Quantification of lean tissue losses during cancer and HIV infection/AIDS

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Purpose of review

Cancer and HIV infection/AIDS are associated with an increased risk of undernutrition and cachexia. During the past decade, patients became older, frequently overweight or obese and sedentary, conditions which are likely to result in fat-free mass (FFM) loss. This review sustains the hypothesis that FFM measurement should be implemented in routine clinical practice, to optimize the management of cancer and AIDS, as well as disease-related undernutrition.

Recent findings

Undernutrition and FFM loss are associated with worse clinical outcome and increased therapy toxicity in cancer and AIDS patients. The emergence of the concept of sarcopenic obesity in cancer patients, a condition associated with decreased survival, demonstrates the necessity to assess their body composition with easily available methods, such as dual energy X-ray absorptiometry, computerized tomography and bioelectrical impedance analysis. FFM measurement could be helpful for guiding the choice of both disease-specific and nutritional therapies and for evaluating their efficacy and putative toxicity.

Summary

FFM measurement at different steps of disease course could allow improving the guidance and efficacy of both cancer and HIV/AIDS-specific and nutritional therapies. The repeated measurement of FFM could allow reducing undernutrition-related morbidity, mortality and global healthcare costs, and could improve response and tolerance towards therapy, and quality of life.

Keywords

AIDS, body composition, cancer, fat-free mass, HIV infection

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Introduction

Undernutrition is characterized by a loss of lean tissues (fat-free mass, FFM). Hospitalized or at home patients with cancer and HIV infection/AIDS are at increased risk of undernutrition. During the next decade, the prevalence and the clinical impact of undernutrition are expected to increase in these patients. Indeed, the improvements in medical technology and therapy prolong the patient survival, even in elderly patients with pre-existing sarcopenia. As a consequence, the proportion of cancer, HIV-infected and AIDS patients with FFM loss will increase, leading to an impairment of their overall health and quality of life. Indeed, the FFM decrease has been repeatedly associated with a worsening of the clinical outcome, that is increased rate of infections, complications and hospitalizations, increased length of hospital stay and recovery, increased mortality [1], decrease in quality of life [2•,3] and ultimately increased global healthcare costs [1]. Therefore, in patients with cancer and HIV infection/AIDS, the clinical assessment of nutritional status by calculating BMI and the percentage of weight loss in comparison with usual weight, is recommended on a regular basis. Nevertheless, in some chronic conditions, this clinical assessment is insufficient for linking nutritional status to clinical outcome, which requires the measurement of FFM mass by a technique of body composition assessment (Table 1). Recently, the increased prevalence of obesity in Western countries has led to the recognition of a new nutritional entity, the 'sarcopenic obesity', in adults [6,7,8••] as well as in children [9•]. Sarcopenic obesity is defined by a pattern of body composition characterized by an excess in fat mass, together with a loss in FFM. The emergence of such a concept is the demonstration of the lack of accuracy of the clinical assessment of nutritional status for the early detection of undernutrition and lean tissue loss. In the course of cancer and HIV infection/AIDS complicated or not with pulmonary tuberculosis, the measurement of body composition allows a more accurate

Table 1 Chronic diseases with a demonstrated relation between reduced fat-free mass (assessed by, i.e. bioelectrical impedance analysis or dual energy X-ray absorptiometry) and clinical outcome

Criteria of clinical outcome	Conditions
Reduced survival	Chronic obstructive pulmonary disease, chronic heart failure [4], renal insufficiency and hemodialysis, amyotrophic lateral sclerosis, cancer with sarcopenic obesity, nursing home elderly residents [5], ageing
Disease severity	Chronic obstructive pulmonary disease, cystic fibrosis, chronic heart failure, liver cirrhosis

Only the references corresponding to studies published during recent years are indicated.

assessment of the nutritional status. As lean tissues variations are associated with clinical outcome, treatment tolerance and quality of life, this review sustains the hypothesis that the measurement of FFM by a devoted technique of body composition measurement should be implemented on a regular basis in the clinical practice, with the aim to optimize the management of cancer and HIV infection/AIDS, as well as disease-related undernutrition and cachexia.

