Daily variations of gut microbial translocation markers in ART-treated HIV-infected people

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Short report

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Abstract

Background

Gut microbial translocation and increased intestinal barrier permeability are significant contributors to inflammatory non-AIDS co-morbidities in people living with HIV (PLWH). However, daily variations of markers of bacterial and fungal translocation along with intestinal damage are not characterized yet. Herein, we assessed the variation of these markers over 24 hours in PLWH receiving antiretroviral therapy (ART) in a well-controlled environment.

Methods

A total of 11 male ART-treated PLWH were recruited for the study. Blood samples were collected every 4 hours over 24 hours before snacks/meals from 8:00 in the morning to 8:00 the next day. All participants consumed similar meals at set times, and had a comparable amount of sleep, physical exercise and light exposure. Plasma levels of bacterial lipopolysaccharide (LPS) and fungal (1→3)-β-D-Glucan (BDG) translocation markers, along with markers of intestinal damage fatty acid binding protein (I-FABP) and regenerating islet-derived protein-3α (REG3α) were assessed by ELISA or the fungitell assay.

Results

Plasma levels of BDG and REG3α were stable during the day. In contrast, plasma levels of LPS and I-FABP were subject to daily variations, with the lowest levels at 12:00 and 16:00, respectively, and the highest levels at 00:00 and 4:00-8:00, respectively.

Conclusions

Conversely to the fungal translocation marker BDG and the gut damage marker REG3α, time of blood collection matters for the proper evaluation for LPS and I-FABP as markers for the risk of inflammatory non-AIDS co-morbidities. These insights are instrumental for orienting clinical investigations in PLWH.

Background

The gastrointestinal (GI) tract is a distinctive tissue with physical, biological and immunological barriers, allowing nutrient absorption while preventing the translocation of microbes and their products. HIV infection is associated with modification of the gut microbiota, disruption of the gut epithelial barrier, and increased intestinal permeability [1–4]. In contrast to the global health improvement occurring in people living with HIV (PLWH) receiving antiretroviral therapy (ART), gut damage persists and translocation of microbial products from the gut lumen into the circulation contributes to inflammatory non-AIDS comorbidities [5]. Microbial translocation is one of the main drivers for the development of such comorbidities including cardiovascular disease, depression and cancer in ART-treated PLWH [6–10].

In order to assess the risk of developing non-AIDS co-morbidities and evaluate therapeutic interventions, the measurement of microbial translocation plasma markers is clinically relevant. Circulating levels of lipopolysaccharide (LPS) are commonly measured to assess the level of bacterial translocation. LPS is a bacterial cell wall polysaccharide and is a well-known inducer of innate immune activation [11]. Besides bacterial translocation, there is increasing awareness regarding fungal translocation [12–15]. Fungi contribute greatly to opportunistic infections in PLWH, including Pneumocystis jirovecii in the respiratory tract and Candida albicans in the gastrointestinal tract [16]. (1→3)-β-D-Glucan (BDG) is a major component of most fungal cell walls and serves as a potent pathogen-associated molecular pattern (PAMP) in triggering antifungal immunity [17]. Circulating BDG is currently used for the clinical diagnosis of Candida, Aspergillus, and Pneumocystis jirovecii invasive infections [18]. Recently, we and others have found that plasma levels of BDG are associated with epithelial gut damage and risk of developing inflammatory non-AIDS comorbidities in PLWH without invasive fungal infection (IFI) [12–14, 18–22]. These findings show converging evidence that BDG is a clinically significant fungal translocation marker in PLWH.

Circulating intestinal fatty acid binding protein (I-FABP) and regenerating islet-derived protein-3α (REG3α) are two validated gut damage markers in PLWH [23, 24]. I-FABP, an intracellular protein constitutively expressed in enterocytes, is released upon cell death and subsequently detected in the blood in inflammatory bowel diseases (IBD) and HIV infection [25, 26]. REG3α, an antimicrobial peptide secreted by intestinal Paneth cells into the gut lumen and upon gut damage, translocates into the blood [24]. We observed that REG3α plasma levels were correlated with HIV disease progression, microbial translocation and immune activation in PLWH [24].

Information on the influence of food intake and daily variation of microbial translocation markers is still not reported. Knowing daily variations of these markers could improve clinical care and research. Herein, we assessed the variation of the microbial translocation markers, LPS and BDG, and the gut damage markers, I-FABP and REG3α, over the course of 24 hours in ART-treated PLWH in a well-controlled environment.

