

# “Obesity Paradox” in Chronic Obstructive Pulmonary Disease

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**ABSTRACT:** **Background:** The “obesity paradox” is defined as an inverse association of good health, survival and obesity. Usually in healthy persons the more obese you are the more metabolic complications you have; however, thin patients with chronic obstructive pulmonary disease (COPD) have more cardiovascular complications and a higher mortality rate.

**Objectives:** To explore whether atherosclerosis and peripheral artery disease (PAD) contribute to the higher morbidity and mortality of patients with COPD.

**Methods:** This prospective study included 87 patients with chronic COPD who were treated in the pulmonary outpatient clinic; all signed a consent form before enrollment. We documented their lung function (FEV1%), body mass index (BMI) and ankle brachial index (ABI). The primary endpoints were to find an association between atherosclerosis and BMI in patients with COPD, and between atherosclerosis and severity of lung disease.

**Results:** Average ABI was  $1.01 \pm 0.20$ , BMI was  $29.33 \pm 7.48 \text{ kg/m}^2$ , and the abdominal circumference was  $107.34 \pm 18.87 \text{ cm}$ . A positive correlation was found between BMI and ABI ( $P = 0.001$ ) and between abdominal circumference and ABI ( $P = 0.000$ ). Patients with peripheral artery disease were older ( $73.6 \pm 11.5$  vs.  $68.1 \pm 11.6$  years old,  $P = 0.04$ ), were thinner (average BMI  $25.5 \pm 6.2$  vs.  $31.06 \pm 7.3$ ,  $P = 0.001$ ), and had a lower abdominal circumference ( $97.7 \pm 18.3$  vs.  $111.7 \pm 17.5 \text{ cm}$ ,  $P = 0.001$ ). No such difference was observed for years of smoking. Male PAD patients with COPD had a lower BMI ( $25.2 \pm 5.6$  vs.  $29.9 \pm 7.4$ ,  $P = 0.016$ ), and their abdominal circumference was smaller ( $96.1 \pm 18.0$  vs.  $110.2 \pm 16.5 \text{ cm}$ ,  $P = 0.004$ ). Female PAD patients with COPD had a lower BMI ( $26.3 \pm 8.2$  vs.  $33.1 \pm 7.0$ ,  $P = 0.045$ ), but their abdominal circumference was not different from females without PAD ( $102.0 \pm 19.7$  vs.  $114.0 \pm 19.4 \text{ cm}$ ,  $P = 0.162$ ). Patients with PAD had a worse lung disease (FEV1%  $34 \pm 8\%$  vs.  $45 \pm 16\%$ ,  $P = 0.01$ ). During the 1 year of follow-up five patients died: two PAD patients due to acute myocardial infarction and three non-PAD patients died from pulmonary insufficiency (two patients) and pulmonary emboli (one patient).

**Discussion:** We found that COPD patients with PAD were older and thinner and had a lower abdominal circumference and a more progressive lung disease. Extensive atherosclerosis in patients with COPD may partly explain the “obesity paradox” observed in patients with COPD.

**KEY WORDS:** obesity, peripheral artery disease, chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible [1]. Cardiovascular disease and lung cancer play an important role in the clinical outcome of these patients [2,3]. Weight loss and loss of fat-free mass have an impact on the prognosis of COPD patients [4,5]. The visceral adipose tissue has been identified to be an important source of pro-inflammatory cytokines such as interleukin 6, which induces the synthesis of C-reactive protein by hepatocytes. Accordingly, obesity as the prerequisite of the metabolic syndrome is a major determinant of systemic inflammation and close relationships are reported between body mass index, waist circumference and systemic inflammation [6,7].

Patients with peripheral artery disease are characterized by a high rate of comorbidity that includes diabetes, hypertension, lipid disorders, and cerebrovascular events [8]. Lower ankle brachial index categories ( $< 0.9$ ) were associated with increased risk of cardiovascular events and death. The risk of mortality was similar in symptomatic and asymptomatic patients with PAD, and was significantly higher than in those without PAD [9]. Poly-vascular atherosclerotic disease in PAD patients was found to be independently associated with an increased risk for all-cause mortality and cardiovascular mortality during 6 years of follow-up [10]. The underlying mechanism could be endothelial dysfunction due to the longstanding vascular inflammation, and indeed, endothelial dysfunction and to a lesser extent, endothelium-independent dilation were found to be impaired in patients with COPD, and the impairment was proportional to the severity of bronchial obstruction [11].

