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The Physiological Effects of Obesity in HIV-Infected Patients

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Abstract

Barely two decades ago, HIV disease deemed a terminal illness accompanied by severe wasting. Today, HIV disease has become a chronic illness, largely due to the success of highly active antiretroviral therapy (ART). In the U.S., this increased longevity has naturally led to HIV-infected persons becoming increasingly overweight and obese, with rates of weight excess similar to that of the general population. This article reviews existing literature on the impact of obesity on HIV-infected patients, and the management of obesity with a focus on older persons. Weight excess in the general and HIV-infected populations is associated with adverse medical conditions, such as hypertension, dyslipidemia and diabetes mellitus. Obesity in HIV-infected patients, and particularly older patients, is associated with decline in physical function and frailty. However, more research is needed to fully understand the complications of obesity in HIV-infected patients and its pathophysiologic mechanisms. Clinicians should be aware of these trends with respect to obesity in this population, and consider implementing customized weight management programs as part of routine HIV care. In that respect, future research is sorely needed to develop evidence-based guidelines to manage obesity in HIV-infected patients, and particularly those who have functional impairments or medical complications that can benefit from customized weight management programs.

Keywords: HIV; Obesity; Older adults; Cardiovascular disease; Frailty

Introduction

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse eȣect on health. More than one-third of U.S. adults (over 72 million people) and 17% of U.S. children are obese. Additionally, obesity rates have markedly increased in population groups, regardless of race, ethnicity, socioeconomic status, education or geographic region [1].

HIV-infected patients mirror the trends in the general population and are increasingly overweight or obese both at diagnosis and during HIV infection [2]. Weight gain in HIV-infected patients appears to re ect improved health status, as severe weight loss and wasting has been traditionally associated with HIV-infected status. However, as seen in the general population, HIV-infected patients also show an association between weight excess and adverse medical consequences. Indeed, obesity leads to the onset of metabolic imbalances. Central adiposity is associated with the metabolic syndrome and related risks for type 2 diabetes mellitus (DM), atherosclerosis, dyslipidemia, hypertension and malignancies [3,4]. e prevalence of these metabolic complications has increased among HIV-infected patients receiving ART and these metabolic complications currently outnumber AIDS associated conditions in these patients and develop at a younger age compared to controls even a er adjusting for factors related to HIV disease progression and development of co-morbidities [5,6].

Prospective clinical studies using anthropometric measures have demonstrated. an increase in the proportion of overweight or obese at time of HIV infections and also weight gain over time [2]. Overall rates of obesity in HIV-infected patients are similar to HIV-uninfected controls [7]. Additionally, patients have reported to gain weight during the course of HIV infection [2,7]. Toxicities from prolonged exposure to ART add to the complexity of obesity and are suspected to lead to changes in body composition and metabolic abnormalities.

In light of these trends, this article reviews existing literature on the impact of general obesity on HIV-infected patients and the management of general obesity with a particular focus on aging.

Methods

Articles published in peer reviewed journals were identi ed through search strategies using PubMed, OvidSP and MEDLINE. Keywords included: HIV, obesity, weight gain, aging, telomeres, physical function, cardiovascular risk, bone and cognition. ese terms were used in combination to address each topic area of interest: impact of obesity in HIV-infected individuals on their immune function/aging, metabolic abnormalities, cognitive function, bone mineral density, physical function and frailty and interventions and management of obesity/weight gain among HIV infected individuals. ese topics were selected to address issues presented as a follow-up to the seminal publication by Guenter et al. [8] that reported on the association between low body weight and a greater relative risk of death before eȣective antiretroviral therapy became available, providing an important comparator for the work published a er the availability of ART. Hence, only articles published in English between 1993 and 2012 were searched for relevance and inclusion in this critical review. References from signi cant articles led to additional papers to be reviewed, for a total of 65 studies included in this analysis.