Methods

Participants and Study Design

A total of 11 men living with HIV, receiving ART for more than 3 years, were enrolled and hospitalized for 40 hours at the phase I clinic of the Centre Hospitalier de l'Université de Montréal, Montreal, Canada. Study timeline is shown in Fig. 1. Blood samples were collected using a catheter fixed to the median cubital vein throughout their hospitalization to prevent repeated venipuncture and disturbing participants' sleep cycles. Samples were collected 15 hours after participant admission to establish a baseline, then every 4 hours from 8:00 am to 8:00 am the next morning for a total of seven timepoints. Plasma was isolated from whole blood and frozen at -80 ℃. All participants had similar meals/snacks at set times (8:30, 13:00, 16:30 and 20:30), and had a comparable amount of sleep, physical exercise and light

exposure. Scientific and artistic educational presentations were organized as part of a knowledge transfer and exchange with participants and research nurses. All participants agreed to take part in a 60 minutes low-intensity yoga session in the afternoon. Neither alcoholic beverages nor recreational drugs were permitted during the time of hospitalization.

Laboratory Measurements

Plasma HIV-1 p24 antigen/antibody and confirmatory Western blot tests were used to confirm HIV-infection, as previously reported [12]. Quantification of plasma viral load (VL) was done using the Abbott Real-Time HIV-1 assay (Abbott Laboratories, Abbott Park, Illinois, USA). CD4 and CD8 T-cell counts were measured using flow cytometry. LPS was quantified using a human lipopolysaccharide enzyme-linked immunosorbent assay (ELISA) (Cusabio, Wuhan, China) to avoid cross-reactivity with BDG in existing limulus amebocyte lysate (LAL) assays [12]. Plasma BDG level was measured by the Fungitell® LAL assay (Associates of Cape Cod, Inc., East Falmouth, MA, USA) [12]. I-FABP and REG3α were quantified in plasma using ELISA (Hycult Biotech, Uden, Netherlands and R&D systems, Oakville, ON, Canada, respectively) [24].

Statistical analyses

Statistical analyses were conducted using GraphPad Prism 6.0 (La Jolla, CA, USA). The individual raw data were converted to Z scores, based on subject-specific mean and standard deviation (SD), calculated using all samples collected during seven time points of 24 hours in order to reduce the interindividual variability [27]. Comparisons were conducted using non-parametric Kruskal-Wallis test with Dunn's post hoc test. An α-level of 5% was used for statistical significance.

Results

Study Participant Characteristics

Participant characteristics were summarized in Table 1. All participants were male, with a median (interquartile range [IQR]) age of 57 (54–58) years. Participants received ART for a median of 17 (13–21) years. Plasma VL of all participants were below the level of detection (< 20 copies/ml). Median CD4 T-cell count was 606 (410–800) cells/μl and median CD8 T-cell count was 613 (498–924) cells/μl.

Table 1

Participant Characteristics (n = 11)

ID	Age	Body mass index(kg/m^2)	CD4 count (cells/ µL)	CD8 counts (cells/ µL)	ART duration (years)	Viral load	Current ART medication
1	60	27.8	602	1321	10	undetectable	emtricitabine, TDF, raltegravir
2	52	27.1	491	613	21	undetectable	emtricitabine, TDF, raltegravir
3	57	28.4	606	855	12	undetectable	emtricitabine, TDF, raltegravir
4	57	32.9	846	901	22	undetectable	emtricitabine, TDF, darunavir, cobicistat
5	57	24.9	410	924	31	undetectable	emtricitabine, TDF, efavirenz
6	63	27.7	667	553	15	undetectable	abacavir, dolutegravir, lamivudine
7	50	34.9	379	498	19	undetectable	emtricitabine, TDF, raltegravir
8	58	26.1	311	331	21	undetectable	emtricitabine, TDF, elvitegravir, cobicistat,
9	57	24.6	800	597	13	undetectable	abacavir, dolutegravir, lamivudine
10	58	32.1	675	494	13	undetectable	abacavir, dolutegravir, lamivudine
11	54	23.9	1082	1425	17	undetectable	lamivudine, abacavir, raltegravir,

TDF = Tenofovir disoproxil fumarate

Daily variation of the microbial translocation markers LPS and BDG

LPS levels varied significantly over time ($p < 0.001$) and tended to decrease between 8:00 to 12:00 (Z-score − 0.22 ± 0.31 vs. -1.15 ± 0.18), without reaching statistical significance (Fig. 2C). A significant increase of LPS was observed from 12:00 to 16:00 (Z-score of -1.15 ± 0.18 vs. 0.16 ± 0.15, $p = 0.02$) (Fig. 2C). Similarly, a difference was also noticed between 12:00 and 24:00 (Z-score of -1.15 ± 0.18 vs. 0.89 ± 0.26, $p < 0.001$) (Fig. 2C). At 8:00 on the second day, levels of LPS were comparable to levels observed at 8:00 on the preceding day (Fig. 2C).

