A study of body composition and its association with disease severity in stable chronic obstructive pulmonary disease patients in HUSM

By

Dr. Mohammad Faisal bin Asmee

PUM 0065/07

Dissertation submitted in partial fulfilment of the requirement for the Degree of Master of Medicine

Universiti Sains Malaysia (Internal Medicine)

November 2011

Acknowledgement

Praise to Allah s.w.t the most compassionate and most merciful, whose blessing have helped me through the entire completion of this dissertation. I wish to express my utmost gratitude to my supervisor Dr. Shaharudin Abdullah, Dr. Hamid Jan and Dr. Rosediani who had helped me a lot with their suggestion, interest and sharing the ideas and encouragement. Without their contribution this thesis would have been incomplete.

My gratitude also goes to Dr. Kamarul Imran for helping in the statistical analysis and toward stuff nurse and technician in respiratory clinic for helping in completing the data collection.

I am most grateful to my parents, wife and children's for their love, support and understanding which provided me the inspiration to work hard. Thank you very much and great appreciation to make this dissertation come true, may Allah blesses us all.

Mohammad Faisal B. Asmee

November 2011

Table of contents

Chapter 4

4.0 Methodology

Chapter 5

5.0 Results

5.1 Descriptive analysis   37

5.2 Clinical variables

5.3 Univariate analysis   49

List of tables

List of figures

List of abbreviations

n	number of patients
COPD	Chronic Obstructive Airway Disease
BMI	Body Mass Index
ffm	fat free mass
ffmi	Fat Free Mass Index
6mwd	six minutes walking distance
DM	diabetes mellitus
GERD	gastroesophageal reflux disease
Bph	benign prostate hypertrophy
Hpt	Hypertension
Ihd	Ischaemic heart disease
Hb	haemoglobin
FEV1	forced expiratory volume in one second
FEV1/FVC	forced expiratory volume in second to forced vital capacity ratio
CRP	C-reactive protein
HUSM	Hospital University Sains Malaysia
DEXA	dual energy X-ray absorptiometry
BIA	bioelectric impedance analysis
SFA	skin fold anthropometry

Abstrak (Versi bahasa Melayu)

Latar belakang : Penyakit sumbatan paru-paru kronik bukannya hanya berkaitan dengan paru-paru sahaja tetapi ia mempunyai manifestasi menyeluruh disebabkan proses keradangan yang menjadi penyebab penyakit ini berlaku. Ukuran komposisi badan (indeks jisim tubuh dan indeks jisim tubuh bebas lemak) sebagai manifestasi menyeluruh penyakit ini telah menunjukkan bahawa ia berkait rapat dengan kadar keterukan dan kematian kepada pesakit.

Objektif utama kajian ini adalah untuk melihat kaitan antara komposisi badan dengan tahap keterukan pesakit sumbatan paru-paru kronik yang stabil (tidak mengalami keterukan yang bertambah dalam jangkamasa tiga bulan sebelum kajian).

Kaedah : Kami mengkaji 38 pesakit paru-paru kronik stabil yang datang ke klinik paru-paru HUSM dan mengukur indek jisim tubuh, indek jisim tubuh bebas lemak, ujian berjalan selama enam minit dan ujian darah untuk CRP.

Keputusan : Kajian ini menunjukkan perbezaan ukuran komposisi badan tidak mempunyai kaitan dengan tahap keterukan penyakit sumbatan paru-paru kronik yang stabil ($p > 0.05$).

Kesimpulan : Ukuran komposisi badan tidak boleh digunakan untuk menilai tahap keterukan pesakit paru-paru kronik yang stabil.

Abstract (English version)

Background: COPD is not just a disease of the lungs alone; it has systemic manifestations due to the underlying pathogenesis of inflammatory reaction. Systemic manifestations in term of reduction in body composition (Body Mass Index and Fat Free Mass Index) has been shown to be an independent risk factor for disease severity and mortality in COPD.