Our purpose was to study the association between atherosclerosis (peripheral artery disease) and severity of COPD, and to determine whether peripheral artery disease could partially explain the “obesity paradox” of patients with COPD.

PAD = peripheral artery disease

ABI = ankle brachial index

BMI = body mass index

## PATIENTS AND METHODS

This was a prospective study that evaluated the association of atherosclerosis (peripheral artery disease), severity of COPD, and BMI. The primary endpoints were to find an association between atherosclerosis and BMI in COPD patients, and whether atherosclerosis is associated with progressive lung disease. All signed a consent form before enrollment to the study.

Ankle brachial index is defined by the ratio between blood pressure that was measured in the ankles of both legs and the blood pressure that was measured in both arms – using the higher blood pressure of the arms to define and calculate ABI. An ABI < 0.90 is 95% sensitive and 99% specific for documented peripheral artery disease [12]. This cutoff point has been related to the prevalence and incidence of cardiovascular disease and all-cause mortality in several studies [13–17]. Participants who had an ABI < 0.90 in either leg were categorized as having low ABI and as having an asymptomatic PAD and atherosclerosis. Participants were defined as having a normal ABI if both ABI measurements were between  $\geq 0.90$  and  $\leq 1.40$ .

## STATISTICAL ANALYSIS

To estimate the difference between the group of patients with PAD (ABI lower than 0.9) and the group without PAD we used the chi-square test. For the continuous variables we used the independent *t*-test. We also used univariate and multivariate analyses to determine if the significant variables that differ between subjects with or without PAD (age, BMI, abdominal circumference) remain significant when pooled with each other and with risk factors for PAD such as smoking, diabetes mellitus, known cardiovascular disease, hypertension).

## RESULTS

There were 87 COPD patients – 58 men (67%) and 29 women (33%); 63 patients were active smokers (73%), 18 smoked in the past (20%), and 6 had never smoked (7%). The mean age was  $69.8 \pm 11.8$  years. Thirty-seven patients had diabetes mellitus type 2 (43%), 44 patients (51%) had a history of cardiovascular disease (coronary artery bypass graft, coronary intervention, ischemic stroke), and 63 patients (72.4%) had hypertension. Six patients (6.9%) died during the 1 year follow-up.

Overall, the average ABI was  $1.0 \pm 0.2$ , the BMI was  $29.3 \pm 7.4$  kg/m<sup>2</sup>, and the abdominal circumference was  $107.3 \pm 18.8$  cm [Table 1]. According to Spearman's correlation there was a positive correlation between BMI and ABI ( $P = 0.001$ ), as well as between AC and ABI ( $P = 0.000$ ).

ABI = ankle brachial index categories  
AC = abdominal circumference

**Table 1.** Overall data of the 87 patients with COPD

Ankle brachial index	$1.0 \pm 0.2$
Body mass index (kg/m <sup>2</sup> )	$29.3 \pm 7.4$
Abdominal circumference (cm)	$107.3 \pm 18.8$

**Table 2.** Association between peripheral artery disease and clinical parameters

	Patients with PAD	Patients without PAD	P value
No. of patients	27	60	
Age (yrs)	$68.1 \pm 11.6$	$73.6 \pm 11.5$	0.001
ABI	$0.8 \pm 0.1$	$1.1 \pm 0.1$	0.01
BMI (kg/m <sup>2</sup> )	$25.5 \pm 6.2$	$31.1 \pm 7.3$	0.001
AC (cm)	$97.7 \pm 18.3$	$111.7 \pm 17.5$	0.001
FEV1%	$34 \pm 8$	$45 \pm 16$	0.01

## PATIENTS WITH PAD

Twenty-seven patients had an ABI lower than 0.9 (31%) and are considered COPD patients with PAD. For these COPD patients the mean ABI was  $0.8 \pm 0.1$ , while COPD patients without PAD had a mean ABI of  $1.1 \pm 0.1$  (statistical difference of  $P = 0.01$ ) [Table 2]. When we checked for an association between ABI (lower or higher than 0.9) and hypertension ( $P = 0.453$ ), smoking ( $P = 0.204$ ), diabetes mellitus ( $P = 0.808$ ), cardiovascular disease ( $P = 0.120$ ), death ( $P = 0.9$ ) and gender ( $P = 0.326$ ), we found that there was no difference between the two groups of patients.