Prevalence of undernutrition and fat-free mass loss in cancer and HIV-infected/AIDS patients

FFM loss together with a decrease in body cell mass are the features of adult and children patients with cancer [9•,10] and HIV infection/AIDS, complicated or not with tuberculosis, in comparison with patients without HIV infection [11–14]. The mechanisms of FFM loss in patients with cancer and HIV infection/AIDS are shown in Fig. 1. In cancer patients, the prevalence of undernutrition depends on the cancer location and stage; it is higher in the upper gastrointestinal tract and pancreatic cancers (around 60%) than in breast, colon-rectum or prostate cancers (20–30%) [19]. In some types of cancer, such as pancreas cancer, undernutrition is integrated into the cachexia syndrome [20] (Fig. 1). The impact of HIV infection/AIDS on FFM and body cell mass loss does not depend on the race or the ethnicity [11]. In African HIV-infected patients, tuberculosis and $CD4^+$ lymphocytes 200/μl or less are associated with a higher risk of undernutrition [12,13].

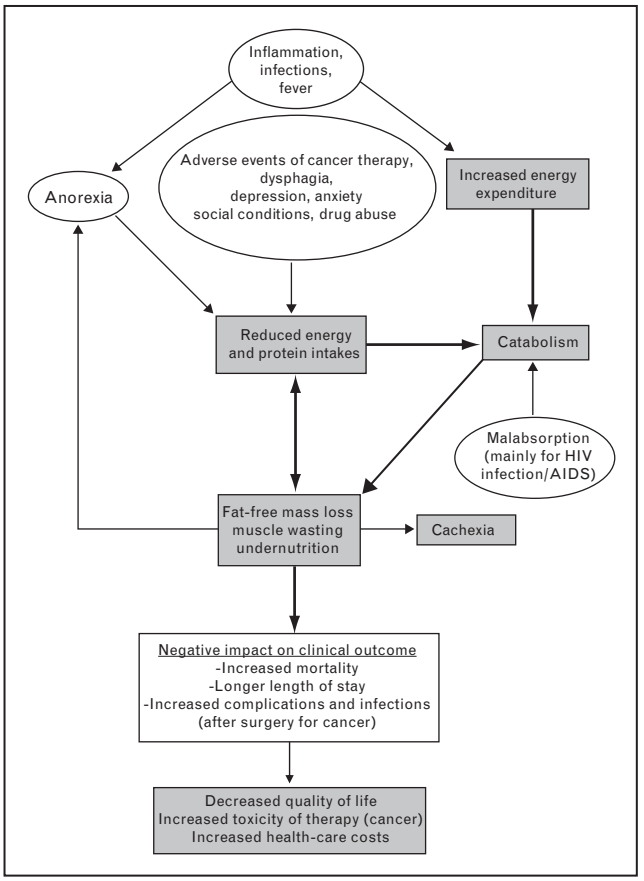
How to determine fat-free mass in cancer and HIV infection/AIDS?

Given the high risk of FFM loss, it is critical to analyse FFM during the course of cancer and HIV infection/AIDS. FFM could be assessed by two ways: a quantitative assessment with a specific method of body composition assessment and a qualitative assessment with the aim to rely FFM changes with muscle function and molecular modifications.

Quantitative assessment of fat-free mass

The advantages and inconveniences of the different methods of body composition assessment in patients with

Figure 1 Mechanisms and clinical impact of fat-free mass loss in patients with cancer and HIV infection/AIDS