The objective of this study is to determine the association of body composition with disease severity in stable COPD patients (patients who had no exacerbation in the past three months).

Methods: We evaluated 38 stable COPD patients attending Respiratory Clinic in HUSM and calculated their Body Mass Index, Fat Free Mass Index and determined their six minutes walking distance and serum CRP values.

Results: There was no satisfactory significant difference between body composition and disease severity in COPD patients noted in this study ($p > 0.05$).

Conclusion: Body composition (BMI,FFMI) is not suitable for assessment of disease severity in stable COPD patients.

CHAPTER 1

INTRODUCTION

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the most common respiratory disorder that effect many people worldwide besides asthma, common cold and chest infections. One of the major leading worldwide work in this illness is the Global Initiative of Chronic Obstructive Lung Disease (GOLD), that is been conducted by the World Health Organization. They had produced a guideline to define and further manage COPD. The GOLD guideline had been accepted worldwide including in Malaysia whereby base on it, Malaysia has produce its own guideline in 2009 under the Malaysian Clinical Practice Guideline by the Ministry of Health. All this is done to improve and educate health care professional to manage patient appropriately.

The definition by GOLD guideline updated in 2010 had included that COPD have significant extra pulmonary manifestations which may contribute to the severity of the disease. The systemic illnesses for example are nutritional abnormality (Daniel A King et al., 2008), weight loss and skeletal muscle depletion (M. Jeffery Mador and Boskanat., 2001), osteoporosis (Lidwien Graat-Verboom et al., 2009), depression (Wanning Xu et al., 2008) and anaemia (T. Similowski et al., 2006).

The extra pulmonary manifestation of COPD will be the main focus of this study whereby its association with COPD severity based on the lung fuction test will be assessed. The extra pulmonary manifestation that will be look into is the body composition. This is because based on the previous study, body composition had been shown to be an independent predictor of disease severity and mortality(Jorgen

Vestbo *et al.*, 2006). This is the main evaluation that will be observed in this study as to further confirm the previous finding to our local data in Malaysia.

From this study, hopefully the use of body composition as one of the assessments in prevention and treatment of COPD will be established. Another aspect that would be assesses in this study is patient's functional capacity according to their severity of COPD. This is important because body composition was noted to have a significant correlation with exercise capacity in COPD patients (Eleni Ischaki *et al.*, 2007).

As for the underlying cause of the extra pulmonary manifestation of COPD, this study will look into the role of C-reactive protein as the inflammatory marker to predict the COPD severity. Systemic inflammation had been shown to be the underlying pathogenesis of COPD and few inflammatory markers was observed to be elevated in COPD including CRP(Abdullah A. eid *et al.*, 2001).

In conclusion, hopefully from this study data, we could determine the correlation between body composition and disease severity in COPD patients that might be helpful in managing COPD patient rather than concentrating on their respiratory symptoms alone. Further pulmonary rehabilitation or nutritional point of view might be considered to help improving patient's quality of life and also in reducing the mortality related to the illness.

CHAPTER 2

LITERATURE REVIEW

2. Literature review

2.1 Definition:

In 2006, the Global Initiative of Chronic Obstructive Airway Disease(GOLD) had produced a guideline for chronic obstructive airway disease (COPD) and defined it as "Preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. The airflow limitations is usually progressive and associated with an abnormal inflamatory response of the lung to noxious particle". In the updated version of 2010 this definition remains unchanged. Worlwide, ciggarete smoking is the most commonly encountered risk factor for COPD, although in many countries, air pollution resulting from the burning of wood and other biomass fuels has also been identified as a COPD risk factor(Nanshan Zhong *et al.*, 2007)

The primary physiological abnormality in COPD is an accelerated decline in the forced expiratory volume in one second(FEV1). FEV1 is defined as the maximal air of a person can exhaled in one second and will shows the degree of airway obstruction. The COPD symptoms starts from asymptomatic phase in which lung function deteriorates without associated symptoms. The onset of the subsequent symptomatic phase is variable and usually starts when the FEV1 fall to less than 50%.

