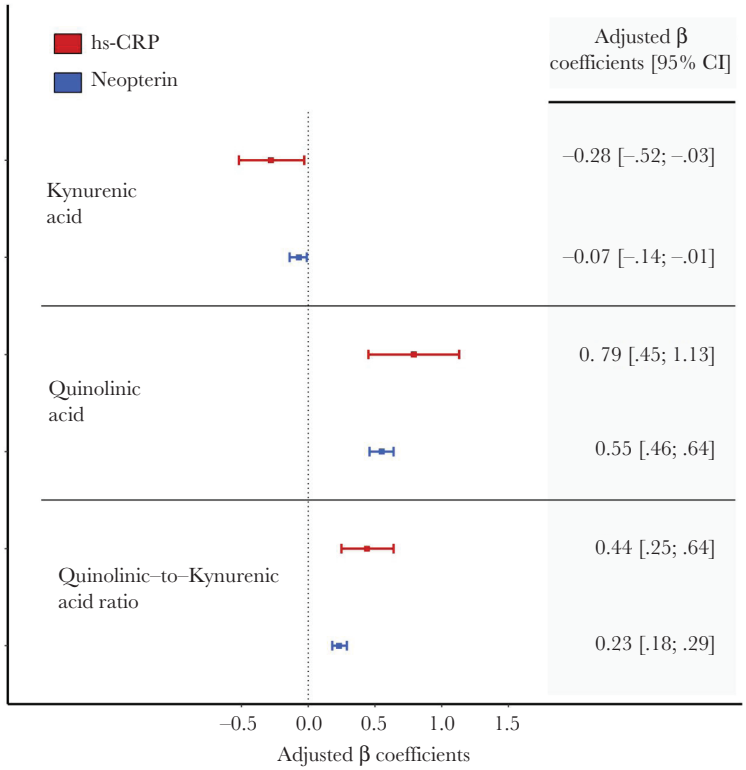


**Figure 1.** Association of kynurenic acid, quinolinic acid, and quinolinic-to-kynurenic acid ratio with high-sensitivity C-reactive protein and neopterin concentrations in people with human immunodeficiency virus. Results are shown as adjusted β coefficients. Confounders included in the models were age, sex, smoking, origin, body mass index, waist-to-hip ratio, and kynurenine concentrations. Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein.

remained associated with lower total cholesterol and LDL, and kynurenine-to-tryptophan ratio remained associated with lower total cholesterol, but not LDL. No associations were found between kynurenine metabolites and hypertension and diabetes, respectively (Supplementary Table 1).

In explorative linear regression models adjusted for age, sex, origin, BMI, and smoking, no associations were found between cumulative duration of cART and kynurenine ($P$ = .228), tryptophan ($P$ = .855), kynurenine-to-tryptophan ratio ($P$ = .222), quinolinic acid ($P$ = .557), kynurenic acid ($P$ = .089), or quinolinic-to-kynurenic acid ($P$ = .375).

## DISCUSSION

In the present study, we found well-treated PWH to have increased levels of several kynurenines compared to uninfected controls. Furthermore, in PWH increase in waist-to-hip ratio was associated with a shift from the production of kynurenic acid toward quinolinic acid which, in turn, was associated with increase in markers of systemic inflammation and macrophage activation. Accordingly, we observed a strong association between systemic inflammation and abdominal adipose tissue in the context of HIV infection. Finally, we found that in PWH, kynurenines were associated with lower concentration of circulating lipids, which is in contrast to previous observations in uninfected individuals [19, 26].

While the incidence of lipoatrophy has declined with the reduction in the use of old-generation cART, abdominal obesity is still observed in PWH in the contemporary cART era [1]. Accordingly, recent studies suggested modern cART regimens, particularly integrase inhibitors, to be associated with weight gain [2–4]. Thus, investigating the impact of fat accumulation on immunomodulatory molecule is of primary importance. Adipose tissue distribution and its metabolic consequences have been widely studied in the context of HIV infection [1, 6], but studies on adipose tissue–related immune functions, especially macrophage infiltration, are scarce and results contradicting [27, 28]. In uninfected persons, obesity has been associated with increased IDO-1 activity [16]. Accordingly, we observed positive association of kynurenine-to-tryptophan ratio with waist-to-hip ratio. Local inflammation, previously shown to accompany abdominal fat accumulation, has been suggested to be a key determinant in IDO-1 activity associated with obesity [16, 17]. However, gut microbiome alterations (ie, bacterial translocation and IDO-like enzymes producing bacteria) have also been associated with both increased activity of the kynurenine-pathway of tryptophan metabolism and adipose tissue accumulation. In particular, previous studies described bacterial