Cancer and HIV infection/AIDS are associated with a chronic inflammatory state and an increased risk of infections and fever. These three phenomena lead to an increase in resting energy expenditure (REE) [15,16•,17] and a cytokine-mediated anorexia [18]. In cancer patients, the increase in REE is not constant and depends on the location, the type and the stage of the cancer and of the presence of an acute phase response [18–20]. In HIV-infected/AIDS patients, the degree of increase in resting energy expenditure (REE) is depending on the presence of opportunistic infections [15]. The reduction of protein-energy intake could also be induced by the adverse events of chemotherapy and radiotherapy, dysphagia (head–neck and oesophageal cancers), depression and anxiety related to the disease, and financial problems, related to social conditions or drug abuse (mainly for HIV-infected and AIDS patients). The combination of reduced protein-energy intake and increased energy expenditure would induce a catabolism of lean tissue and undernutrition. The catabolism of lean tissue could be worsened by malabsorption in HIV-infected and AIDS patients or of cancer cachexia. In turn, fat-free mass (FFM) loss has a negative impact on clinical outcome, decreasing quality of life and increasing morbidity, mortality, length of stay, toxicity of therapies, and healthcare costs.

cancer and HIV infection/AIDS are described in Table 2. In summary, dual energy X-ray absorptiometry (DEXA) is the gold standard for the assessment of body composition in cancer [22••] and HIV-infected or AIDS patients with muscle wasting [25]. However, the use of DEXA for the assessment of body composition in the daily clinical practice is limited in the majority of centres because of its reduced accessibility and high cost. Therefore, we believe that bioelectrical impedance analysis (BIA) and computerized tomography (CT) represent the techniques of choice to assess body composition of cancer and HIV-infected/AIDS patients in clinical practice. Indeed, in HIV-infected/AIDS patients, the use of specific modelled BIA equations was shown to be sufficiently precise to detect change in FFM for use in clinical investigation and practice, in comparison with total body potassium, DEXA, isotope dilution and densitometry [21]. On the contrary, in cancer patients, no BIA-specific equations have been validated and the accuracy of BIA is limited. However, in cancer patients, the regional analysis of fat and fat-free tissue at the third lumbar vertebra by CT strongly predicted whole-body fat and FFM as compared with DEXA [8••,23]. CT presents great practical significance because of its routine use in patient diagnosis and follow-up, and allows an accurate quantification of whole-body composition [23]. Also, CT images targeted on the third lumbar vertebrae could be performed solely, as they result in similar X-ray exposition than a chest radiography. Therefore, FFM could be alternatively measured with both BIA and CT in cancer patients.

Table 2 Advantages and inconveniences of the different techniques of body composition measurements in cancer and HIV infection/AIDS

	Anthropometry	Bioelectrical impedance analysis (BIA)	Dual-energy X-ray absorptiometry (DEXA)	Computerized tomography
Advantages	Noninvasive, transversal follow-up, very low cost	Easy, noninvasive, excellent reproducibility: noninvestigator-dependent, transversal follow-up, low cost, multifrequency BIA: calculation of phase angle for prognosis evaluation, for HIV-infected/AIDS patients: specific modelled BIA equations adapted for clinical practice [21]	Gold standard, well validated, reproducible	Integration with routine care assessment of body composition coupled with the staging and surveillance of cancer treatment, assessment of FFM by regional analysis of the third lumbar vertebra validated against DEXA [23]
Inconveniences	Low reproducibility among different investigators, nonvalidated in patients with cancer and HIV infection/AIDS, low sensitivity and specificity for the assessment of FFM as compared with DEXA and BIA	In cancer patients, low accuracy for FFM estimation compared with DEXA [22••,23,24], poor accuracy in advanced colorectal cancer; for HIV-infected/AIDS patients, standard equations not accurate for patients with AIDS wasting [25]	Low accessibility, limiting its use for clinical practice, necessity of trained investigator, X-ray exposition, high cost	X-ray exposition, cannot be performed outside of cancer follow-up: had to be coupled with another technique of FFM measurement, necessity of a specific software for FFM assessment

FFM, fat-free mass.

Qualitative changes of lean tissue mass

In cancer and HIV-infected/AIDS patients, the quantitative study of FFM has to be reinforced by the study of muscle function and muscle strength, the last being associated with mortality independently of FFM. Indeed, in a study performed in 800 elderly patients in England, after adjustment for potential confounding factors, including arm muscle area (calculated by anthropometry) and BMI, and secondly for FFM and body fat, poorer handgrip strength was associated with increased mortality from all causes, from cardiovascular disease, and from cancer in men, though not in women [26•].