2.2 Global Initiative of Chronic Lung Disease (GOLD) guideline :

The GOLD guideline was initiated in 1998 by the World Health Organization to bring more attention and awareness to COPD, its management and its prevention. Therefore it can reduced the morbidity and mortality due to chronic obstructive airway

disease. The first GOLD guideline was published in 2001, and since then continous work were been done to update the guideline yearly by the corresponding commity. This is because eventhough COPD is considered a major public health problem, its awareness among the public are still low as compared to other non communicable disease such as diabetes mellitus, hypertension or ischaemic heart disease (Barbara P Yawn and Wollan., 2008). The nihilistic attidude among some health care providers towards managing COPD are still present due to the dissapointment in improving patient symptoms despite the treatment given (GOLD guideline updated version 2010).

2.3 Prevalance and burden of COPD :

The prevalance of COPD varies in between countries. In year 2006 a meta-analysis of 37 studies showed that the pooled prevalance was estimated at 7.6% of the general population(R.J. Halbert *et al.*, 2006) worlwide. In Malaysia, based on the regional working group 2009, the prevalance of moderate to severe COPD patients age 30 years or above is estimated at 4.55%. The Global burden of disease study has estimated that by the year 2020, COPD would be ranked as the third leading cause of death just after ischaemic heat disease and cerebrovascular accident (Christopher J L Murray and Lopez, 1997). This had made it moving three steps further as it is just ranked at number 6th in year 1990. The prevalance and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factor and the changing age structure of the world's population. In 2007 alone, according to World Health Organization, 210 million people have COPD worlwide with 80 million of them experiencing moderate to severe chronic disease (Mathers C).

Its going to be challenging as this disease is related to lifestyle especially smoking as the incidence of smoking is increasing and as also as increasing age of the population(Chen JC and DM., 1999). It would be a burden to patient as it would be a condition of chronic disability and a burden to the country to manage COPD. Approximately in year 2000, 2.7 million deaths occurred due to COPD and more than half of it ocurrs in the Asia-Pasific region including Malaysia(A.d. Lopez *et al.*, 2006).

2.4 Airflow limitations in COPD

The airflow limitations in COPD is due to a mixture of small airway disease (chronic bronchitis) and lung parenchymal destruction(emphysema). It is associated with abnormal inflammatory reactions towards noxius particles or gases. The most common noxious particle is from ciggerates smoking and if the exposures remained it will progressively worsening (A Sonia Buist *et al.*, 2007). Chronic airway inflammations causes changes and narrowing of the small airways and this leads to loss of the alveolar attachments to the small airways. Because of this there is a decreases in the lung elastic recoil that diminishes the ability of the airways to remain open during expiration. The airway limitations is measured by using the coventional lung function test which is the spirometry test (Nilva Regina Gelamo Pelelegrino *et al.*, 2009).

2.5 Risk factor for developing COPD :

There are multiple risk factor that would contribute to the developement of COPD including genetics, exposure to noxious particles (eg : tobacco smokes, organic and inorganic occupational dust), lung growth and development, oxidative stress, gender, age, respiratory infections and socioeconomic status.

7

2.5.1 Tobacco smoke

It is estimated that only 15% of smokers develop COPD (A Løkke *et al.*, 2006), however 90% of the cases of COPD have smoking as their risk factor. This shows that there are other factors contributing to the development of COPD. World Health organization estimates that in high-income countries, 73% of COPD mortality is related to smoking, while in low and middle income countries the rate is 40% (A.d. Lopez *et al.*, 2006). Back in 1977, Burrow (Burrow., 1977) has already shown that in a study of general population, there is a highly significant quantitative relationships between pack years of smoking and fucntional impairment of the FEV1.

