EDITORIAL

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Cachexia research in Japan: facts and numbers on prevalence, incidence and clinical impact

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Abstract

Even though most clinical data on cachexia have been reported from Western countries, cachexia may be a growing problem in Asia as well, as the population in this area of the world is considerably larger. Considering the current definitions of obesity and sarcopenia in Japan, which are different from the ones in Western countries, the lack of a distinct cachexia definition in Japan is strinking. Only one epidemiological study has reported the prevalence of cachexia using weight loss as part of the definition in patients with stage III or IV non-small cell lung cancer. Although the reported prevalence of 45.6% is within the range of that in Western countries (28–57% in advanced cancer), we cannot compare the prevalence of cachexia in other types of cancer, heart failure, chronic obstructive pulmonary disease (COPD), and kidney disease (CKD) between Japan and Western countries. In patients with heart failure, one third of Japanese patients has a body mass index $<20.3\,kg/m^2$ whereas the prevalence of underweight is 13.6% in reports from Western countries. These results may suggest that there are more cachectic heart failure patients in Japan, or that using the same definition like Western countries leads to gross overestimation of the prevalence of cachexia in Japan. The rate of underweight patients in COPD has been reported as 31–41% in COPD and seems to be high in comparison to the prevalence of cachexia in Western countries (27–35%). The reported lowest quartile value of BMI ($19.6\,kg/m^2$) in CKD may match with the prevalence of cachexia in Western countries (30–60%). The number of clinical trials targeting cachexia is very limited in Japan so far.

Keywords Cachexia; Japan; Prevalence; Incidence; Treatment

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Cachexia is a complex metabolic syndrome associated with underlying illness, characterized by loss of muscle with or without loss of fat mass, and clinically diagnosed by the criteria including existence of underlying chronic disease, significant weight loss, and several evidences of abnormal metabolism.[1] Because of the increasing prevalence of chronic diseases associated with the development of cachexia in advancing age, there is a large number of cachexia-related hospitalizations with increasing costs in Western countries.[2] Although most clinical data on cachexia have been reported from Western countries, cachexia may be a growing problem because of the larger population in Asia as well.[3]

As the definition of cachexia includes body weight, we have to pay attention to the fact that the body size in Asian people is different from that in Western countries because of difference in diet, lifestyle, and metabolism.[4] For example, the cutoff value of the body mass index (BMI) for the definition of obesity is smaller in Japan than in Western countries ($\geq 25\,kg/m^2$ in Japan[5] and $\geq 30\,kg/m^2$ in Western countries). Hence, there is still some possibility that not only the prevalence but also the ideal therapeutic strategies are different between in Asian people and Caucasians. Research results in Japan as an Asian aged country could become more important both for Asia and western countries.

The present state of cachexia in Japan

Although the researchers in Asia have proposed an Asian definition for sarcopenia, which includes different cutoff values of muscle mass, muscle strength, and physical performance than that for Western countries,[6,7] there has been no distinct Asian definition for cachexia so far. A simple quotation from the global definition of cachexia[8] has been included in the

Clinical Guidelines for Infusion Therapy in Advanced Cancer Patients 2013 edited by the Japanese Society for Palliative Medicine, which is the only one cachexia definition with a cutoff for weight loss in Japan.[9] No other definition of cachexia is shown in guidelines for chronic diseases such as heart failure, chronic obstructive pulmonary disease (COPD), or chronic kidney disease (CKD). Regarding heart failure, unintentional weight loss is alerted as cachexia in Guidelines for Treatment of Acute Heart Failure.[10] For COPD patients, nutritional evaluation including weight assessment are recommended in a section of 'Nutrition management' in the guidelines for the diagnosis and treatment of COPD (3rd edition) without referring to cachexia itself.[11] In CKD guidelines, continual diet therapy is recommended without referring to cachexia itself.[12] Lack of distinct cachexia definitions in Japan does not necessarily mean that researchers have accepted the global definition but may rather suggest that many researchers have not paid much attention to cachexia. In fact, there seems to be only one epidemiological research study reporting the prevalence of cachexia using weight loss as a part of the definition. Kimura *et al.* retrospectively reviewed the clinical data of consecutive patients with stage III or IV non-small cell lung cancer who had received their first-line chemotherapy, after having excluded those who were candidates for curative radiotherapy or who had received palliative radiotherapy.[13] Cachexia, defined as a body weight loss >5% over the past 6 month or >2% in patients with a BMI <20 kg/m^2, was observed in 45.6% of the overall cohort, and its presence was associated with a poor prognosis. Although this number is within the range of Western countries (the prevalence ranging from 28 to 57% in advanced cancer[14] and 50–80% in several types of cancer[15]), we cannot compare the prevalence of cachexia in other types of cancer, heart failure, COPD, and CKD between Japan and Western countries. Hence, here we listed epidemiologic researches 'suggesting' the prevalence of cachexia, which includes BMI data in chronic diseases (Table 1). In recent years, a significant amount of data has been updated. However, many of these reports[16–21] had criteria including only BMI cut-off of 18.5 kg/m^2, which is related to the World Health Organization definition of 'malnutrition'.[22] Table 1 includes the data with tertile or quantile value of BMI, if the value is close to 20 kg/m^2, which is one of the criteria in universal cachexia definition.[1] The lack of data with regards to weight loss in most of

