Frailty Is Associated With Insulin Resistance in Chronic Human Immunodeficiency Virus Infection

To the Editor—We read with interest the article by Kelly et al [1] who described frailty as an independent risk factor for chronic diseases and mortality in persons living with human immunodeficiency virus (HIV; PLWH). Specifically, the authors observed that slow gait speed (GS) was associated with diabetes mellitus (DM). We add to their findings that measures of abnormal glucose metabolism prior to DM development can be linked to prefrail and frail conditions.

Data from the Hawaii Aging with HIV-Cardiovascular Disease study [2] were analyzed to assess the association of frailty with insulin resistance (IR). Frailty was characterized using Fried's frailty phenotype (frail ≥3 criteria; prefrail = 1–2; nonfrail: 0) [3]. To assess IR, the homeostatic model assessment of IR (HOMA-IR) and oral disposition index (DIo) were calculated. DIo is also used to assess β-cell function [4].

Of 73 PLWH in our cohort, median age was 51 years and median CD4 count was 466 cells/mm^3. The majority were male (89%) with plasma HIV RNA <50 copies/mL (84%). We found that 42 participants were nonfrail, 26 were prefrail, and 5 were frail. We ran separate analysis of variance models with a Tukey adjustment to assess the association between handgrip strength (HGS), GS, and IR between frailty groups. Frail and prefrail groups demonstrated significantly lower HGS compared with nonfrail participants (Table 1). Frail participants showed significantly slower GS compared with prefrail and nonfrail participants. HOMA-IR was significantly increased in frail participants compared with nonfrail participants. DIo was significantly lower in frail participants compared with nonfrail participants. DIo correlated with GS (rho = –0.245, P = .036) but not with HGS. Given the limited number of frail participants, we combined the prefrail and frail participants and performed sensitivity analyses on the above results to determine which associations still held. In our comparison of frail and nonfrail participants, we found that HGS and DIo remained significantly lower and GS remained significantly higher.

Frailty reflects reduced mobility related to poor skeletal muscle glucose uptake, suboptimal glycemic control, and IR [5]. Of Fried's phenotypes, HGS and GS are the only parameters that provide objective measures of frailty. In clinical practice, implementing HGS and GS may also determine the degree of sarcopenia [6]. In older populations, guidelines to improve sarcopenia [7] have suggested specific measures such as prescription of resistance-based physical activity and protein supplementation. Similar interventional methods should be considered for frail and sarcopenic PLWH. The AIDS Clinical Trials Group A5322 study found that the development of slow gait was associated with baseline hemoglobin A1c [8]. A limitation of our study was that not all participants' frailty measurements were performed at the same time as the IR measurement. Frailty and IR assessment were within 2 years of each other. Additionally, to address confounding by diabetes, participants with DM were removed from the analyses. Despite these limitations, frailty and lower HGS were significantly associated with worsening IR.

In summary, we found that frailty was significantly associated with reduced insulin sensitivity and increased IR. The role of chronic inflammation or persistent immune activation in frailty needs to be further explored as well as the utility of objective measures such as HGS and GS.

Notes

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Table 1. Characteristics of Persons Living With Human Immunodeficiency Virus Stratified by Frailty Score

Characteristic	Nonfrail (n = 42)	Prefrail (n = 26)	Frail (n = 5)
Frail characteristic			
Average grip strength, kg (IQR)	41 (36–48)	30 (27–38)[a]	29 (26–30)[a]
Average gait speed, seconds (IQR)	3.3 (3.0–3.7)	3.7 (3.5–4.2)[a]	5.2 (4.5–5.6)[a,b]
Low physical activity, n (%)[c,d]	0 (0)	10 (38)	5 (100)
Exhaustion, n (%)[e,d]	0 (0)	6 (23)	5 (100)
≥10 lb or ≥5% unintentional body weight loss, n (%)[d]	0 (0)	3 (11)	1 (20)
Glucose metabolism			
Insulin sensitivity (IQR)	0.02 (0.01–.03)	0.02 (0.01–.03)	0.008 (0.007–.017)[a,b]
Homeostatic model assessment of insulin resistance (IQR)	1.44 (0.88–2.14)	1.48 (0.89–1.93)	4.06 (1.78–4.35)[a]
Oral disposition index (IQR)	2.90 (1.79–3.90)	1.91 (1.45–3.43)	1.35 (1.14–1.61)[a]

Abbreviation: IQR, interquartile range.