Smoking prevention is the most effective intervention to reduce the risk of developing COPD and stop its progression. Smoking cessation has been shown that it would reduced inflammatory markers both in patient with or without having chronic respiratory symptom(B.W.M. Willemse *et al.*, 2004). Stopping from tobacco smokes also been shown to result in a sustained 50% reduction in the rate of lung function decline in patient with COPD(Nicholas R. Anthonisen *et al.*, 2002). In the lung health study, Anthonisen showed that men who stopped smoking at the beginning of the study and follow up over the 11 years period had a decline of FEV1 rate of 30.2 ml/year compared to those who continue smoking had an FEV1 declined at rate of 66.1 ml/year. This was also true in women where the reduction was 21.5 ml/years in those who stopped smoking versus 54.2ml/year in those who continued smoking.

2.5.2 Occupational exposure

According to American thoracic Society statement in 2003 (J.Balmes *et al.*, 2003) occupational exposure may attributed to COPD in 15% of smokers and 31% of non smokers. Occupational exposure to dust, gas and fumes may cause chronic

bronchitis, chronic emphysema, and irreversible airflow obstruction and studies from both population based and occupational cohort have shown that occupational exposure is associated with an increased incidence of COPD irrespective of smoking (Esther Rodríguez *et al.*, 2008).

2.5.3 Genetics

Genetics susceptibility to developed COPD was instituted by the data that only a minority of cigarette smokers developed COPD. The effects of smoking to lung function in monozygotic and dizygotic twins shows that when one monozygotic twin was susceptible to the effects of cigarette smoke, both twins developed reductions in lung function, whereas other monozygotic twin pairs appeared to be non susceptible and, despite similar smoking intensity, maintained normal function(Webster PM *et al.*, 1979). Studies of families and twins suggest that genetic factors also contribute to the development of COPD. The only established genetic risk factor for COPD is homozygosity for the Z allele of the alfa-1 antitrypsin gene(A.J. Sandford *et al.*, 1997). Polymorphism for the genes including alpha 1-antichymotrypsin, vitamin D-binding protein, microsomal epoxide hydrolase, cytochrome P450 1A1, Glutathione S-transferase and immunoglobulin A, have also been associated with the development of COPD(Miki M and k., 1999).

2.6 Diagnosing and assessing COPD severity

The diagnosis of COPD must be considered in patient who has symptoms of dyspnoea, chronic cough or sputum production with history of exposure to risk factors for the disease especially to cigarette smoking. Spirometry test is important for confirmation of COPD and it provides a useful description of the severity of the

airflow obstruction in COPD. Spirometry should be done after an adequate dose of an inhaled bronchodilator to minimise the variability and exclude asthma(Pellegrino R *et al.*, 2005). A study in a random population sample (Johannessen A *et al.*, 2006) found the post bronchodilator FEV1/FVC exceeded 70% in all age groups, supporting the use of this fixed ratio to diagnosed airway obstruction.

2.6.1 Spirometry test

In staging the severity of COPD the Malaysian COPD guideline 2009 had followed the GOLD guideline 2006 that it is being classified into four groups according to the post bronchodilator forced expiratory volume in one second (FEV1):

Stage 1: mild FEV1 >80 % predicted

Stage 2: moderate 50 % < FEV1 < 805 predicted

Stage 3 : severe 30 % < FEV1 < 50% predicted

Stage 4 : very severe FEV1 < 30 % predicted or FEV1 < 50 % predicted

plus chronic respiratory failure.

However the relationship between the degrees of limitation based on the spirometry alone is not perfect. The degree of dyspnoea and disability should also be use to asses severity which reflects the overall disease impact (D A Mahler and Wells., 1988) such as by using the Modified Medical Research Council (MMRC) dyspnoea scale as suggested in the Malaysian Guideline 2009.