Conversely, levels of BDG did not vary significantly over the course of the study (Fig. 2D, 2E, and 2F, $p = 0.261$).

Daily variation of the gut damage markers I-FABP and REG3α

Over the course of the study, I-FABP levels varied significantly ($p < 0.001$). I-FABP levels decreased from 8:00 to 16:00 with a Z-score 0.48 ± 0.26 vs. -0.92 ± 0.09 ($p = 0.002$) (Fig. 2I). After 16:00, levels of I-FABP increased [Z-score of 0.73 ± 0.27 at 4:00 ($p < 0.001$) and 0.88 ± 0.27 at 8:00 ($p < 0.001$)]. Similar levels of I-FABP were observed at 8:00 of the first day and 8:00 of the second day ($p > 0.05$) (Fig. 2G).

Levels of the gut damage marker REG3α did not vary significantly over the course of the study (Fig. 2J, 2K, and 2L, $p = 0.570$).

Discussion

We observed that LPS and I-FABP circulating levels fluctuated significantly over the course of 24 hours. Previous work in mouse models has shown a postprandial increase in LPS levels [28]. We observed a clinically relevant decrease of LPS after breakfast and an increase after dinner which might be explained by natural variations in circadian rhythm [29, 30]. These results suggest a need to sample LPS from fasting PLWH in order to decrease variation throughout the day. Similarly, I-FABP was subject to daily variations with the lowest level at 16:00 and highest at 4:00–8:00. However, plasma levels of BDG and REG3α showed no significant variation and were not affected by food intake, time of sampling, or day/night shifts. These findings further validate the use of BDG and REG3α as markers of microbial translocation and gut damage, respectively in ART-treated PLWH.

Translocation of bacterial and fungal products are driven by epithelial gut damage and depletion of intestinal CD4-T cells and contribute to immune activation in HIV [21, 31]. Clinical studies commonly use circulating I-FABP to evaluate gut damage as a measure of enterocyte cell lysis. However, in the absence of enterocyte lysis, I-FABP poorly correlates with microbial translocation [24]. Our results show that circulating I-FABP levels varied greatly throughout the course of a day, which limits its value as a marker of gut damage, since it is dependent on the time of sampling and fasting status. In contrast to I-FABP, REG3α appeared stable over the course of 24 hours. Therefore, our results and previous work favor REG3α as a reliable gut damage marker independent of sampling time and food intake in PLWH [24].

LPS is a bacterial translocation marker, responsible for chronic immune activation in HIV-infected patients [32]. However, increasing evidence indicates that diet and food intake affect the plasma level of LPS in mouse and human models. Cani et al.[28] first reported in 2007 that plasma levels of LPS increased after feeding mice with a high-fat diet. Furthermore, López-Moreno et al.[33] reported that the consumption of diet rich in saturated fat increased plasma levels of LPS which in turn, increase the postprandial inflammatory response in subjects with metabolic syndrome. Our results also indicated that food intake was associated with an increase in plasma level of LPS in ART-treated PLWH up to four hours after lunch and supper. Although the underlying mechanism is unclear, it may be related to changes in microbiota composition, increases in the proportion of LPS producing Gram-negative bacteria in the presence of nutrients [34]. LPS detoxification by the intestinal alkaline phosphatase [35], or fat intake promoting gut translocation of LPS [28, 33]. Therefore, monitoring LPS levels in PLWH should take into account feeding state and time of specimen acquisition.

Unlike LPS, we showed that the fungal translocation marker BDG is stable throughout the day and independent of food intake. BDG can be found in food such as mushroom and seaweed [36, 37]. Interestingly, Hashimoto et al. reported that serum BDG value was elevated due to intake of seaweed in a hematopoietic stem cell transplant recipient [38]. However, the elevation of BDG may have been linked to gut damage with increased intestinal permeability during acute graft-versus-host disease (GVHD). Nevertheless, our results showed that BDG is a reliable marker for fungal translocation in ART-treated PLWH. The food provided in our study did not comprise mushroom, seaweed or other material rich of BDG. Thus, further studies need be conducted in order to study the effects of BDG rich food on its plasma level.

