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Potential blood biomarkers in COPD cachexia

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Summary. Weight loss and muscle wasting occur in a quarter of patients with chronic obstructive pulmonary disease (COPD) and are associated with shorter survival and reduced quality of life. Effective intervention for cachexia requires early detection that may help in preventing further depletion. Elevated concentrations of inflammatory biomarkers are observed in COPD patients and have been associated with several complications such as weight loss. In this review, we have studied the circulating inflammatory mediators (tumor necrosis factor, interleukin-6 and c-reactive protein) and energy balance hormones (adiponectin, leptin, ghrelin) as potential biomarker in early detection and management of cachexia in COPD. This review did not find firm support for causal relationship between biomarkers and cachexia. Most studies divided individuals into cachectic and non-cachectic groups based on current body mass index (BMI) or fat free mass index (FFMI) regardless of previous status. Future large longitudinal studies with BMI/FFMI matching are required. Also, combination of inflammatory biomarkers and energy homeostasis hormones may represent valuable biomarkers in the early detection of COPD cachexia.

Key words: COPD cachexia, inflammatory mediators, biomarkers, adiponectin, leptin, ghrelin

Introduction

Chronic obstructive pulmonary disease (COPD) is an obstructed or chronically limited flow of air to the lungs resulting from inflammatory response in the airways and the lung to noxious particles or gases (1). The World Health Organization (WHO) estimates 65 million people are currently suffering from moderate to severe COPD. It is predicted that by 2020, COPD will be the third leading cause of death in the world (2). The disease is associated with various complications including osteoporosis, heart failure, dementia, depression and cachexia (3, 4). Therefore, cachexia is one of the most serious complications of COPD and an essential risk factor for mortality in these patients (5).

Cachexia or wasting syndrome is characterized by unintentional weight loss and wasting of muscle mass (6). Prevalence of cachexia in COPD patients is about 25%, which is associated with exacerbation of clinical symptoms, impaired functional capacity, poor quality of life and increased morbidity rate and shorter life expectancy (7-9). It has growing rate and it is estimated that about 9 million patients (due to any disease) suffer from cachexia around worldwide (10). The etiology of COPD cachexia has not been fully revealed yet. Totally, weight loss is the result of a negative energy balance. It has been postulated that in COPD increased effort to breathe elevates activity-induced and daily metabolism (6). Inflammatory mediators trigger hyper-metabolic state and lead to an overall catabolic/anabolic imbalance (9). Elevated concentrations of blood inflammatory biomarkers are also observed in COPD patients and have been associated with several complications such as weight loss, skeletal muscle dysfunction and osteoporosis (11, 12). Also, the energy homeostasis and appetite regulating hormones including leptin, adiponectin and ghrelin have been known as major cause of cachexia in COPD (13-16).

Cachexia caused by various chronic diseases is suggested as major public health problem and it has devastating consequences (17). Effective management of cachexia depends on early identification of the syndrome (18). In this review, we have discussed about inflammatory mediators (IL-6, TNF-α and CRP) and energy homeostasis hormones (Leptin, Adiponectin and Ghrelin) as diagnostic biomarkers in COPD cachexia.

Search methodology

We searched PubMed in September 2016 using the following search criteria: "Biomarker AND COPD", "cachexia AND COPD", "Pulmonary cachexia" and "biomarker AND cachexia AND COPD"'. Only English language original papers published since 1990 upward 2015 were included. Results from studies in humans were reviewed. Due to the lack of standardized definition for cachexia in chronic illness (19), the studies have used various cut-offs, therefore, reviewed studies cut-offs are listed in table 1.

Biomarkers in cachexia

Biomarkers are biological molecules that often measured and evaluated to examine normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (20). There are a variety of potential biomarkers for cachexia derived from different body compartments including plasma, urine, skeletal muscle and the patient's genome. Computerized tomography and magnetic resonance imaging as precise imaging biomarkers that are considered as gold standards for estimating muscle mass in research (21). However, radiation, high cost and limited resolution in certain organs (e.g. lung) limits their use in routine clinical applications (18, 21). Plasma or serum is easily sampled and important compartment to study for potential biomarkers in many disease including cachexia (18).