Chronic organ pathologies (Table 1) share a common muscle phenotype, that is reductions in lean body mass, muscle performance and oxidative capacity, together with altered muscle histology. Decrease in oxidative type I fibres and an increase in glycolytic type II fibres are the main alterations of muscle structure [27,28]. The decrease in muscle oxidative capacity has already been similarly reported in cachectic cancer patients and could be attributed to the decrease in the activities of both coactivator peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) and AMP-activated protein

kinase (AMPK) [29,30]. Physical exercise may be of major interest for counteracting these effects as already demonstrated in other chronic diseases [31]. The actions of physical exercise on muscle mass, structure, metabolism and function are multiple: anti-inflammatory effects through the up regulation of PPARγ [32], and increase in type 1 fibres, oxidative capacity, GLUT 4 receptors expression, insulin sensitivity and muscle endurance through the PPARδ and AMPK activations [29,30]. Other mechanisms could be involved in muscle wasting during cancer and HIV infection/AIDS. Sorafenib, a multikinase inhibitor, exacerbated muscle mass loss in patients with metastatic renal cancer, consistent with the evidence for a role of kinases in regulating muscle mass [33•]. Myostatin, a member of the transforming growth factor-β superfamily, is an attenuator of skeletal muscle growth and has been shown to contribute to muscle wasting in HIV-infected/AIDS men [34]. Because repeated muscle biopsies cannot be proposed in clinical practice for assessing the qualitative changes in fat-free mass during chronic diseases, further research is needed to develop noninvasive techniques.

Clinical impact of the loss of fat-free mass in cancer and HIV infection/AIDS

FFM loss can change the course of cancer and HIV infection/AIDS by a direct impact on clinical outcome and by modifying the tolerance and efficacy of therapy. Conversely, the disease-specific and nutritional therapies have an impact of FFM. This justifies the assessment of FFM during the course of cancer and HIV infection/AIDS, and the association of disease-specific and nutritional therapies to maintain or improve FFM.

Impact of fat-free mass loss on clinical outcome

Malnutrition, as assessed by clinical and biological parameters, that is BMI, weight loss and hypoalbuminaemia, is associated with increased risk of complications after surgery for cancer [35] and with increased length of stay in cancer patients [36,37•]. In Malawian HIV-infected/AIDS patients receiving antiretroviral therapy, BMI was an independent risk factor of mortality [38]. To our knowledge, the impact of FFM on the risk of complications, length of stay and hospitalization has never been demonstrated in patients with cancer or HIV infection/AIDS. Nevertheless, muscle wasting is specifically associated with mortality in cancer patients. Indeed, sarcopenic obesity as assessed by tomography (total skeletal muscle cross-sectional area) is an independent predictor of survival in solid tumours of the respiratory and gastrointestinal tracts [6], and in pancreatic cancer [7]. Preliminary studies have suggested that low phase angle obtained by BIA is related to survival in advanced digestive and respiratory cancers [39•] and in HIV-infected/AIDS patients [40]. Phase angle is also associated with the severity of AIDS, as it was found to be lower in patients with $CD4^+$ lymphocytes $\leq$200/μl than in those who had $CD4^+$ lymphocytes more than 200/μl [41]. The relation phase angle-prognosis and disease severity reinforces the interest of the use of monofrequency or multifrequency BIA during the clinical management of patients with cancer or HIV infection/AIDS (Table 3).

