Journal of Cachexia, Sarcopenia and Muscle 2021; **12**: 519–522
Published online 7 February 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12681

Does COVID-19-related cachexia mimic cancer-related cachexia? Examining mechanisms, clinical biomarkers, and potential targets for clinical management

Cancer cachexia (CC) is a multi-factorial, pathological disorder of striated muscle (skeletal and cardiac) and adipose tissue, characterized by the cardinal features of loss of skeletal muscle tissue or sarcopenia, with or without loss of adipose tissue, and often accompanied by anorexia, anaemia, asthenia, increased metabolism, altered immune function, decreased functional status, and decreased quality of life.[1–3] Overall, cancer cachexia may afflict 50–80% and cause up to 20% of deaths of cancer patients, with highest prevalence noted in pancreatic and gastric cancers.[3–6] More recently, guidelines to define each of the four stages of CC have been proposed.[5,6] CC begins initially in a pre-cachectic stage involving unplanned weight loss followed by a more severe, irreversible and progressive loss of both muscle and fat, in addition to complications involving compromises in metabolic and immune processes, ultimately resulting in death.[7,8] Despite the clinical significance and decades of research to prevent progression of early stages of CC to the irreversible refractory stages, there is currently no defined standard of care to effectively mount a defence to the multi-factorial disorders associated with CC. CC is a critical problem in clinical oncology.[1,2,9]

Globally, there have been 44 002 003 confirmed cases of COVID-19, including 1 167 988 deaths, reported to the World Health Organization (WHO).[10] To date, there have been 8 683 298 confirmed cases of COVID-19 with 225 073 deaths in the USA.[10] Preclinical and clinical studies consistently report a significant elevation in proinflammatory cytokines in COVID-19,[9,11–13] especially in stages of COVID-19 disease accompanied by acute respiratory distress resulting from 'cytokine storm'.[14–18] Related to the significant increase in proinflammatory cytokines, symptoms, like those observed in cancer patients with cachexia, have also been observed in conjunction with COVID-19.[9,13] Symptoms, similar to those observed in CC including sarcopenia, anorexia, unplanned weight loss, fatigue and functional loss, have been observed to be accelerated in patient populations at all stages of patients diagnosed with COVID-19.[11–13] However, the data regarding the prevalence and prognosis of COVID-10-related cachexia accounting for age, stage at presentation, and other co-morbidities have not been comprehensively evaluated. Additionally, with factors such as anorexia, age at presentation, immobility due to mechanical ventilation or oxygen supplementation, preexisting nutritional deficiencies and decreased physical activity due to isolation, fatigue, hypoxemia, sarcopenia, and weight loss has been observed to be accelerated in patient populations with COVID-19.[11–13] It is unknown if COVID-19-related sarcopenia and cachexia persists post recovery and if it is reversible. A recent report of results of a preclinical study has shown that suppression of host inflammatory response in early stages of COVID-19 with interventions can reverse cachexia and increase survival.[12] Based on this early and evolving observations, it can be hypothesized that if early COVID-19-related cachexia mimics early stages of cancer-related cachexia, cachexia in these patient populations can be targeted early and potentially reversed, thus reducing mortality in these patient populations. In addition, cancer patients presenting with COVID-19 may be at exceptional risk of sarcopenia and cachexia. The goal of the current editorial is to compare the mechanisms and clinical biomarkers and discus the potential targets for clinical management of this phenomena in both COVID-19 and cancer-related sarcopenia and cachexia. Our understanding of these mechanisms may potentially identify targets and inform management of early stages of both cancer-related and COVID-19-related cancer cachexia.