Table 1: The Modified Medical Research Council (MMRC) Dyspnoea Scale:

Grade of dyspnoea	Description
0	Not troubled by breathless except on strenuous execise
1	Shortness of breath when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 m or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

On top of that, base on the Malaysian guideline 2009 for COPD also they added the symptoms that may be present according to the level of COPD :

Table 2: COPD stage and its symptoms

COPD stage	Symptoms that may be present
1 (Mild)	Chronic cough and sputum production may be present. At this stage, the individual is usually unaware that his or her lung function is abnormal.
2 (Moderate)	Dyspnoea typically on exertion, cough

	and sputum production sometimes also present. This is the stage at which patients usually seek medical attention because of chronic respiratory symptoms or an exacerbation of COPD.
3 (Severe)	Greater dyspnoea, reduced exercise capacity, fatigue, and repeated exacerbations that almost always have an impact on the patient's quality of life
4 (Very severe)	Respiratory failure may lead to cor pulmonale with signs which include elevation of the jugular venous pressure and pitting ankle oedema. At this stage, quality of life is markedly impaired and exacerbations may be life threatening.

A multidimensional grading system, the BODE index (Body mass index, airflow obstruction, dyspnoea and exercise capacity) have a better survival prediction in COPD patient than FEV1 alone(Bartolome R.Celli *et al.*, 2004). This is because COPD is not just a disease confined to the lung, but have systemic effects (Agustı, 2005) that would contributes to the COPD morbidities and mortalities that was not reflected by the FEV1 alone. The BODE index is a multidimensional 10 point scale in which higher scores indicate a higher risk of death.

Table 3: The BODE index score

Variable	Points on BODE index			
	0	1	2	3
FEV1	≥65	50-64	36-49	≤35
6 Minute Walk test (meters)	≥350	250-349	150-249	≤149
MMRC Dyspnoeic score	0-1	2	3	4
Body Mass Index	≥21	≤21		

2.6.2 Six minutes walking test

The functional exercise capacity can be determine using the 6 minutes walking distance(Nilva Regina Gelamo Pelelegrino *et al.*, 2009). This test is to evaluate objectively the functional exercise capacity for COPD patient. Subjective questions can be asked to assess functional capacity for example "How many flights of stairs can you climb" or "How far can you walk", however this may overestimates or underestimates the true functional capacity of a patient. The initial walking test was developed in early 1960's (Balke, 1963) by measuring the distance walked during a defined period of time. Later on, a 12 minutes field performance test was developed to evaluate the functional disability in chronic bronchitis patient (MC Gavin CR *et al.*, 1976).

The 6 minutes walking test was developed to accommodate patient with COPD, where a 12 minutes walking test was too exhausting (Butland RJA *et al.*,

1982). It is easier to administer, better tolerated and more reflective of activities of daily living than the other test(Solway S *et al.*, 2001). This test measures the distance a patient can walk on a flat, hard ground in a period of 6 minutes. Optimal reference from healthy population samples using standardization 6mwd methods is not yet available. A mean of 630 metres was reported in healthy adults (Damien Stevens *et al.*, 1999). Other study had found the mean of 580m for men and 500m for women(Miyamoto S *et al.*, 2000). In COPD patient, the walking distance was found to be less in patient with more severe stage; a mean of 207±40m in stage 4 COPD as compared to a mean of 455±37m in stage 1 COPD(Eleni Ischaki *et al.*, 2007).

However in Malaysia the walking distance for the 6 minutes walking test was somewhat more less than other countries. The mean walking distance is about 308.9±160.6m (Ayiesah Ramli *et al.*, 2008) in a study regarding pulmonary rehabilitation in stable COPD patients at Hospital Universiti Kebangsaan Malaysia. While comparing among countries(C. Casanova *et al.*, 2011) the mean distance among different countries are 446±99m for Spain, 225±40m for Venezuela and 311±121m for United States.