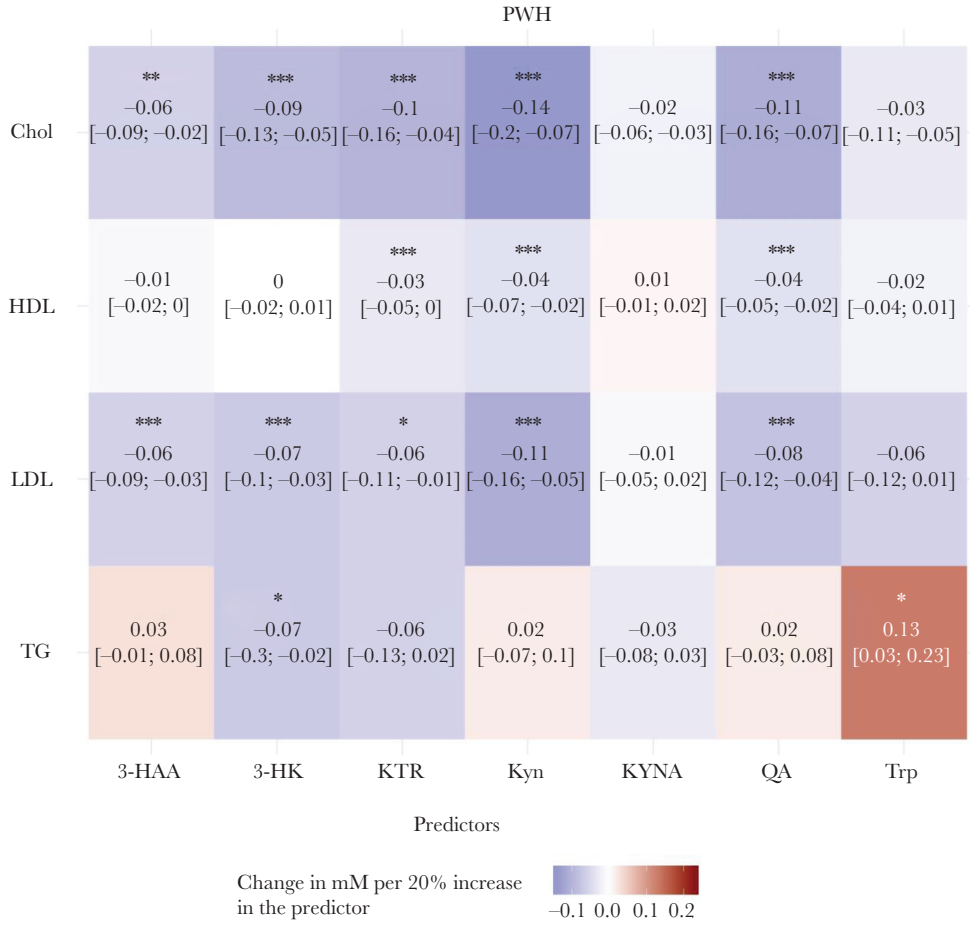


**Figure 2.** Change in lipid levels per 20% increase in kynurenine-to-tryptophan ratio and kynurenine metabolites after adjusting for confounders in people with human immunodeficiency virus. Association between lipid levels and 3-hydroxy-anthranilic acid, 3-hydroxykynurenine, kynurenine-to-tryptophan ratio, kynurenine, kynurenic acid, quinolinic acid, and tryptophan. β coefficients (95% CI) represent the mM change in the corresponding lipid level for 20% increase in the predictors. Confounders included in the models were age, sex, smoking, body mass index, and anti-dyslipidemia treatment. *$P < .05$; **$P < .01$; ***$P < .001$. Abbreviations: 3-HAA, 3-hydroxy-anthranilic acid; 3-HK, 3-hydroxykynurenine; Chol, total cholesterol; HDL, high-density lipoprotein; KTR, kynurenine-to-tryptophan ratio; Kyn, kynurenine; KYNA, kynurenic acid; LDL, low-density lipoprotein; PWH, people with human immunodeficiency virus; QA, quinolinic acid; TG, triglycerides; Trp, tryptophan.

translocation-associated increase in lipopolysaccharide levels to be able induce both IDO-1 activity [29, 30] and obesity [31]. We speculated that the association between kynurenine-to-tryptophan ratio and waist-to-hip ratio may be the result of a complex interplay between endogenous (eg, obesity-associated adipose tissue local inflammation) and exogenous (bacterial translocation and dysbiosis) stimuli.