Table 1. Cachexia definitions used in COPD studies with body wasting

Cachexia Definition	References
BMI< 20 kg/m2	Ying (33), Tomoda (31), Brúsik (52), Deveci (30), Eid (37), Itoh (80), Skyba (50)
BMI< 21 kg/m2	Matsumoto (86), Uzum (27), Kao (51), Miki (85)
BMI< 18.5 kg/m2	Chan (61)
Weight loss> 7.5% over 6 month	Nagaya (84), Koehler (9)
FFMI> 14 kg/m2 for women FFMI< 17 kg/m2 for men	Eagan (23)
FFMI< 15 kg/m2 for women FFMI< 16 kg/m2 for men	Broekhuizen (46), Van Helvoort (47)
%fat< 20%)	Takabatake (68)

Identifying a diagnostic serum biomarker of COPD cachexia seems vital, which no ideal clinical biomarker has been defined yet. Diagnostic criteria for cachexia have been suggested to include inflammatory mediators such as C-reactive protein, interleukin (IL)-6 and tumor necrosis factor (TNF)-α levels. Altered levels of these biomarkers contributes to muscle atrophy and lipolysis (22, 23). In addition, Investigations focusing on adipose tissue have identified that leptin and adiponectin in plasma are indicators of weight alterations in health and diseases. Also, ghrelin, as an active peptide in metabolism, is a considerable biomarker in cachexia (24, 25). This mediating energy homeostasis and appetite regulating peptides are considered predictors of weight loss (13, 26). Therefore, circulatory levels of mentioned inflammatory mediators and these hormones may represent valuable biomarkers in the early detection and management of cachexia in COPD.

Inflammatory mediators

COPD is a chronic inflammatory disorder, and many studies have shown higher systemic levels of inflammatory mediators, such as IL-6, TNF-α and CRP in patients with COPD compared with control subjects (27-31). Several studies have suggested that serum levels of inflammatory mediators are important factors in the development of complications in COPD, including cachexia (28, 31-33). Increased resting energy expenditure (REE) has been shown in some COPD patients (34, 35). It has been suggested that elevated REE may contribute to weight loss and cachexia. Systemic inflammation play a significant role in increased REE in COPD (35, 36).

Tumor necrosis factor

TNF- α is suggested to play a central role in COPD cachexia (12, 37). TNF- α was originally des-

ignated as "cachectin" in recognition of its catabolic actions (38). Also, TNF- α blocking antibodies have been investigated as a new target for the treatment of COPD associated cachexia, but the protocol was not effective (39). TNF- α affects muscle cells by nuclear factor-ϰB (NF-ϰB) activation, which can upregulate inducible nitric oxide synthase and degradation of myosin and lead to skeletal muscle atrophy and weight loss (40, 41). Several studies have compared circulatory levels of TNF-α between cachectic and non-cachectic COPD patients. The data are shown in table2. Findings about the potentiality of serum TNF-α in COPD cachexia is controversial. Some studies have indicated TNF-α as reliable and diagnostic biomarker and some the others have rejected that. It is suggested that short half-life characteristic of TNF-α in plasma and wide different assays to measure its plasma level lead limitations and contradictory results (42)

Interleukin (IL)-6

IL-6 is considered as active cytokine in cachexia due to some reasons: 1. Important target organs (adipose, skeletal muscle, gut, and liver tissue), 2. Increase hormone sensitive lipase and adipose triglyceride lipase activity 3. Induction of proteasome and autophagy protein degradation pathways in skeletal muscle, 4. Indirect association with AMP-activated protein kinase (AMPK) and NF-ϰB activation (43, 44). As shown in table 2, most of studies have shown that serum level of IL-6 is different according to body composition.

C-reactive protein

C-reactive protein (CRP) is an acute phase protein, which its levels rise in response to a systemic inflammation (45). However, increased levels of CRP have been found in COPD patients with cachexia (46, 47). Inhaled or orally administration corticosteroids, as common treatments in COPD, can decrease CRP levels up to 50% (48) and also blood CRP level increases in response to various inflammatory conditions (49). Therefore, it is not specific to COPD. Further research on CRP and COPD cachexia is need to evaluate its reliability.

Of the 15 studies reviewed (table2) in three studies none of inflammatory mediators (IL-6, TNF-α and CRP) showed any significant differences between cachectic and non-cachectic COPD patients (50-52). Kao et al. mentioned in their study that it could be due to high variability in the concentrations and small sample size (51). In other study serum levels of inflammatory mediators was not significantly different but adipose tissue-relative expressions of the mediators was significantly different between groups (50). In brusik et al. study medication history was not taken from the patients and anti-inflammatory drugs use by patients is supposable (52).

Adiponectin

Adiponectin is an adipose tissue-derived specific protein that has anti-inflammatory and anti-obesity effects (53). It has an active role in energy homeostasis through the regulation of glucose and fatty acid metabolism in peripheral tissues such as muscle and liver via AMPK (54, 55). Qi et al. showed that administration of adiponectin in mice decreases body weight mainly by stimulating thermogenesis and energy expenditure (56). Also, suppressions of adiponectin receptors 1 and 2 have been shown in obesity state (57).