In addition to the diagnosis of cancer, CC is characterized by unplanned weight loss including loss of both skeletal and visceral muscles and fat stores, manifesting in the cardinal features of emaciation, anorexia, hypo albuminuria, myalgia, weakness affecting functional status, hypo albuminuria, significant increase in proinflammatory cytokines, dysfunction of the metabolic processes, and compromised quality of life.[1,3,19–26] Similarly, coronavirus disease (COVID-19) is characterized by a pneumonic process of varying degree

depending on the stage at diagnosis, significant increase in proinflammatory cytokines (cytokine storm),[14] anorexia, dysgeusia, anosmia, unplanned weight loss, sarcopenia, myalgia, hypo albuminuria, increased C-reactive proteins, ferratin and proinflammatory cytokines-TNF-alpha, Il-1 and Il-6,[14,15,27] which are symptoms similar to cancer cachexia. Inflammatory organ injury has been reported in severe cases.[16] Although not evaluated and characterized in this patient population to date, the prevalence of sarcopenia and cachexia has been reported in this population at all stages with COVID-19, underscoring the need to understand the pathogenesis of COVID-19-related cachexia based on the similarities to CC. Data from both experimental and clinical studies have demonstrated that CC is mediated or modulated by an interplay of a highly complex and multiple biologic pathways. Angiotensin I and angiotensin II levels (Ang II) are increased in patients with CC,[17] leading to elevated levels of proinflammatory cytokines such as TNFα, IL-1, and IL-6.[17,18,26,28–33] Being produced by both tumour and host, these pro-inflammatory cytokines have frequently been suggested as possible mediators in cachexia.[32,33] It has been hypothesized that the cytokines that are important in the initiation of the acute phase response (APR) contribute to the genesis of CC.[26,31] Significant increases in TNF-α have been observed specifically in cachectic patients.[32] TNF-α has been demonstrated to produce direct catabolism of skeletal muscle, increases in protein degradation in conjunction with depression of protein synthesis and catabolism of adipose tissue leading to induction of muscle atrophy. Studies have shown that these changes in protein degradation occurs via the ubiquitin-proteasome pathway, with the formation of reactive oxygen species leading to activation of NF-κB.[34,35] NF-κB, a critical regulator protein degradation and skeletal muscle proteasome expression, has been shown to be up-regulated in CC.[8,34–42] This up-regulation of NF-κB has been shown to increase the rate of myosin heavy chain and telethonin degradation, compromising sarcomere integrity.[43] Sarcopenia in CC is the thus a result of imbalance between protein synthesis and degradation.[44]

The Coronovirus-2 spike protein uses angiostensin converter enzyme 2 (ACE2) receptor, that are ubiquitously present in all cells, known to bind to cells resulting in fusion of the viral envelope to fuse with cell membrane, permitting the viral genetic material to enter the cells, contributing to cellular damage at the organ level.[45] Additionally, ACE2 is present in ample quantities in the epithelia of the human lung, small intestine, arterial and venous endothelial cells and arterial smooth muscle cells in all organs studied, providing the first clues in our understanding of the pervasive pathogenesis of the main SARS disease.[46] ACE2 is present in muscle tissue which may explain in part the effect of the virus in sarcopenia. Angiotensin I and angiotensin II levels i (Ang II) have been shown to increase protein breakdown, lower muscle regeneration, and increase apoptosis in muscle tissue.[47,48] Similar to patients with CC, Ang II are increased in patients with COVID-19[17] and act as an inflammatory mediator leading to elevated levels of proinflammatory cytokines such as TNF-α, Il-1, I1–6,[14,15] through a variety of mechanisms including increasing reactive oxygen species and NF-κB.[49] Thus, there are several similarities in the pathogenesis of both CC and COVID-related cachexia.