In the context of HIV infection, infiltrating macrophages, rather than adipocytes, are the primary source of proinflammatory molecules within the adipose tissue and have been proposed as a possible important contributor to systemic inflammation [27]. IDO-1 catalyzes the formation of kynurenine, which is further metabolized into either kynurenic acid, catalyzed by kynurenine aminotransferase, or, after several steps, to quinolinic acid, via kynurenine monooxygenase [8]. Within the adipose tissue, kynurenine aminotransferase is normally expressed in adipocytes and preadipocytes, whereas kynurenine monooxygenase is mainly expressed in infiltrating proinflammatory macrophages [10], and is a key enzyme in maintaining the physiological balance between quinolinic acid and kynurenic acid production [9]. Quinolinic-to-kynurenic acid ratio has been used as an indirect measure of the balance between these 2 metabolic branches [8, 9]. Increased activity of kynurenine monooxygenase has been linked to morbid obesity, possibly due to macrophage infiltration in the adipose tissue [10]. Interestingly, in the context of HIV infection, abdominal adipose tissue may affect the balance between kynurenine aminotransferase and kynurenine monooxygenase activity. In particular, increase in waist-to-hip ratio was associated with increase in quinolinic-to-kynurenic acid ratio, which may reflect an increase in macrophage infiltration. Consequently, a shift toward the kynurenine monooxygenase-mediated pathway of kynurenine metabolism in macrophages may occur in the abdominal adipose tissue of PWH, thus causing reduction of kynurenic acid concentration in favor of the production of quinolinic acid. Accordingly, we found a negative association

between waist-to-hip ratio and kynurenic acid concentration in Kynurenic acid has previously been proposed to have important and beneficial effect on adipose tissue environment, acting as anti-inflammatory and tissue protective modulator, by activating the Gpr35 receptor [12, 13]. The negative association between kynurenic acid concentrations and both systemic inflammation and macrophage activation found in PWH supports this hypothesis. On the other hand, quinolinic acid is known to impose oxidative stress and inflammatory responses [32] and was positively associated with hs-CRP and neopterin in the present study. Taken together, our results suggest that the reduction in kynurenic acid levels in favor of quinolinic acid production found to be associated with abdominal fat accumulation may be an important contributor to the proinflammatory environment in adipose tissue in PWH.

While the association between kynurenines and adverse immunological outcome is well described in HIV infection [14, 15], less is known about the role of kynurenine and kynurenine metabolites in non-AIDS-associated comorbidities [21, 33]. In uninfected individuals, IDO-1 activity has been associated with increase in lipid levels and other CVD risk factors [19, 26]. One recent study reported a relationship between alterations of kynurenines and atherosclerosis in PWH [21]. In exploratory analyses, we set out to investigate possible associations between kynurenines with lipids levels in PWH. In contrast to previous results in uninfected individuals, which showed associations with adverse lipid profile [19, 26], we found increase in concentrations of kynurenines to be associated with lower total, LDL, and HDL cholesterol levels in PWH. We hypothesized that the inverse associations of kynurenines with both LDL and HDL found in HIV infection may suggest an effect of kynurenines on lipid synthesis. Interestingly, previous studies described 3-hydroxyanthranilic acid to have a potent lipid-lowering and atheroprotective effect in murine models, supposedly as a result of a lipid-modifying effect [34, 35]. We speculated that this effect may be a consequence of conditions characterized by high levels of kynurenine metabolites, such as following exogenous administration [34] or increase in IDO-1 activity due proinflammatory environment, known to occur in HIV infection. Further studies are needed to investigate the effect of kynurenine metabolites on lipid metabolism in HIV infection and their possible role as therapeutic targets.

The present study has limitations. Due to its cross-sectional design, no conclusion on causality can be drawn. Furthermore, clinical data for uninfected controls were not available. This prevented us from evaluating possible interactions between HIV infection and abdominal adipose tissue on kynurenine metabolite concentrations. Finally, kynurenines concentrations were measured systemically, and adipose tissue biopsies were not available to confirm our hypotheses. Thus, while we described kynurenines concentrations and ratios to be associated with abdominal adipose tissue, we could not account for kynurenines production possibly taking place in other organs.