There **are a lot factors** that make the reference range of the 6mwd to be underestimated or overestimated. Factors that influence the variability of the test was stated in the American Thoracic Society Statement for the 6 minutes walking test as stated below:

Table 4: 6MWD sources of variability

Reducing factor	Increasing factor
Shorter height	Taller height
Older age	Male sex

Higher body weight	High motivation
Female sex	Patient who had previously performed the test
A shorter corridor	Just taken medication for the disabling disease
Pulmonary Disease	
Cardiovascular disease	Oxygen supplement
Musculoskeletal disorder	

2.6.3 Body composition

Body composition refers to the proportion of fat and fat free mass in the body. Fat mass contains the metabolic inactive energy store while fat free mass contains the metabolic active organs especially the skeletal muscle. Reduction in this skeletal muscle will directly cause the reduction in lung function and general functional activity. People who have higher proportion of fat free mass compared to body fat are considered healthier as they have less weight related problem.

A large study involving 1218 participants (Charlotte Landbo *et al.*, 1999) demonstrated COPD mortality was significantly higher in underweight subjects as defined by a low body mass index. Further analysis of the study shows that BMI and COPD mortality was significantly higher in patient with FEV1 less than 50%. This indicates that there is a strong interaction between BMI with COPD severity and its prognosis.

But we still need to consider that body mass index (BMI) includes both the fat mass and fat free mass index. Therefore measuring BMI alone could be an incorrect way to measure the skeletal muscle mass in COPD patient. Fat free mass index

(FFMI) in the other hand would reflect better prediction of decline in the skeletal muscle mass.

Therefore the usage of fat free mass index rather than body mass index could be a more significant parameter of prognostic value in COPD patient. This is observed from COPD patient from Copenhagen City Heart Study(Jorgen Vestbo *et al.*, 2006), where even though they have normal BMI, 26.1% of them had a low fat free mass index. In term of looking into COPD severity, they observed that patients with normal BMI in stage 3 and 4 COPD according to the FEV1 value, 50% of them had a low FFMI. Comparing from stage 1 to stage 4 COPD, the FFMI also shows a decreasing trend from mean of 17.2kg/m^2 to 16.1kg/m^2 respectively.

Both of the above study used bioelectric impedance analysis to measure the body composition. The observation of reduction in body composition related to COPD prognosis was also found when other method being used. This was shown by using the measurement of mid thigh muscle area using CT scan(Karine Marquis *et al.*, 2002). They found that depletion in mid thigh muscle area was a strong predictor of mortality in COPD patient with FEV1 less than 50%.

2.6.4 C-Reactive Protein

C-reactive protein is an acute phase protein which is found in the blood in response to inflammation. It is synthesized by the liver in response to factors released by fat cells. Its physiological role is to bind to phospholipids expressed on the surface of the dead or dying cells in order to activate the complement system via the C1Q complexes. In COPD patient it is expected to be elevated as the pathogenesis of COPD includes inflammatory reaction. As it is an acute phase

reactant, CRP will be elevated in patients who have exacerbation of COPD or infection, therefore patient in this study only includes those who are stable whereby they were not having any acute exacerbation for the past three months prior to study date as the inclusion criteria.

Recent advances are looking at local and systemic biomarkers in correlation with the lung function assessment. CRP in advance COPD were raised in 48 among 102 patients and in these patients their resting energy expenditure were higher and the six minutes walking test were lower(R. Broekhuizen *et al.*, 2006).

This is supported by other studies that shows not only CRP but Interleukin 6, fibrinogen and tumour necrosis factor (Jorgen Vestbo *et al.*, 2006) are elevated in even at a mild stage of COPD and it correlates well with low fat free mass index which is an independent predictor of mortality despite the lung function test value.

Mainly the studies in CRP level were looking at the highly sensitive CRP level. When comparing the level between stable COPD patient and control, it was noted to be significantly higher (4.1 mg/l versus 1.8mg/l, respectively $p < 0.001$) (J.P. de Torres *et al.*, 2006). Other than that it was also shown that the distance of walking was significantly reduced in patient with higher CRP level.

2.7 Systemic effect of COPD

COPD as defined before is not a disease only confined to the lung but also have systemic effects that complicate the disease. This systemic illnesses leads to a pronounced deterioration in health status and diminished quality of life (R.Shoup *et al.*, 1997). Although the underlying mechanism of these systemic effects are unclear, there is growing evidence that it involves systemic inflammation, tissue hypoxia,

oxidative stress and inactivity due to skeletal muscle dysfunction(Abdullah A. eid *et al.*, 2001).