We acknowledge that our study presents some limitations as we did not study the underlying mechanism of daily variation of I-FABP or LPS levels. Daily changes in the external environment may also influence those markers and studies have identified the molecular underpinnings of oscillations in circadian clock gene expression occurring over the 24-hour day [30]. Our study population only included a small sample size of male participants over the age of 50, therefore younger participants and inclusion of female participants will be needed to infer study findings on a larger population.

To our knowledge, we are the first to report the daily variation of different microbial translocation with gut damage markers in ART-treated PLWH. We showed that conversely to I-FABP and LPS, plasma levels of REG3α and BDG can be considered as reliable markers of gut damage and fungal translocation respectively, and are not influenced by food intake, time of sampling, or day/night shifts. Such findings may have immediate clinical implications for making appropriate diagnosis and prognosis assessment in care and clinical trials involving persons living with HIV.

Abbreviations

ART:antiretroviral therapy; LPS:lipopolysaccharide; BDG:(1→3)-β-D-Glucan:GI:gastrointestinal; GVHD:graft-versus-host disease; LAL:limulus amebocyte lysate; IBD:inflammatory bowel diseases;

IQR:interquartile range; I-FABP:intestinal fatty acid binding protein; IFI:invasive fungal infection; PAMP:pathogen-associated molecular pattern; PLWH:people living with HIV; REG3α:regenerating islet-derived protein-3α; SD:standard deviation; VL:viral load.

Declarations

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Authors' contributions

JO, SI wrote the manuscript. JO, SI, JL and BF participated in laboratory testing, statistical analysis, and drafting of the manuscript. DC, TRWS, DP, AF, AC, EMG, LRM performed isolation of plasma and PBMC during the study. YZ and MF performed the Fungitell assay. YC, DEK, NC, PA and JPR conceived and designed the study. All of the authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by the ethical committee of the McGill University Health Centre (MUHC, number MEO-02-2019-4872) and the Centre Hospitalier de l'Université de Montréal (CHUM, number MP-02-2017-6677). All study participants provided written consent for enrollment before participation. The study was conducted in accordance with the declaration of Helsinki.