Several studies have shown that serum level of adiponectin is significant prognostic and diagnostic biomarker in COPD patients (58, 59). Higher levels of adiponectin have been reported in COPD patients (59-61). Brusik et al have shown that COPD patients with body mass index (BMI) < 20 kg/m^2 had significantly elevated plasma adiponectin levels compared to those with BMI ≥ 20 kg/m^2 (52). Other similar studies have investigated adiponectin levels in different states of COPD, such as serum levels of adiponectin in obese (62) and normal-weight subjects with and without COPD. Also comparison between non-obese and obese COPD patients, cachectic and normal weight COPD patients (31) have done. Significant negative correlations between adiponectin and COPD cachexia related factors such as: BMI, fat free mass index, total body water and muscle mass index have been found (63). High RMR has been seen in COPD patients compared to control groups (51, 64). Also, increased RMR has reported in cachectic COPD patients in comparison with normal weight patients and significant correlation between RMR and adiponectin level is revealed (52).

Association between adiponectin with RMR, as well as negative relationship between BMI, FFMI and

Table2. TNF- α, IL-6 and CRP blood levels in chronic obstructive pulmonary disease (COPD)

First author	Group	BMI/ FFMI	TNF-α (pg/ml)	P-value	IL-6 (pg/ml)	P-value	CRP (mg/l)	P-value
Di Franci (28)	COPD	BMI 18.1	70.2	<0.001	ND	-	ND	-
	COPD	BMI 26.2	6.7					
Itoh (80)	COPD	BMI 18	6.8	<0.01	4.2	< 0.05	ND	-
	COPD	BMI 24.2	4.3		2.3			
Eid (37)	COPD	BMI 21.2	3.2	< 0.04	4.2	0.001	4.55	NS
	COPD	BMI 24.4	2.4		2.2		2.83	
Gaki (32)	COPD	FFMI 17.2	2.9	< 0.001	8.2	0.003	6	0.002
	Health	FFMI 20.6	1.5		6.5		2	
Broekhuizen (46)	COPD	FFMI 14.2	1.34	NS	3.98	< 0.001	4.23	< 0.001
	COPD	FFMI 16.9	1.22		3.71		3.12	
	Health	FFMI 20.2	1.23		1.76		1.76	
Van Helvoort (47)	COPD	FFMI 14.5	0.39	NS	3.6	0.05	16	< 0.001
	COPD	FFMI 18.6	0.46		2		10.8	
Von Haehling (29)	COPD	BMI 23.5	2.1	< 0.01	ND	-	ND	-
	Health	BMI 26.1	1.1					
Deveci (30)	COPD	BMI 23.7	20	< 0.001	12.2	< 0.001	ND	
	Health	BMI 26.6	10.62		6			
Kao (51)	COPD	BMI 18.7	4.4	NS	9.7	NS	2.4	NS
	COPD	BMI 25.4	5.3		3.7		2.6	
	Health	BMI 26.4	7.7		3.6		1.7	
Brúsik (52)	COPD	BMI 18.2 FFMI 16.1	9.75	NS	4.3	NS	ND	-
	COPD	BMI 25.2 FFMI 17.8	13.5		3.5			
	COPD	BMI 36 FFMI 21.2	15.2		4.4			
Ying (33)	COPD	BMI 17.63	6.34	< 0.01	4.5	< 0.01	ND	-
	COPD	BMI 24.65	4.31		2.4			
Tomoda (31)	COPD	BMI 17.7	6.8	< 0.05	3.7	< 0.01	ND	-
	COPD	BMI 23.8	4.3		1.4			
Koehler (9)	COPD	BMI 19	6.5	NS	19.5	< 0.05	ND	-
	COPD	BMI 25.6	3.9		6.3			
Chan (61)	COPD	BMI 20.7	ND	-	4.19	< 0.05	8.75	< 0.05
	Health	BMI 23.7			2.40		3.71	
SKYBA (50)	COPD	BMI 18.3 FFMI 16.1	9.8	NS	4.3	NS	ND	-
	COPD	BMI 22.9 FFMI 17.4	13.1		2.9			
	COPD	BMI 27.7	13.9		3.8			
	COPD	FFMI 18.2						

BMI, Body Mass Index. FFMI, Fat Free Mass Index. ND, Not determined. NS, Not significant

serum adiponectin level suggests an important role of this biomarker as potential biomarker of COPD cachexia. The most important limitation of these studies is that all have been done without BMI matching. Thus future studies are required to evaluate serum adiponectin levels in COPD patients with BMI matching done to evaluate the net effect of weight loss on serum adiponectin level. Also, adiponectin serum level comparing between underweight subjects with and without COPD can be useful.