Patients with a diagnosis of cancer and COVID-19 are at exceptional risk for sarcopenia and cachexia. Advanced cachexia is refractory and has a high mortality rate. Cachexia and sarcopenia continue to impact mortality in cancer and potentially in COVID-19. In patients with early stage disease, sarcopenia and cachexia may impact function, prognosis, and quality of life in patients with cancer and COVID-19. Several studies, including our own, suggest that maintenance of lean body mass including myofibrillar proteins are difficult to achieve in CC, unless we have a clear understanding of the underlying aetiology that can be targeted and reversed/corrected.[1,2,26,31,50,51] Research to understand the pathogenesis, incidence, course, and prognosis of various stages of presentation of disease for both CC and COVID-19-related cachexia and strategies to mitigate the immune response and deliver improved outcomes is much needed. Our current knowledge and evolving evidence from the fields of oncology and COVID-19 may inform management of cachexia in both diseases. The use of dexamethasone in patients diagnosed with COVID-19 and receiving either mechanical ventilation or oxygen alone demonstrated a lower 28-day mortality compared with those patients who did not receive any form of respiratory support.[16] Early evidence including preclinical studies have shown promise with IL-1, IL-6 receptor antagonists to treat COVID-related increase in proinflammatory cytokines. It can be hypothesized that multimodal approaches in early stages of this disease may offer promise and can include (i) early identification of reversible (Stage I) stage of sarcopenia and cachexia, (ii) therapeutic agents to lower viral load (COVID-19)/appropriate treatment to reduce tumour burden (cancer), (iii) timely evaluation of intervention with targeted agents to reduce proinflammatory cytokine levels (dexamethasone, IL-1, IL-6 receptor antagonists),[14–18] (iv) addition of appetite stimulants to treat anorexia (v) in combination with a nutritionally enriched diets with high quality proteins, antioxidant/anti-inflammatory foods,[1,3] and (vi) incorporating proactive respiratory and physical rehabilitation interventions to improve pulmonary status and muscle mass towards preventing sarcopenia and improving physical function. Effectiveness and safety of these approaches can be evaluated using established as well as recently identified novel biomarkers relevant to the mechanistic pathways. Finding from these studies promise

DOI: 10.1002/jcsm.12681

to inform management of CC, COVID-19-related cancer cachexia as well as cachexia in cancer patients with COVID-19.

Nagi B. Kumar
Division of Population Sciences and Genitourinary and Breast Oncology Departments, H. Lee Moffitt Cancer Center & Research Institute, Inc, 12902 Magnolia Drive, MRC/CANCONT, Tampa, FL 33612, USA
nagi.kumar@moffitt.org