[a]$P \leq .05$ with nonfrail as the reference variable using Tukey adjustment.

[b]$P \leq .05$ with prefrail as the reference variable using Tukey adjustment

[c]Low physical activity defined as health limiting vigorous activities.

[d]Proportions of low physical activity, exhaustion, and weight loss were significantly different between groups by exact χ^2 test.

[e]Exhaustion defined as having little energy 3 or more days per week.

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Assessing the Ecological Benefit of Antibiotic De-escalation Strategies to Elaborate Evidence-Based Recommendations

To the Editor—We read with interest Zaira R. Palacios-Baena and colleagues' article, "Impact of de-escalation on prognosis of patients with bacteremia due to *Enterobacteriaceae*: a post hoc analysis from a multicenter prospective cohort" [1]. In this study, the authors have shown that de-escalation in patients with monomicrobial bacteremia due to *Enterobacteriaceae* was not associated with a detrimental impact on clinical outcomes. De-escalation refers to a strategy aiming at decreasing the antibiotic pressure on intestinal microbiota and the associated risk of multidrug-resistant organism (MDRO) acquisition, while maintaining a similar clinical efficacy. In this perspective, we can regret that the de-escalation strategy used by Zaira R. Palacios-Baena and colleagues was not assessed for its impact either on the risk of MDRO acquisition or on the intestinal microbiota.

Because of their remarkable, broad spectrum of activity, carbapenems are intuitively believed to be the beta-lactam drugs with the greatest collateral effects on the intestinal microbiota [2]. Hence, a switch toward non-carbapenem beta-lactams to treat infections due to susceptible strains is generally considered relevant as de-escalation. However, whether the ecological impact and the risk of MDRO acquisition associated with these alternatives are actually lower than with carbapenems remains to be demonstrated. We recently reviewed the available literature on the intestinal impact of carbapenems and their main alternatives in infections involving extended-spectrum beta-lactamase–producing *Enterobacteriaceae* [3]. Unexpectedly, published data on this topic are scarce and do not currently allow us to draw any firm conclusions on whether carbapenems may exert a stronger impact on intestinal colonization resistance than alternatives. In contrast, molecules with high biliary excretion and powerful anti-anaerobic properties, such as piperacillin/tazobactam and cephamycins, seem to be associated with major disturbances of the intestinal microbiota [4].

We agree that the overuse of certain last-line molecules should be avoided in order to preserve their efficacy and that antibiotic re-evaluation belongs to good practices. However, drawing de-escalation upon the narrowing of the clinical spectrum of the antibiotics currently has no scientific substratum, and has never demonstrated any ecological benefit [5]. In fact, assigning an ecological impact to an antibiotic by analogy with its clinical spectrum is inadequate and should be changed for multifaceted approaches that have already been suggested [6]. For these reasons, we believe that both the consensus ranking of beta-lactams used [2] and the positioning of other antibiotic classes, as proposed in this work, should be entirely revisited in light of their true ecological impact. To this aim, we need to define a standardized protocol to assess the impact of antibiotics, new and old, and push regulatory agencies to include such analyses for any new drug releases.

Despite the large number of studies assessing the safety of de-escalation strategies [7–9], their putative ecological benefits on intestinal microbiota or on the risk of MDRO acquisition have never been assessed. It is time now to precisely assess the ecological impacts of antibiotics on intestinal microbiota and colonization resistance when comparing antibiotic therapy strategies, so that strong and efficient recommendations on de-escalation strategies can be reached and MDRO dissemination can be efficiently addressed.