Leptin

Leptin, is a product of obese gene which is secreted mainly by adipocytes in proportion to fat mass and regulates several metabolic and inflammatory functions, both centrally and peripherally (32). Many other factors such as insulin, glucocorticoids, TNF-α, reproductive hormones, and prostaglandins influence leptin synthesis and secretion in adipocytes (65).

There is high positive correlation between circulating levels of leptin with BMI, % fat and TNF-alpha in COPD patients (66-69). Leptin is suggested to play a key role in systemic inflammation of COPD (69) and has known to possess vitally important role in body mass regulation by acting on the central nervous system to induce higher energy expenditure and lower food intake (70), by affecting the balance between orexigenic and anorexigenic hypothalamic pathways.

Significantly lower serum levels of leptin have been shown in the COPD patients versus healthy controls (66). It is known that reduced leptin levels are generally associated with weight loss, and high levels with weight gain (71). Also, Leptin serum level comparison between cachectic and non-cachectic COPD patients indicated a significant reduction in cachectic patients (46, 52, 68, 69, 72). In contrast, one study in COPD patients compared with healthy controls (27) demonstrated that serum leptin levels may not be a good biomarker of weight loss. It is considerable that in this study, underweight patients had lower BMI than control group but there were no significant differences in fat mass percentages between the two groups.

Despite low levels of leptin in COPD cachectic patients, they do not have increased appetite or lower energy expenditure, this unexpected feature is attributed to resistance to the effects of hypoleptinemia (73). Increased resting energy expenditure (REE) in underweight COPD patients is associated with reductions in serum and adipose tissue leptin (52, 71).

The reduction in adipose tissue expression of leptin has been reported in cachectic COPD patients (52). Therefore, lower circulating leptin levels in COPD-related cachexia are not only because of the adipose tissue loss, but also due to the decrease in relative leptin gene expression in the adipose tissue

Since the reduction in leptin levels reflects a higher metabolic rate and loss of adipose tissue in COPD-cachexia, potentially low circulating leptin levels in COPD patients is considering catabolic biomarkers in clinics and researches.

Ghrelin

Ghrelin, a 28-amino acid peptide, mainly isolated from the stomach that stimulates growth hormone (GH) secretion and regulation of energy homeostasis by stimulating food intake. GH increases insulin-like growth factor (IGF)-I levels. GH and IGF-1 are the major mediators involved in the regulation of energy balance. Also, Ghrelin has some anti-inflammatory activities including inhibition of IL-1β, IL-6, and TNF-α synthesis (74-76). The combination of these actions suggest this peptide as a proper biomarker of cachexia.

Many factors influence ghrelin synthesis and secretion such as glucagon, estrogen, Insulin, somatostatin, leptin and aging (77, 78). In addition, plasma ghrelin level is inversely related to BMI and weight loss (74, 75). Elevated levels of plasma ghrelin has been observed in cachectic conditions caused by a variety of chronic disorders such as congestive heart failure, COPD, cancer, end stage renal disease (33, 79-82).

Itoh et al. assessed plasma level of ghrelin in 26 cachectic and 24 weight stable COPD patients. Cachexia was defined as BMI < 20. Lower lean body mass and higher plasma ghrelin were observed in underweight patients than in normal weight. Also a negative correlation between ghrelin level with BMI and fat-free mass was revealed (80). Similar results were obtained later in different investigations (27, 30, 33, 69, 83).

It is suggested that elevated endogenous ghrelin is a compensatory action in the cachectic state and

may provide important clues to improve the catabolic-anabolic imbalance in such patients (80). Thus ghrelin administration was examined in COPD cachectic patients to evaluate its possible therapeutic effect (84, 85). Nagaya et al and Matsumoto et al in two separated study showed that daily administration of ghrelin for 3 consecutive weeks increased mean body weight, food intake, FFM, and peripheral and respiratory muscle strength (84, 86). High ghrelin concentrations could be considered a result, not a cause of cachexia, which significantly relates to low BMI and fat-free-mass in COPD cachexia. Therefore, serum Ghrelin may be a promising biomarker to diagnose cachexia in COPD patients.

Conclusion

Finding a robust diagnostic serum biomarker for muscle mass wasting and cachexia in COPD patients is challenging. This study did not find firm support for causal relationship between inflammatory mediators and COPD cachexia. Decision about biomarkers diagnostic potentiality in cachectic state needs proper study design. Future large longitudinal studies with BMI/FFMI matching between cachectic and non-cachectic patients helps to reveal biomarkers exact ability to assess the wasting state. Besides that, future studies are necessary to increase specificity and sensitivity of evaluation methods. Combination of inflammatory mediators and energy homeostasis hormones may represent valuable biomarkers in the early detection and management of COPD cachexia, as no study has assessed various combinations.

Declaration of interest

The authors report no conflict of interest.

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