Table 1 Epidemiologic researches suggesting the prevalence of cachexia

Disease	Inclusion criteria	Exclusion criteria	Reference	Definition used		*N*	Prevalence (%)
Cancer	Advanced NSCLC planned to CT	Patients planned to radiotherapy	Kimura *et al*. 2015 [13]	Cachexia	Weight loss >5% over 6 month or >2% in patients with a BMI <20 kg/m^2	134	46
	Head and neck cancer	None	Takenaka *et al*. 2014 [16]	Underweight	BMI <18.5 kg/m^2	726	18
	Breast cancer planned to CT and surgery	Distant metastasis	Iwase *et al*. 2014 [17]	Underweight	BMI <18.5 kg/m^2	248	7
	Stomach cancer	None	Minami *et al*. 2015 [18]	Underweight	BMI <18.5 kg/m^2	1033	8
Chronic HF	Stable HF	None	Nochioka *et al*. 2010 [19]	Underweight	BMI <18.5 kg/m^2	972	9
	Hospitalized HF	Acute CVD, dialysis, cancer	Takiguchi *et al*. 2014 [20]	Underweight	BMI <18.5 kg/m^2	648	13
	Hospitalized HF	None	Hamaguchi *et al*. 2010 [23]	Lower tertile in BMI	BMI <20.3 kg/m^2	2488	(33)
	Hospitalized HF	AMI, dialysis, cardiac surgery	Komukai *et al*. 2012 [42]	Lowest quartile in BMI	BMI ≤21.4 kg/m^2	219	(25)
CKD	Hemodialysis	Acute CVD, active infection, cancer	Takahashi *et al*. 2012 [25]	Lowest quartile in BMI	BMI <19.6 kg/m^2	1228	(25)
COPD	Stable COPD	Tuberculosis, cancer	Higashimoto *et al*. 2011 [26]	Low BMI	BMI <20 kg/m^2	69	41
	Hospitalized COPD (>65 y)	None	Yamauchi *et al*. 2014 [21]	Underweight	BMI <18.5 kg/m^2	263 940	31

BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, Chemotherapy; CVD, cardiovascular diseases; HF, heart failure; NSCLC, non-small cell lung cancer.

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the listed reports may be because of the fact that such data cannot be assembled from many databases in retrospect, if the researchers did not record the history of weight loss at the beginning of the studies. According to the epidemiologic data with BMI, one-thirds of Japanese heart failure patients had a BMI $<20.3\,kg/m^2$[23] whereas the prevalence of underweight (BMI $<20.7\,kg/m^2$) was 13.6% in reports from Western countries.[24] These data may suggest that there are more cachectic heart failure patients in Japan than in Western countries, or that the use of the same definition as in Western countries can overestimate the prevalence of cachexia in Japan. Although direct comparisons between Japan and Western countries cannot be performed either in CKD and COPD, the reported lowest quartile value of BMI (19.6 kg/m^2) in CKD[25] may match the prevalence of Western countries (30–60%[14]). In COPD, the rate of low BMI ($<20\,kg/m^2$) and underweight (BMI $<18.5\,kg/m^2$) patients were 41%[26] and 31%,[21] which seem to be high in comparison with the prevalence of cachexia in Western countries (27–35%).[14]