The extra pulmonary condition or the co-morbid illness that are associated with COPD are; cachexia and malnutrition (Daniel A King *et al.*, 2008); normochromic normocytic anaemia (T. Similowski *et al.*, 2006); skeletal muscle wasting and peripheral muscle dysfunction (Noritoshi Nagaya *et al.*, 2005); ischemic heart disease(José Luis Izquierdo *et al.*, 2010), osteopenia, osteoporosis and bone fractures (Lidwien Graat-Verboom *et al.*, 2009); sleep disorders, anxiety and depression (Wanning Xu *et al.*, 2008). The relationships between these pulmonary and non pulmonary co morbidities are not fully understood, and this further complicates the assessment of disease severity and prognosis.

2.7.1 Nutritional abnormalities and weight loss

The observation of nutritional abnormalities in COPD had well been established for many years. Among the earliest evidence of a relationship between body weight and COPD emerged from a study investigating metabolic imbalances in severe bronchial obstruction (Vandenbergh E *et al.*, 1967). Nutritional abnormalities includes alterations in caloric intake, basal metabolic rate, intermediate metabolism and body composition(Schols, 2000).

There are a growing interest in this parameter as it had been proven that nutritional abnormalities reflected by the body mass index and fat free mass index to be an independent predictor of mortality (Jorgen Vestbo *et al.*, 2006), functional capacity and also in expressing disease severity (Eleni Ischaki *et al.*, 2007). The study by Jorgen Vestbo in 2006, found that patient who is in the lowest 10th

percentile of the general populations for fat free mass index have a higher risk of COPD related mortality.

The study by Eleni Ischaki in 2007 showed that there were a significant relationship between FFMI and the 6 minutes walking distance ($P< 0.0001$). This significance however was poorly observed if BMI was used to see the correlation with the 6 minutes walking distance ($P>0.01$). Therefore body composition measurement is an important abnormality that would be use for screening and preventive measure in COPD patient.

Unexplained weight loss occurs in about 50% of patients with severe COPD and chronic respiratory failure, but it can also be seen in about 10-15 % of patients with mild to moderate disease (Creutzberg., 1998). Loss of skeletal muscle mass is the main cause of weight loss in COPD while loss of fat mass contributes to a lesser extent. The pathophysiological cause of weight loss is most likely attributed to a high metabolic rate that is not compensated by a corresponding increase in caloric intake(Creutzberg., 1998).

Because of the close relation between nutritional abnormalities and prognosis of COPD, further study was done to correct the nutritional aspect of patient. A meta-analysis (Ivone Martins Ferreira *et al.*, 1998) looking at 272 references, found that nutritional support by giving caloric supplement for at least 2 weeks, had no effect on improving anthropometric measures, pulmonary function, respiratory muscle strength and functional exercise capacity in stable COPD patients. Further study in 2002, contradict this meta-analysis, whereby oxandrolone (an anabolic steroid) had been shown that it can restore lean body mass in COPD patient after four months of clinical trial(Shing-Shing Yeh *et al.*, 2002).

2.7.2 Skeletal muscle dysfunction

Muscle mass dysfunction is an important feature of COPD despite the spirometry value. It has significant contribution to patient symptoms and prognosis. The presence of muscle dysfunction was first recognised in a study demonstrating that many patients with COPD have limited exercise capacity owing to skeletal muscle dysfunction(Killian., 1992).

The pathogenesis of skeletal muscle dysfunction in COPD patient is probably due to inactivity, tissue hypoxia and systemic inflammation. Cytokines such as tumour necrotic factor alpha and oxidative stress can contribute to the protein inactivation and degradation, resulting in dysfunction, atrophy and apoptosis (Alvar G. N. Agustí *et al.*, 2002). Other than that, the treatment for COPD itself by giving steroids can leads to muscle dysfunction by causing skeletal muscle myopathy(Decramer., 1994).