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Results

Impact of obesity HIV infected individuals

Impact of obesity on the immune system/aging: Before the advent of ART, studies showed that being underweight was associated with lower $CD4^+$ cell counts and shorter survival while higher weights were associated with slower HIV progression [8,9]. e impact of excess weight on the immune system of patients with HIV has not been systematically studied since; few studies have examined the impact of excess weight on the immune system of HIV-infected patients.

e HIV Epidemiology Research (HER) Study examined the association of body mass index (BMI) and HIV disease outcomes in women followed longitudinally [10]. is multicenter epidemiological cohort study reported that the mean $CD4^+$ cell count was progressively higher and the mean log HIV viral load progressively lower as the BMI increased, with no signi cant di erence in age, duration of HIV positivity, income or education by BMI weight group. Regression analysis showed an association between BMI and a risk of HIV disease progression, whether immunological, clinical or mortality related. e improved outcomes were interpreted as associated with higher BMI due to increased fat mass rather than an increase in lean muscle mass. is was endorsed by the fact that the participants were largely poor, inner city women who were unlikely to engage in any systematic exercise or weight training activities, were not pregnant, and were not enrolled in any clinical trials of human growth hormone. e authors proposed that higher levels of leptin, which are in direct proportion to fat cell mass, may be responsible for the potential protective e ect of obesity. In support of this explanation, are the facts that $CD4^+$ cells have leptin receptors [11]. Moreover, *in vitro* studies have demonstrated that the addition of physiologic concentrations of leptin induces a dose dependent increase in the proliferative responses of highly puri ed $CD4^+$ T-lymphocytes. Along the same note another recent study reported that obese HIV-infected individuals with well suppressed viremia had signi cantly higher CD3 and CD8 cells and total lymphocyte counts [12].

Telomeres are key markers of cellular and biological aging. With increasing aging a slow and gradual loss of telomere length has been reported [13]. Oxidative stress and in ammation are major contributors to aging and aging related chronic diseases; shorter telomeres have been described in cancer, diabetes, metabolic syndrome, in individuals with increased cardiovascular disease risk factors and in response to psychosocial stress [14]. Studies in humans have shown that high total and abdominal adiposity are directly related to decrease telomere length suggesting that obesity may accelerate the aging process [15]. Telomere length was inversely associated with BMI and waist to hip ratio independent of sex, age, fasting glucose and insulin, lipid and lipoprotein concentration, habitual physical activity, smoking and other metabolic risk factors [15]. ese ndings support a role of oxidative stress and in ammation in telomere attrition with obesity.

e cause of accelerated aging with HIV disease is subject of much discussion and research at this time, and immune activation and ongoing in ammation are being considered as important potential mechanisms [6,16]. Many HIV-infected patients also have atherogenic lipid pro les which are described as negatively associated with telomere length. Ameliorating persistent in ammation and oxidative stress or nding strategies to decrease adiposity might in uence premature aging, and other long term complications in HIV infected patients.

Impact of obesity on metabolic abnormality: In general, obesity causes increased risk of cardiovascular disease (CVD), hypertension, dyslipidemia and DM [17]. Obesity, particularly abdominal obesity, is independently associated with CVD independent of DM, hypertension and dyslipidemia [18]. Further, excessive abdominal fat particularly visceral fat is commonly associated with multiple metabolic abnormalities as part of the "metabolic syndrome", even in patients with normal BMI [19].

HIV-infected patients appear to frequently develop increased visceral fat and metabolic syndrome a er starting ART regimens. Indeed, HIV-infected patients are known to have signi cantly greater amounts of abdominal fat compared to age -matched HIV-uninfected individuals [20]. Increased upper trunk and abdominal fat has been shown to correlate strongly with insulin resistance and dyslipidemia in HIV-infected patients [21,22]. Similarly, among HIV-infected receiving ART patients, epicardial and visceral fat is signi cantly associated with the progression of coronary calcium scores, a marker of CVD [23].

HIV-infected patients are prone to a great number of lipid and lipoprotein disturbances, as a result of both the infection itself and direct e ects on lipid metabolism. ese lipid disorders account for at least part of the increased risk of CVD seen in this population. Additionally, some studies report that the risk of CVD is higher among HIV-infected patients compared to uninfected patients [24,25]. Furthermore, HIV-infected patients who are overweight and obese are at increased risk of CVD [25]. Clinical imaging studies have shown an increased prevalence of subclinical atherosclerosis in HIV-infected patients on ART [26]. A multi-factorial etiology has been proposed to contribute to higher rates of MI and subclinical atherosclerosis in this cohort. is include a state of hypercoagulation or in ammatory changes within the vessel wall or direct damage to endothelial tissues by HIV infection [27]. Further, elevated levels of adipose tissue derived cytokines (adipokines) not only contribute in the initiation and progression of vascular damage, but may also be involved in metabolic abnormalities and fat redistribution/lipodystrophy associated with HIV infection [28,29]. ese adipokines favor the increase of intracellular conversion of inactive cortisone to active cortisol, in adipose tissue; this would cause increased lipolysis and release of FFAs which could then be deposited in ectopic tissues (Figure 1).