Impact of fat-free mass loss on therapeutic strategy

Sarcopenic obesity has a direct impact on the therapeutic strategy, especially for determining the chemotherapy

Table 3 Time point and aims of FFM assessment during the course of cancer and HIV infection/AIDS

Time point	Aims
At diagnosis	Screening of FFM loss and/or cachexia Early initiation of nutrition support Optimization of nutritional therapy Assessment of prognosis: FFM loss and low phase angle (only with BIA)
At the initiation of antiretroviral therapy or radiotherapy/chemotherapy	Choice of chemotherapy doses with regard to FFM (cancer) To obtain a reference value to follow the therapeutic response Assessment of prognosis
During the antiretroviral therapy or radio therapy/chemotherapy	Screening of undernutrition Diagnosis of cachexia Optimization of nutritional therapy Adaptation of chemotherapy doses with regard to FFM (cancer) Assessment of prognosis
At the end of antiretroviral therapy or radio therapy/chemotherapy	Assessment of the therapeutic response towards FFM Optimization of the nutritional therapy if worsening of FFM Assessment of prognosis
After remission	Screening of undernutrition Optimization of nutritional therapy Assessment of prognosis
Palliative stage	Assessment of prognosis Assessment of the impact of nutritional status on quality of life Help for the decision of therapy continuation Assessment of prognosis

BIA, bioelectrical impedance analysis; FFM, fat-free mass.

dose. Administering the same doses of chemotherapy drugs in a patient with low FFM compared to a patient with normal FFM would increase the risk of toxicity of chemotherapy [6]; FFM loss deserves a reduction of the doses of the chemotherapy drugs. It is mandatory to consider FFM, thus to identify sarcopenic obesity, for stratification of patients entering clinical trials, systemic therapy or support care programs [6]. To our knowledge, no data support the hypothesis that FFM loss could modify the efficacy or the tolerance of HIV infection/AIDS-specific therapy. Therefore, up-to-date, no tailoring of antiretroviral therapy according to FFM could be indicated in HIV-infected or AIDS patients.

Impact of therapeutic strategy on fat-free mass

One of the main goals of the assessment of body composition during the courses of cancer and HIV infection/AIDS is to follow FFM changes during disease-specific and/or nutritional therapies.

Impact of disease-specific therapy on fat-free mass

Several studies have shown that antiretroviral therapy for HIV-infected/AIDS patients could improve FFM [42,43]. In two randomized clinical trials performed in 422 and 213 HIV-infected/AIDS patients, 5-year and 64-weeks long antiretroviral therapies were associated with an increase in FFM [42,44], together with a reduction of subcutaneous fat [42]. White race, lower CD4 cell count at study entry, assignments to the efavirenz and zidovudine–lamivudine treatment arms independently predicted greater absolute change in FFM at week 64 [44].

Conversely, anticancer therapies could have a negative impact on body composition by inducing muscle wasting [33•,45]. In a randomized, double-blinded clinical trial performed in patients with advanced renal cell carcinoma [33•], sorafenib-treated patients reported a significant loss of skeletal muscle at 6 months (decrease of 4.9%) and 12 months (decrease of 8.0%) [33•]. In turn, muscle wasting in patients with BMI less than 25 significantly predicted sorafenib toxicity in metastatic renal cell cancer [46••]. The importance of FFM loss during chemotherapy may be predicted by pre-existing nutritional status. In a population of 174 cancer patients with a majority of breast and gynaecologic cancers receiving chemotherapy, a significant loss of FFM was only observed in patients with severe malnutrition at admission [47]. Radiotherapy is similarly associated with FFM loss. Janiszewski *et al.* [45] have shown that cranial radiotherapy performed in young adults with children acute lymphoblastic leukaemia was associated with a decrease in FFM, together with an increase in visceral fat mass.

Impact of nutritional therapy on fat-free mass

Recent evidence suggests that, in cancer and HIV-infected or AIDS patients, targeted nutritional support has a positive impact on FFM. In patients with stage 3 nonsmall cell lung cancer, Van der Meij *et al.* [48••] have shown oral nutritional supplements (ONS) containing polyunsaturated fatty acids (PUFAs) allow a better FFM maintenance than the control group after 3 and 5 weeks. These beneficial nutritional effects may be related to a reduced resting energy expenditure and a higher energy and protein intake. In patients undergoing oesophageal cancer surgery, a double-blinded randomized controlled trial showed a preservation of lean body mass in patients receiving an enteral nutrition enriched with the omega-3 PUFA eicosapentaenoic acid, in comparison with patients receiving a standard enteral nutrition whose mean FFM decreased by 1.9 kg [49]. Omega-3 PUFAs could exert these beneficial effects through PPAR δ stimulation [50•].