References

1. Kumar NB. *Nutritional Management of Cancer Treatment Effects*, Edition 1 ed. New York: Springer-Verlag; 2012. p 65–80.
2. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers* 2018;**4**:17105.
3. Kumar NB, Kazi A, Smith T, Crocker T, Yu D, Reich RR, et al. Cancer cachexia: traditional therapies and novel molecular mechanism-based approaches to treatment. *Curr Treat Options Oncol* 2010;**11**:107–117, Review.
4. Loberg RD, Bradley DA, Tomlins SA, Chinnaiyan AM, Pienta KJ. The lethal phenotype of cancer: the molecular basis of death due to malignancy. *CA Cancer J Clin* 2007;**57**:225–241.
5. Blum B, Omlin A, Fearon K, Baracos V, Radbruch L, Kaasa S, et al. European Palliative Care Research Collaborative. Evolving classification systems for CC: ready for clinical practice? *Support Care Cancer* 2010;**18**:273–279.
6. Bozzetti F, Mariani L. Defining and classifying CC: a proposal by SCRINIO Working Group. *JPEN J Parenter Enteral Nutr* 2009;**33**:361–367.
7. Deans DA, Tan BH, Wigmore SJ, Ross JA, de Beaux AC, Paterson-Brown S, et al. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-esophageal cancer. *Br J Cancer* 2009;**100**:63–69.
8. Hamerman D. Molecular-based therapeutic approaches in treatment of anorexia of aging and CC. *J Gerontol A Biol Sci Med Sci* 2002;**57**:M511–M518, Review. PMID: 12145364.
9. Dewey A, Baughan C, Dean T, Higgins B, Johnson I. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of CC. *Cochrane Database Syst Rev* 2007;**24**:CD004597.
10. WHO. WHO Coronavirus Disease *(COVID-19) Dashboard*. Available online at: https://covid19.who.int/ (accessed October 29, 2020).
11. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Front Immunol* 2020;**11**:1708.
12. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev* 2020;**54**:62–75.
13. Morley JE, Kalantar-Zadeh K, Anker SD. COVID-19: a major cause of cachexia and sarcopenia? *J Cachexia Sarcopenia Muscle* 2020;**11**:863–865.
14. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents* 2020;**34**:327–331.
15. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmun Rev* 2020;**19**:102537.
16. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020;https://doi.org/10.1056/NEJMoa2021436 Online ahead of print. PMID: 32678530 26. Sanders PN 2005.
17. Penafuerte CA, Gagnon B, Sirois J, Murphy J, MacDonald N, Tremblay ML. Identification of neutrophil-derived proteases and angiotensin II as biomarkers of cancer cachexia. *Br J Cancer.* 2016 Mar 15;**114**:680–687. https://doi.org/10.1038/bjc.2016.3
18. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev* 2020 Aug;**54**:62–75.
19. Jatoi A. Weight loss in patient with advanced cancer: effects, causes, and potential management. *Curr Opin Support Palliat Care* 2008;**2**:45–48, PMID: 18685394.
20. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. *Clin Nurt* 2008;**27**:793–799.
21. Behl D, Jatoi A. Pharmacological options for advanced cancer patients with loss of appetite and weight. *Expert Opin Pharmacother* 2007 Jun;**8**:1085–1090.
22. Morley JE. Pathophysiology of anorexia. *Clin Geriatr Med* 2002;**18**:661–673.
23. Melstrom LG, Melstrom KA Jr, Ding XZ, Adrian TE. Mechanisms of skeletal muscle degradation and its therapy in cancer cachexia. *Histol Histopathol* 2007;**22**:805–814.
24. Giacosa A, Rondanelli M. Fish oil and treatment of cancer cachexia. *Genes Nutr* 2008 Apr;**3**:25–28.
25. Bosaeus I. Nutritional support in multimodal therapy for CC. *Support Care Cancer* 2008;**16**:447–451.
26. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology. *Group Am J Med* 1980;**69**:491–497.
27. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020;**324**:782–793.
28. Mantovani G, Madeddu C, Gramignano G, Ferreli L, Massa E, Contu P, et al. Association of serum IL-6 levels with comprehensive geriatric assessment variables in a population of elderly cancer patients. *Oncol Rep* 2004 Jan;**11**:197–206.
29. Barber MD, Wigmore SJ, Ross JA, Fearon KC, Tisdale MJ. Proinflammatory cytokines, nutritional support, and the cachexia syndrome: interactions and therapeutic options. *Cancer* 1998;**82**:1000, PMID: 9486598.
30. Adamsen L, Quist M, Andersen C, Møller T, Herrstedt J, Kronborg D, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomized controlled trial. *BMJ* 2009;**339**:b3410.
31. Sun LC, Chu KS, Cheng SC, Lu CY, Kuo CH, Hsieh JS, et al. Preoperative serum carcinoembryonic antigen, albumin and age are supplementary to UICC staging systems in predicting survival for colorectal cancer patients undergoing surgical treatment. *BMC Cancer* 2009 Aug 20;**9**:288.
32. Fortunati N, Manti R, Birocco N, Pugliese M, Brignardello E, Ciuffreda L, et al. Pro-inflammatory cytokines and oxidative stress/antioxidant parameters characterize the bio-humoral profile of early cachexia in lung cancer patients. *Oncol Rep* 2007 Dec;**18**:1521–1527.
33. Gould DW, Lahart I, Carmichael AR, Koutedakis Y, Metsios GS. Cancer cachexia prevention via physical exercise: molecular mechanisms. *J Cachexia Sarcopenia Muscle* 2013 Jun;**4**:111–124.