Impact of obesity on cognitive function: In the general population, vascular risk factors and obesity play a role in the development of dementia including Alzheimer disease (AD) [30]. In one study, clustering of these vascular risk factors increased the risk of dementia and AD in an additive manner so that persons with all 3 risk factors had around a 6 times higher risk for dementia than persons having no risk factors [31].

Another study contributing to our further understanding of the association between central obesity and the development of dementia is a study of 6,583 continual members of the Kaiser Permanente (KP) Medical Care Program of Northern California (reference). Findings revealed that central obesity is associated with an increased risk of dementia independent of demographics, DM, cardiovascular co-morbidities, and BMI [32]. Central adiposity seems to add signi cant risk even in those who are not overweight. e visceral fat is known to secrete several in ammatory cytokines which are associated with greater cognitive decline [33].

In patients with HIV-infection, the prevalence HIV-associated dementia was estimated at 16% in AIDS cases before the availability of e ective ART, while recent estimates indicated a prevalence of less than 5%. Despite this obvious improvement, the neurocognitive responses to e ective ART have been varied across individuals and

studies of HIV- associated neurocognitive disorders (HAND) have documented persistent rates of mild to moderate neurocognitive impairment [34]. Moreover, there are several reports providing evidence of neuropsychological impairment, abnormal brain electrical activity related to cognition, brain changes detected by MRI or MR spectroscopy, alterations in CSF markers of monocyte activation and CNS injury and brain pathology detected at autopsy. A recent report using MRI to study changes in brain volume in a small group of treated HIV-infected patients showed evidence of continued tissue loss primarily in the white matter that may indicate ongoing brain injury in HIV-infected patients on ART [35].

The causes of continuing high rates of HAND in patients receiving effective ART are unclear. Metabolic abnormalities and associated vascular pathology seem plausible given what is known about the association between central adiposity and dementia in the general population. Central adiposity and metabolic abnormalities are very common in treated HIV-infected patients who are aging. Because these metabolic complications are occurring at an early age in HIV-infected patients than in HIV-uninfected patients, accelerated aging has been proposed [6].

The association between central adiposity, which is common in HIV-infected patients receiving ART who are aging, and cognitive decline, has not been studied in the HIV-infected population.

Impact of obesity on bone mineral density: Numerous studies have shown that lower BMI is independently associated with lower BMD in the general population [36,37]. Studies which focus on HIV-infected patients, confirmed this relationship in this cohort [38,39]. A growing body of literature presents associations between low BMD and both HIV-infection and ART [40,41]. In addition to being associated with low BMD, HIV-infected patients are also at increased risk of bone loss and fragility factures [42,43].

Further, it is known that obesity is associated with increased BMD and decreased osteoporosis and hip fracture in the general population [36]. Body fat mass and lean mass are both directly correlated with BMD. Despite the mechanical burdens that come with obesity-related increases in BMD, one must also acknowledge the protective effects of obesity on non-weight-bearing bones [44]. Hormonal factors that are increased in obese persons, such as circulating estrogens, insulin, and leptin, may contribute to the beneficial effects of obesity on BMD by stimulating bone growth and bone remodeling [45]. The increase in both BMD and the extra cushioning effect of fat adjacent to important areas such as the hip might provide protection against fractures during a fall [46]. Therefore, obesity may provide some beneficial effects to bone health in HIV-infected patients.

Impact of obesity on physical function and frailty: It is commonly known that obesity exacerbates age-related decline in physical function [47,48]. Studies which have looked at the general population demonstrate that obesity is an important cause of frailty. In light of the growing prevalence of obesity, it is not surprising that the most common phenotype of frailty in the years to come is described as the obese, disabled older adult [49]. Given the demographic shift and the rapid increase in the aging population, frailty has been recognized as a major challenge facing the world today. Frailty in the geriatric and gerontology literature is defined as a syndrome of decreased physiological reserve which increases vulnerability to negative outcomes such as loss of independence, increased nursing home admissions, and increased morbidity and mortality [50].