In a randomized controlled trial performed in 491 Malawian HIV-infected/AIDS adults with BMI less than 18.5 kg/min^2 beginning an antiretroviral therapy, Ndekha *et al.* [51] reported that a 3-month supplementation with a ready-to-use fortified spread led to a better improvement in BMI and lean body mass than the corn–soy blend. However, this effect was not sustained after the end of the supplementation [38]. It seems that nutritional therapy is insufficient to increase FFM in the absence of anabolic stimuli. An Indian prospective intervention study indicated that ONS associated with nutritional counselling failed to improve FFM in 636 HIV-infected/AIDS individuals after adjusting for baseline differences [52•]. Other studies suggest that a specific treatment of muscle wasting with testosterone (by gel or intramuscular injection), as compared with a placebo, could increase FFM and decrease fat mass, assessed by DEXA or BIA [53,54]. Intramuscular injection of nandrolone may have a positive effect on weight and a tendency to a better increase in FFM in comparison with testosterone [54].

Summary

In HIV-infected or AIDS patients with FFM loss, antiretroviral therapy *per se* could induce an FFM increase. Moreover, the choice of the antiretroviral therapy could affect the nutritional response, particularly for the most severely affected patients. The best strategy to correct muscle wasting in HIV-infected/AIDS patients could be the combination of antiretroviral therapy together with the association of nutrition support and anabolic stimuli, such as exercise and androgen therapy, as already demonstrated for the management of chronic obstructive pulmonary disease. The subgroup of HIV-infected/AIDS malnourished patients could display the best benefits from this strategy. Chemotherapy and radiotherapy have a strong negative impact on FFM in patients with cancer, particularly in undernourished patients. Nutritional support, especially if containing PUFAs, was reported to be

able to preserve FFM in cancer patients. Therefore, it is mandatory to combine anticancer therapies with a targeted nutritional therapy to maintain FFM. Prospective randomized studies are now needed to assess whether the correction of the loss of FFM improves the clinical outcome of undernourished patients with cancer and HIV infection/AIDS.

Perspectives for the future

The main objective for the future is to implement routine assessment of body composition during the course of cancer and HIV infection/AIDS. This could be done by systematic use of BIA and/or CT. We propose (Table 3) to assess FFM at different steps of cancer and HIV infection/AIDS course time points, for specific aims. We assume that, based on a more scientific approach, the assessment of FFM is necessary for the management of the disease, but also for a better recognition of the nutrition therapy by health politics. The integration of body composition assessment in the follow-up of cancer and HIV infection/AIDS will become mandatory in the future because of the expected increase in elderly, overweight and/or obese patients in the whole population. This will result in an increased prevalence of sarcopenic obesity, especially in the subgroup of cancer, HIV-infected or AIDS patients who are at higher risk of muscle wasting.

Conclusion

The combination of ageing, obesity and sedentarism, together with the improvements of medical technology, increases the risk of FFM loss in patients with cancer and HIV infection/AIDS. These clinical characteristics are likely to be more frequent during the next decade, which could translate into worse clinical outcome and increased toxicity towards therapy. Recent evidence indicates that the measurement of FFM by a technique of assessment of body composition is more accurate than the nutritional clinical evaluation to detect early FFM loss. Such a FFM measurement should be implemented in the clinical practice at each step of the disease course with the aim to optimize the management of cancer and HIV infection/AIDS, as well as the prevention and the treatment of disease-associated undernutrition and cachexia. The repeated measurement of FFM could allow reducing undernutrition-related morbidity, mortality and global healthcare costs, and could improve the response and the tolerance towards therapy, as well as quality of life.

Acknowledgement

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References and recommended reading

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- •• of outstanding interest

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