34. Chen S, Fribley A, Wang CY. Potentiation of tumor necrosis factor-mediated apoptosis of oral squamous cell carcinoma cells by adenovirus-mediated gene transfer of NF-kappaB inhibitor. *J Dent Res* 2002;**81**:98–102.
35. Ghosh S, Karin M. Missing pieces in the NF-kappaB puzzle. *Cell* 2002;**109**:S81–S96.
36. Mitch WE, Price SR. Transcription factors and muscle cachexia: is there a therapeutic target? *Lancet* 2001;**357**:734–735, PMID: 11253960.27. Barton BE. IL-6-like cytokines and CC: consequences of chronic inflammation. Immunol Res. 2001;23(1):41–58. Review.
37. Voges D, Zwickl P, Baumeister W. The 26S proteasome: a molecular machine designed for controlled proteolysis. *Annu Rev Biochem* 1999;**68**:1015–1068.
38. Fearon KC, Van Meyenfeldt MF, Moses AG, Van Geenen R, Roy A, Gouma DJ, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in CC: a randomised double blind trial. *Gut* 2003;**52**:1479–1486, PMCID: PMC177 3823.
39. Das SK, Eder S, Schauer S, Diwoky C, Temmel H, Guertl B, et al. Adipose triglyceride lipase contributes to cancer-associated cachexia. *Science* 2011;**333**:233–238.
40. DasRhoads MG, Kandarian SC, Pacelli F, Doglietto GB, Bossola M. Expression of NF-kappaB and IkappaB proteins in skeletal muscle of gastric cancer patients. *Eur J Cancer* 2010 Jan;**333**:191–197. https://doi.org/10.1016/j.ejca.2009.10.008
41. Peterson JM, Bakkar N, Guttridge DC. NF-κB signaling in skeletal muscle health and disease. *Curr Top Dev Biol* 2011;**96**:85–119.
42. Guttridge DC, Mayo MW, Madrid LV, Wang CY, Baldwin AS Jr. NF-kappaB-induced loss of MyoD messenger RNA: possible role in muscle decay and cachexia. *Science* 2000;**289**:2363–2366.
43. Attaix D, Combaret L, Béchet D, Taillandier D. Role of the ubiquitin-proteasome pathway in muscle atrophy in cachexia. *Curr Opin Support Palliat Care* 2008 Dec;**2**:262–266.
44. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;**12**:489–495.
45. Kai H, Kai M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors-lessons from available evidence and insights into COVID-19. *Hypertens Res* 2020;**43**:648–654, Epub 2020 Apr 27.PMID: 32341442.
46. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;**203**:631–637.
47. Bahat G. Covid-19 and the Renin Angiotensin System: Implications for the Older Adults. *J Nutr Health Aging* 2020;**24**:699–704.
48. Delafontaine P, Yoshida T. THE RENIN-ANGIOTENSIN SYSTEM AND THE BIOLOGY OF SKELETAL MUSCLE: MECHANISMS OF MUSCLE WASTING IN CHRONIC DISEASE STATES. *Trans Am Clin Climatol Assoc* 2016;**127**:245–258.
49. Cabello-Verrugio C, Morales MG, Rivera JC, Cabrera D, Simon F. Renin-angiotensin system: an old player with novel functions in skeletal muscle. *Med Res Rev* 2015;**35**:437–463.
50. Solheim TS, Vagnildhaug OM, Laird BJ, Balstad TR. Combining optimal nutrition and exercise in a multimodal approach for patients with active cancer and risk for losing weight: Rationale and practical approach. *Nutrition* 2019;**67–68**:110541.
51. Aapro M, Arends J, Bozzetti F, Fearon K, Grunberg SM, Herrstedt J, et al. ESMO (European School of Medical Oncology)Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. *Ann Oncol* 2014;**25**:1492–1499.