As a result of the advances in ART, the life span of HIV-infected patients has increased dramatically. Attendant to these effects are signs of premature aging with notable changes in the musculoskeletal system. Studies suggest that HIV-infected individuals have reduced physical function, muscle weakness and fatigue, and are at increased risk of frailty [51,52]. In fact, some HIV-infected patients manifest frailty characteristics at a much younger age compared to HIV-uninfected patients with frailty [52], thereby suggesting that the HIV-infected population may experience a form of accelerated aging.

HIV-infected patients with obesity represent an important cohort because this population may be most vulnerable for accelerated functional decline given that HIV-infected patients experience muscle weakness and fatigue in the face of increased body mass [53]. This accelerated functional decline in the HIV-infected patient population is further compounded by the normal aging process.

A recent study evaluated the impact of obesity on physical function in HIV-infected patients compared to non-obese HIV-infected and obese HIV-uninfected [54]. This study found that patients who were both obese and HIV-infected were more impaired in mobility and balance than those who were non obese HIV-infected and obese HIV-uninfected patients. Specifically, HIV-infected obese patients were more impaired in fast gait initiation time and cadence, non-preferred leg stance time, 360-degree turn time, and sway strategy scores. Another recent study which investigated the functional status and prevalence of frailty and in community-dwelling HIV-infected older adults (HOA, age > 50) demonstrated that greater fat mass and higher BMI is associated with frailty and functional impairment in the HOA population. Moreover, the study found that central obesity and fat redistribution were important predictors of functional status among community-dwelling HOA [55].

Management of obesity in HIV-infected patients

Considering that there is paucity of research in this field, strategies of assessing and managing obesity in HIV-infected patients have been borrowed largely from those that are recommended for the general US population. It is important to examine the differences between HIV-infected population and the general population with regards to obesity measurement and management.

A limitation of using the common methods of measuring obesity (BMI and waist circumference) to estimate disease risk among the HIV-infected is the effect of the disease and antiretroviral therapy (ART) on fat redistribution in patients with normal weight. Risk factors (i.e. visceral fat, intramuscular fat, and intrahepatic fat) for insulin resistance and metabolic diseases increase not only with HIV and ART, but also with aging [56]. The size of these fat depots is therefore more likely to be greater in HIV-infected older patients compared to HIV-infected younger patients and HIV-uninfected older patients at any given BMI. Waist circumference has been found to be an adequate method for estimating intrabdominal fat content or visceral fat [57]. However, because it is common for HIV-infected patients to have increased abdominal girth [29], it is helpful to distinguish whether one's increased waist circumference is accompanied by other characteristics of lipodystrophy or lipodystrophy syndrome such as altered fat distribution and related metabolic syndrome.

Most studies that have looked at the effects of weight loss on obesity-related medical complications have been done on the general population, among which weight loss therapy is a proven strategy to

reduce fat mass, improve obesity related problems and is of minimum complication risks to the patient [58,59]. In the HIV literature, one study presents the results of a small-scale intervention study designed to promote weight loss in obese (BMI > 30) HIV-infected patients [60]. In that study, 18 HIV-infected women completed a 12-week weight loss program (through dietary energy restriction combined with aerobic and resistance exercise) with moderate weight loss (7%). Similar to the results observed in the general population, this study also showed improvement in weight, body composition, strength, and tness in the HIV-infected patient that completed the intervention. Contrary to the results of the general populations, HIV-patients showed a lack of improved insulin sensitivity and other surrogate markers of cardiovascular risk. ere was a high drop-oa rate (36%) in this HIV-speci c study, which highlights the di culty of compliance in this unique population. More research is needed, and preferably on a larger scale, to con rm the above-mentioned results.