In conclusion, results from the present study indicate that abdominal fat is associated with higher activity of kynurenine metabolism via the proinflammatory kynurenine monooxygenase-mediated pathway, with reduction in anti-inflammatory molecules and with higher levels of systemic inflammation in PWH. Taken together, our findings suggest central adipose tissue to be accompanied by increase in macrophage infiltration and activation and to be a primary source of chronic low-grade inflammation in the context of HIV infection. Due to increasing evidence suggesting an association between modern generation cART and weight gain, interventional studies are warranted to address accumulation and distribution of adipose tissue with the prospect to prevent systemic inflammation and potential harmful complications on cardiometabolic health.

## Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

***Acknowledgments.*** The authors thank all of the study subjects for their participation, as well as the staff at the Department of Infectious Diseases at Rigshospitalet and at Hvidovre Hospital for their dedicated participation.

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

***Financial support.*** This work was supported by Rigshospitalet Research Council, Region Hovedstaden, the Lundbeck Foundation, the Novo Nordisk Foundation, and the Danish National Research Foundation (grant number 126).

***Potential conflicts of interest.*** M. G. has received unrestricted travel grants from Gilead. A. M. has received honoraria, lecture fees, and travel support from ViiV and Gilead. S. D. N. has received unrestricted research grants from the Novo Nordisk Foundation, the Lundbeck Foundation, the Augustinus Foundation, and the Rigshospitalet Research Council; has received travel grants from Gilead and GSK/ViiV; and has served on advisory boards for Gilead and GSK/ViiV. All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References


1. Gelpi M, Afzal S, Lundgren J, et al. Higher risk of abdominal obesity, elevated LDL cholesterol and hypertriglyceridemia, but not of hypertension, in people living with HIV: results from the Copenhagen Comorbidity in HIV Infection (COCOMO) study. Clin Infect Dis **2018**; 67:579–86.
2. Debroy P, Sim M, Erlandson KM, et al. Progressive increases in fat mass occur in adults living with HIV on antiretroviral therapy, but patterns differ by sex and anatomic depot. J Antimicrob Chemother **2019**; 74:1028–34.
3. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment naïve persons starting dolutegravir-based antiretroviral therapy [manuscript published online ahead of print 17 May 2019]. Clin Infect Dis **2019**. doi:10.1093/cid/ciz407.
4. Menard A, Meddeb L, Tissot-Dupont H, et al. Dolutegravir and weight gain: an unexpected bothering side effect? AIDS **2017**; 31:1499–500.
5. Norwood J, Turner M, Bofill C, et al. Brief report: weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. J Acquir Immune Defic Syndr **2017**; 76:527–31.
6. Erlandson KM, Lake JE. Fat matters: understanding the role of adipose tissue in health in HIV infection. Curr HIV/AIDS Rep **2016**; 13:20–30.
7. Couturier J, Lewis DE. HIV persistence in adipose tissue reservoirs. Curr HIV/AIDS Rep **2018**; 15:60–71.
8. Savitz J, Drevets WC, Smith CM, et al. Putative neuroprotective and neurotoxic kynurenine pathway metabolites are associated with hippocampal and amygdalar volumes in subjects with major depressive disorder. Neuropsychopharmacology **2015**; 40:463–71.
9. Parrott JM, O'Connor JC. Kynurenine 3-monooxygenase: an influential mediator of neuropathology. Front Psychiatry **2015**; 6:116.
10. Favennec M, Hennart B, Caiazzo R, et al. The kynurenine pathway is activated in human obesity and shifted toward kynurenine monooxygenase activation. Obesity (Silver Spring) **2015**; 23:2066–74.
11. McQueen AE, Koliwad SK, Wang JC. Fighting obesity by targeting factors regulating beige adipocytes. Curr Opin Clin Nutr Metab Care **2018**; 21:437–43.
12. Agudelo LZ, Ferreira DMS, Cervenka I, et al. Kynurenic acid and Gpr35 regulate adipose tissue energy homeostasis and inflammation. Cell Metab **2018**; 27:378–92.e5.
13. Dadvar S, Ferreira DMS, Cervenka I, Ruas JL. The weight of nutrients: kynurenine metabolites in obesity and exercise. J Intern Med **2018**; 284:519–33.
14. Routy JP, Mehraj V, Vyboh K, Cao W, Kema I, Jenabian MA. Clinical relevance of kynurenine pathway in HIV/AIDS: an immune checkpoint at the crossroads of metabolism and inflammation. AIDS Rev **2015**; 17:96–106.
15. Gelpi M, Hartling HJ, Ueland PM, Ullum H, Trøseid M, Nielsen SD. Tryptophan catabolism and immune activation in primary and chronic HIV infection. BMC Infect Dis **2017**; 17:349.
16. Mangge H, Summers KL, Meinitzer A, et al. Obesity-related dysregulation of the tryptophan-kynurenine metabolism: role of age and parameters of the metabolic syndrome. Obesity **2014**; 22:195–201.
17. Brandacher G, Hoeller E, Fuchs D, Weiss HG. Chronic immune activation underlies morbid obesity: is IDO a key player? Curr Drug Metab **2007**; 8:289–95.
18. Song P, Ramprasath T, Wang H, Zou MH. Abnormal kynurenine pathway of tryptophan catabolism in cardiovascular diseases. Cell Mol Life Sci **2017**; 74:2899–916.
19. Liu G, Chen S, Zhong J, Teng K, Yin Y. Crosstalk between tryptophan metabolism and cardiovascular disease, mechanisms, and therapeutic implications. Oxid Med Cell Longev **2017**; 2017:1602074.
20. Mangge H, Stelzer I, Reininghaus EZ, Weghuber D, Postolache TT, Fuchs D. Disturbed tryptophan metabolism in cardiovascular disease. Curr Med Chem **2014**; 21:1931–7.
21. Qi Q, Hua S, Clish CB, et al. Plasma tryptophan-kynurenine metabolites are altered in human immunodeficiency virus infection and associated with progression of carotid artery atherosclerosis. Clin Infect Dis **2018**; 67:235–42.
22. Ronit A, Haissman J, Kirkegaard-Klitbo DM, et al. Copenhagen comorbidity in HIV infection (COCOMO) study: a study protocol for a longitudinal, non-interventional assessment of non-AIDS comorbidity in HIV infection in Denmark. BMC Infect Dis **2016**; 16:713.
23. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA **2014**; 311:507–20.
24. World Health Organization. Waist circumference and waist-hip ratio: report of a who expert consultation. Geneva, Switzerland: WHO, **2008**:8–11.
25. Midttun Ø, Hustad S, Ueland PM. Quantitative profiling of biomarkers related to B-vitamin status, tryptophan metabolism and inflammation in human plasma by liquid chromatography/tandem mass spectrometry. Rapid Commun Mass Spectrom **2009**; 23:1371–9.
26. Pertovaara M, Raitala A, Juonala M, et al. Indoleamine 2,3-dioxygenase enzyme activity correlates with risk factors for atherosclerosis: the cardiovascular risk in Young Finns Study. Clin Exp Immunol **2007**; 148:106–11.
27. Shikuma CM, Gangcuangco LM, Killebrew DA, et al. The role of HIV and monocytes/macrophages in adipose tissue biology. J Acquir Immune Defic Syndr **2014**; 65:151–9.