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Figures

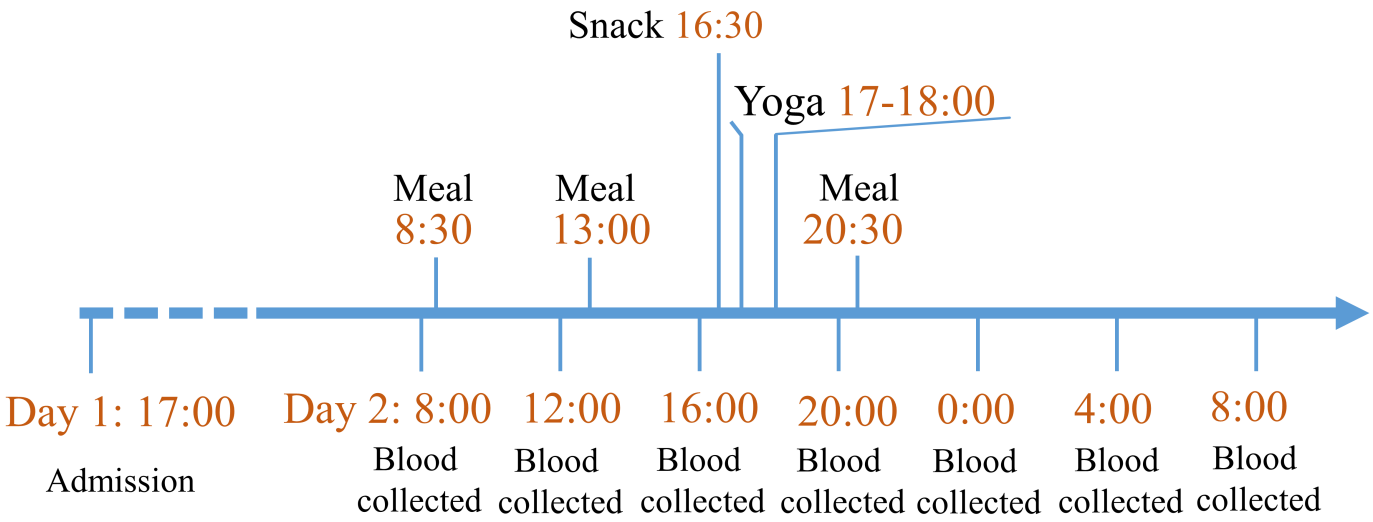

Figure 1

Study timeline

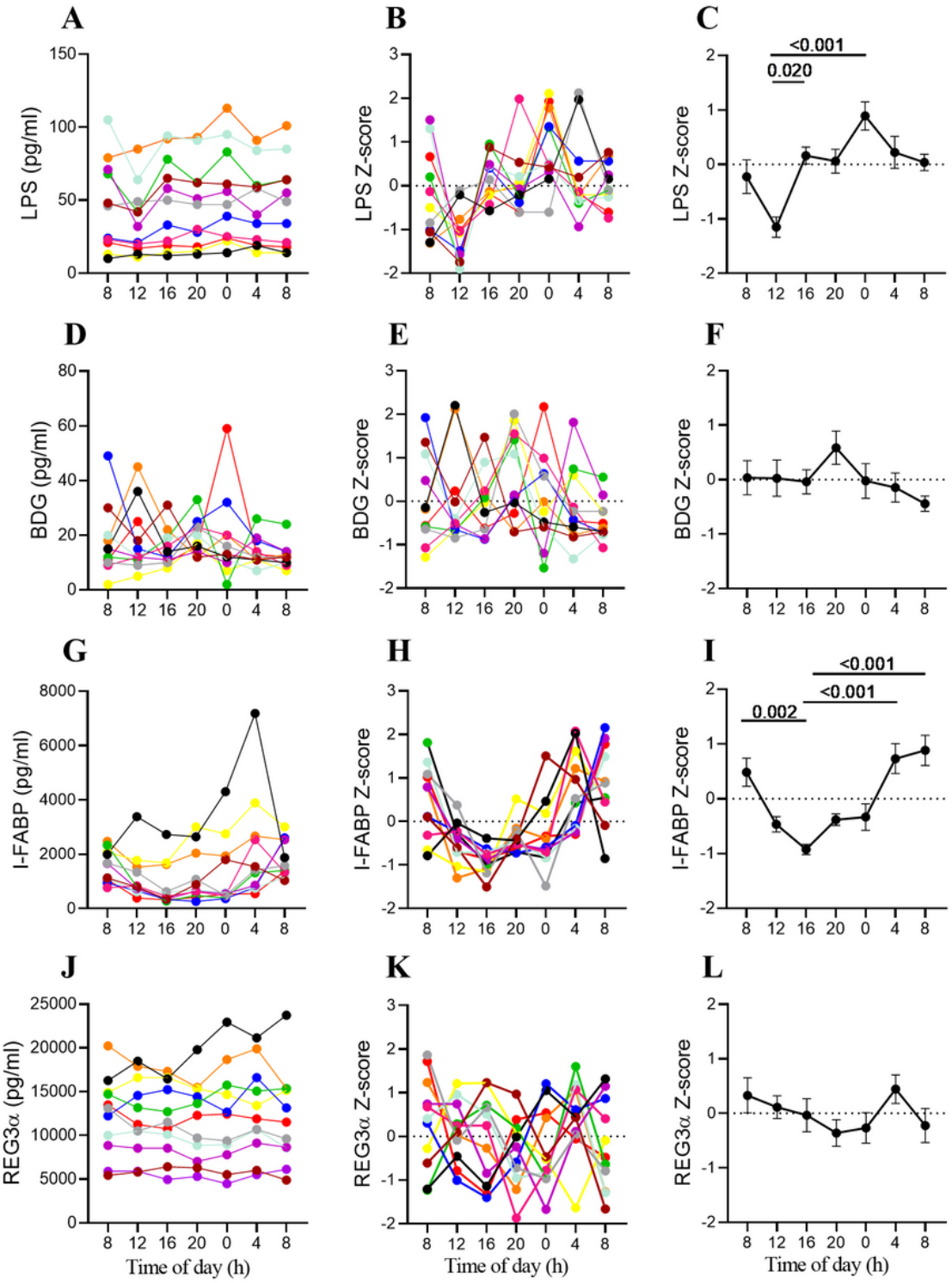

Figure 2

Daily variation of gut damage and translocation markers. Plasma levels of Lipopolysaccharide (LPS) (A, B, C, p<0.001), (1→3)-β-D-Glucan (BDG) (D, E, F, p=0.261), Intestinal fatty acid binding protein (I-FABP) (G, H, I, p<0.001) or Regenerating islet-derived protein 3 α (REG3α) (J, K, L, p=0.570). In figure A, B, D, E, G, H, J and K, different colors represent different participants: red (ID 1); orange (ID 2); yellow (ID 3); green (ID 4);

blue (ID 5); cyan (ID 6); purple (ID 7); pink (ID 8); gray (ID 9); black (ID 10); brown (ID 11). Mean ± standard error of the mean (SEM) of the Z-score are shown in C, F, I and L. Friedman test.