First of all, HIV-infected populations may have more psychiatric diseases, lacking supportive network, substance abuse issues and socioeconomic challenges [61,62]. Further, HIV-infected patients, and particularly older HIV-infected patients, tend to have multiple co morbidities, cognitive or sensory impairments which can aect their compliance [63,64]. erefore, targeted research speci c to this unique cohort is sorely needed in this eld to develop evidence-based guidelines to best manage obesity. Weight management programs have been suggested to achieve successful weight reduction and maintenance in obese HIV-infected patients [2]. However, compliance to strategies to manage or prevent obesity may be more of an issue in HIV-infected patients compared to the general population not only because of the clinical characteristics listed above, but also because of adverse socio-economic characteristics and/or substance abuse present in many HIV-infected patients [61,62]. Finally, there may be hesitatation in recommending weight loss for HIV-infected patients because advanced HIV infection or poorly treated infection is usually accompanied with unintended weight loss, particularly muscle wasting. ere continues to be fear of wasting and some patients take active measures to increase body weight.

Discussion

Although obesity might have a protective eect on HIV disease progression, it has detrimental health consequences, including cardiovascular disease, DM, hyperlipidmia, functional decline and physical frailty. Increased oxidative stress, genetic instability and disturbance of homeostatic pathway are postulated as the mechanism leading to these conditions which are similar to those of obesity and aging.

Our review of the literature suggests that as HIV has become a chronic manageable disease, the prevalence of obesity has increased in the HIV population and is comparable to the general population. While HIV-infected patients are increasingly overweight, we do not completely understand the complications of obesity in HIV-infected patients and its pathophysiologic mechanisms. Moreover, the impact of excess weight on the immune system has not been systematically studied in this population. During the pre-ART era, studies show that being underweight was associated with lower $CD4^+$ cell counts and shorter survival, while higher weights were associated with slower HIV progression. erefore, obesity might have a protective eect on HIV disease progression. is relationship, however, needs to be con rmed with studies in the post-ART era. Further, the association between obesity and telomere length and its eects on aging should also be investigated in the context of HIV disease.

In the general population, obesity is associated with the development of cognitive decline and dementia. e association between obesity, particularly central adiposity (a common trait in HIV-infected older patients receiving ART), and cognitive decline has not been studied in this cohort. is is important because cognitive impairment is a common problem with HIV-infected older adults and can negatively impact their quality of life [65]. Finally, similar to the general population, HIV-infected patients show an association between central adiposity and adverse medical consequences such as DM, atherosclerosis, dyslipidemia, and hypertension and adipokines have been implicated as a mediator of this relationship.

HIV-infected patients have reduced physical function and are at increased risk of frailty. Frailty in HIV-infected patients was previously conceptualized as being a wasting disorder. In the pre-ART era, frailty in HIV-infected patients was commonly observed in the setting of wasting and immunocompromised states with lower CD4 count. In the post-ART era, obesity is seen to be a possible important determinant of functional decline and frailty in community-dwelling HIV-infected patients. e eects of obesity on HIV disease and aging may worsen and increase the risk for functional decline and frailty-related poor outcomes.

Weight-loss therapy is a proven strategy to reduce fat mass and improve obesity-related problems. However, there is a paucity of literature in managing obesity in HIV-infected patients. While it seems reasonable to expect that a signi cant proportion of HIV-infected patients will respond to conventional weight management strategies for improved clinical outcomes, it is unclear whether such strategies are practical or even eective in this population where non-compliance could be a major issue. Finally knowledge of obese status and acceptance of obese status may vary by gender and ethnicity among HIV infected adults, similar to the general population.

Conclusion

Recent reports on the in the prevalence of overweight and obesity in HIV-infected patients emphasize the need for greater attention to early evaluation and subsequent management strategies. Although, we do not fully understand the pathophysiologic mechanisms and complications of obesity in HIV-infected patients, it appears that obesity has important functional implications in HIV disease because it can exacerbate the HIV and aging-related decline in physical function and even cause frailty. erefore, it is important to consider customized weight management strategies to improve physical function in obese older persons, in addition to possibly preventing or improving the medical complications associated with obesity. While it is intuitive that a signi cant proportion of HIV-infected patients will respond to conventional weight management strategies, it is unclear whether such strategies are most eective, especially for better clinical outcomes and long-term maintenance. erefore, future research is urgently needed to develop evidence-based guidelines to assess and manage obesity in HIV-infected patients, and particularly those who have functional impairments or medical complications that can bene t from individualized weight management programs.

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Contribution

Krupa Shah and Amneris E. Luque designed this project, researched, and wrote drafts of the paper. Krupa Shah integrated contributions and prepared the manuscript for submission. Amina Alio and William J. Hall edited the paper. All authors contributed to and approved the final version of the paper.

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