28. Srinivasa S, Fitch KV, Torriani M, et al. Relationship of visceral and subcutaneous adipose depots to markers of arterial injury and inflammation among individuals with HIV. AIDS **2019**; 33:229–36.
29. Vujkovic-Cvijin I, Dunham RM, Iwai S, et al. Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. Sci Transl Med **2013**; 5:193ra91.
30. Byakwaga H, Boum Y 2nd, Huang Y, et al. The kynurenine pathway of tryptophan catabolism, CD4+ T-cell recovery, and mortality among HIV-infected Ugandans initiating antiretroviral therapy. J Infect Dis **2014**; 210:383–91.
31. Everard A, Lazarevic V, Derrien M, et al. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. Diabetes **2011**; 60:2775–86.
32. Lugo-Huitrón R, Ugalde Muñiz P, Pineda B, Pedraza-Chaverrí J, Ríos C, Pérez-de la Cruz V. Quinolinic acid: an endogenous neurotoxin with multiple targets. Oxid Med Cell Longev **2013**; 2013:104024.
33. Hoel H, Hove-Skovsgaard M, Hov JR, et al. Impact of HIV and type 2 diabetes on gut microbiota diversity, tryptophan catabolism and endothelial dysfunction. Sci Rep **2018**; 8:6725.
34. Zhang L, Ovchinnikova O, Jönsson A, et al. The tryptophan metabolite 3-hydroxyanthranilic acid lowers plasma lipids and decreases atherosclerosis in hypercholesterolaemic mice. Eur Heart J **2012**; 33:2025–34.
35. Cole JE, Astola N, Cribbs AP, et al. Indoleamine 2,3-dioxygenase-1 is protective in atherosclerosis and its metabolites provide new opportunities for drug development. Proc Natl Acad Sci U S A **2015**; 112:13033–8.