Although research in attributing the cause of the muscle dysfunction is still going on, we do know now that it has important consequences including exercise limitation, reduced quality of life and reduced survival. Therefore as skeletal muscle depletion is potentially treatable, compared to the pulmonary component; it has a major role as a target in treating COPD patient. The benefit of this approach is mostly by using pulmonary rehabilitation as it improves symptoms and reduced disability (Linda Nici *et al.*, 2006). This would further improve patient quality of life. The mechanism towards pulmonary rehabilitation is largely due to skeletal muscle adaptation to physical training (Maltais., 1996).

2.8 Measurement of nutrition in COPD

Nutritional measurement is based on the body composition which includes the body mass index and the fat free mass index. The term malnutrition and cachexia are often used interchangeably and define as body mass index. In assessing nutritional state for COPD patient, the simple measurement of weight adjusted for height which is the body mass index may not characterized the overall nutritional state because in COPD patient the cachexia is more related to the loss of muscle mass which correlate better to the prognosis even when they have a normal BMI (Annemie M.W.J Schols *et al.*, 2005).

Schols and co-workers distinguished three different types of impaired nutrition: semi starvation (low BMI with normal or above normal fat free mass index), muscle atrophy (low fat free mass index and normal or above normal BMI) and cachexia (low BMI and low fat free mass index). They found that patients in the semi starvation group had better survival compared to the other two groups indicating that a lower fat free mass index better predicts the mortality. They also found out that patients with GOLD stage IV had the highest prevalence of cachexia compared to others.

There is no gold standard method for the measurement of fat free mass index. The choice of measurement method for body composition includes dual energy X-ray absorptiometry (DEXA), bioelectric impedance analysis (BIA) and skin fold anthropometry (SFA). DEXA has been suggested as a suitable clinical reference method for the measurement of body composition (Van Loan and PR., 1992). However because of its cost and inconvenience to patient, the bedside evaluation by using SFA and BIA is the preferred choice.

Compared to DEXA, the sensitivity for detecting nutritional depletion was 86% for BIA and 74% for SFA, while the specificity is 88% for BIA and 98% for SFA (M.C

Steiner *et al.*, 2002). Therefore BIA causes underestimation of fat free mass index relative to DEXA, while SFA causes overestimation. BIA estimates the total body water from measurement of whole body impedance. Fat free mass is calculated from total body water using a prediction equation derived from comparison with a reference method.

In defining the level of fat free mass index there are still ongoing study to define the standard reference range. In a large study involving 5635 young healthy Caucasians adults (Schutz., 2002), the median fat free mass index were 18.9kg/m2 for males and 15.4 kg/m2 for females. To see the variation among different ethnic at different countries, further study was also done (Hull., 2011) involving Caucasian, African American, Hispanic and Asian in 2010 involving 1339 healthy subjects age from 18 to 110 years. The total body fat, total fat free mass and bone mineral density was measured using dual energy X-ray absorptiometry. In this cross sectional study they found that the mean fat free mass index according to the ethnic group for males is 20.5 for Caucasian, 21.1 for African American, 20.6 for Hispanic and 18.8 for Asian. While for female subjects it was 16.6 for Caucasian, 17.4 for African American, 17.9 for Hispanic and 15.0 for Asian. These differences were statistically significance among the ethnic groups (P< 0.05).

CHAPTER 3

STUDY OBJECTIVE

3.0 Objective of the study :

Primary objective :

To determine the association between body composition with severity of disease in Chronic Obstructive Pulmonary Disease patients.

Secondary objectives :

1. To determine the association between BMI and severity of disease in COPD patients.

2. To determine the association between FFMI and severity of disease in COPD patients.

3. To determine the association between functional activity and severity of disease in COPD patients.

4. To determine the association between C-reactive protein (CRP) level and severity of disease in COPD patients.