Recent cachexia research in Japan

As expected by the lack of epidemiologic data in cachexia, most of observational/interventional studies in Japan have been based on various definitions for cachexia. Table 2 shows observational/interventional parallel-group comparison studies using some clear definitions for cachexia. There are wide difference among studies in the definition of cachexia, although some of them have taken weight loss into account as part of the definition.[27–33] Four interventional studies using ghrelin and octanoic acid-rich formula have been reported in the field of COPD, including two studies with weight loss >7.5% over 6 months[32,33] and 2 studies with BMI $<21\,kg/m^2$[34,35] as the definition of cachexia. On the other hand, there is no published interventional research targeting cachexia in cancer, heart failure, and CKD. Most of the studies in cancer and heart failure focused on blood levels of hormones or cytokines in those with and without cachexia, but used definitions for cachexia that are completely

Table 2 Observational and interventional studies for cachexia and definitions

Disease	Classification	Reference	Definition of cachexia	Study endpoints	Type of study	*N*
Cancer	Colorectal and gastric cancer	Shibata *et al*. 2002 [27]	Recurrence or metastasis and >5% weight loss over 3 months or alb <3.0 g/dL	The production of cytokines by peripheral blood mononuclear cells	Observational	61
	Lung cancer	Shimizu *et al*. 2003 [28]	Weight loss >5% over 3 month	Plasma ghrelin levels	Observational	43
	Gastric cancer	Takahashi *et al*. 2009 [36]	Stage IV, subjective symptoms	Plasma ghrelin and leptin levels	Observational	16
	Any cancers	Naito *et al*. 2012 [37]	GPS as a continuous scale	Oxycodone metabolism	Observational	47
	Pancreatic cancer	Fujiwara *et al*. 2014 [29]	Performance Status >0, anorexia, and weight loss >10% over 6 months	Serum metabolite levels	Observational	21
	Any cancers	Suno *et al*. 2015 [30]	Weight loss >5% over 6 month or >2% in patients with a BMI $<20\,kg/m^2$ or with sarcopenia	Dose-adjusted plasma fentanyl concentrations	Observational	21
Chronic HF	Stable HF	Nagaya *et al*. 2001 [31]	Weight loss >7.5% over 6 month	Plasma levels of ghrelin and other cytokines	Observational	74
COPD	COPD	Ashitani *et al*. 2009[32]	Weight loss >7.5% over 6 month or BMI $<21\,kg/m^2$	The effect of an octanoic acid-rich formula on plasma acyl-ghrelin levels	Interventional	23
	COPD	Nagaya *et al*. 2005 [33]	Weight loss >7.5% over 6 month	The effects of ghrelin on body composition, muscle strength, and functional capacity	Interventional	7
	COPD	Miki *et al*. 2012 [34]	BMI $<21\,kg/m^2$	The efficacy and safety of adding ghelin to pulmonary rehabilitation	Interventional	33
	COPD	Matsumoto *et al*. 2015 [35]	BMI $<21\,kg/m^2$	The optimal dose of ghrelin	Interventional	44

BMI, body mass index; COPD, chronic obstructive pulmonary diseases; GPS, the glasgow Prognostic Score; calculated using serum albumin and C reacting protein, HF; heart failure.

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different from each other. Two of them did not include body weight, but only included cancer stage[36] or blood markers[37] as definitions of cachexia. The other studies in cancer had an endpoint of weight loss and inflammatory responses[38,39] without any definition of cachexia. The reasons for such a wide variety of inclusion criteria are not clear, but it could be speculated that the researchers intended to simplify the enrollment of patients.[40] Although the number of clinical trials targeting cachexia is very limited in Japan so far, researchers may have a potential to produce more evidence in this field, having fruitful results as their background especially in the field of basic research.[41] Further studies targeting cachexia patients defined by universal criteria are desirable when we consider to apply the results for Western countries.

Conclusions

In recent years, many epidemiological data have been updated reporting the distribution of BMI in chronic diseases in Japan, however, most of them have not referred to the definition of cachexia. The clinical course and background of cachectic patients in Japan may be different from that of patients in Western countries. There have been several observational studies comparing patients with and without cachexia, but the definitions of cachexia used have widely varied among studies. Interventional clinical trials for cachectic patients are still lacking especially in cancer, heart failure, and CKD. Further studies are needed to assess the epidemiologic/pathological background, as well as the effect of therapeutic approach, in cachexia.

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Conflicts of interest

None declared.

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