Patients with PAD were older ( $73.6 \pm 11.5$  vs.  $68.1 \pm 11.6$  years old) ( $P = 0.001$ ), thinner (average BMI  $25.5 \pm 6.2$  vs.  $31.1 \pm 7.3$ ) ( $P = 0.001$ ), and had a lower abdominal circumference ( $97.7 \pm 18.3$  vs.  $111.7 \pm 17.5$  cm) ( $P = 0.001$ ) [Table 2]. No such difference was observed for years of smoking.

Patients with PAD had a worse forced expiratory volume in the first second ( $34 \pm 8$  vs.  $45 \pm 16\%$ ,  $P = 0.01$ ) compared with COPD patients without PAD [Table 2]. Five patients died during the first year of follow-up. Two COPD patients with PAD died of acute myocardial infarction; two COPD patients without PAD died of pulmonary insufficiency, and one COPD patient without PAD died of pulmonary emboli.

For the multivariable analysis we used the binary logistic regression analysis – and age, BMI, AC, hypertension, diabetes mellitus, and smoking were included – but no single variable was found to be independently significant.

## GENDER DIFFERENCES

Overall, no gender difference was observed in this population ( $\chi^2 = 0.967$ ,  $P = 0.326$ ). Subgroup analysis found that male patients with COPD who had PAD had a lower BMI ( $25.2 \pm 5.6$  vs.  $29.9 \pm 7.4$ ,  $P = 0.016$ ), and their abdominal

**Table 3.** Gender effect on patients with peripheral artery disease

	Patients with PAD	Patients without PAD	P value
<b>Males</b>			
BMI (kg/m <sup>2</sup> )	25.2 ± 5.6	29.9 ± 7.4	0.016
AC (cm)	96.1 ± 18.0	110.2 ± 16.5	0.004
<b>Females</b>			
BMI (kg/m <sup>2</sup> )	26.3 ± 8.2	33.1 ± 7.0	0.045
AC (cm)	102.0 ± 19.7	114.0 ± 19.4	0.162

circumference was smaller ( $96.1 \pm 18.0$  vs.  $110.2 \pm 16.5$  cm,  $P = 0.004$ ) [Table 3].

Female patients with COPD who had PAD had a lower BMI ( $26.3 \pm 8.2$  vs.  $33.1 \pm 7.0$ ,  $P = 0.045$ ), but their abdominal circumference was not different from the group of females without PAD ( $102.0 \pm 19.7$  vs.  $114.0 \pm 19.4$  cm,  $P = 0.162$ ) [Table 3].

## DISCUSSION

We found a significant difference between two groups of COPD patients – patients with peripheral artery disease and those without. COPD patients with peripheral artery disease were thinner, older and had less abdominal obesity.

It is known that patients with peripheral artery disease are characterized by a high comorbidity, particularly with regard to other manifestations of atherosclerosis [8]. Asymptomatic PAD diagnosed by routine screening carries a high mortality and/or vascular event risk. The risk of mortality was similar in symptomatic and asymptomatic patients with PAD and was significantly higher than in those without PAD [9]. It is known that endothelial dependent vasodilatation (endothelial function) is impaired in patients with COPD, and that the impairment is proportional to the severity of bronchial obstruction [11]. It was found that peripheral artery disease is a major limiting factor and an underestimated etiology of exercise intolerance in patients with COPD [5]. When all-cause mortality was studied in 4393 American Indians in the Strong Study (in relation to low and high ABI), it was found that diabetes, albuminuria and hypertension were more frequent among persons with an ABI lower than 0.9 and also among patients with an ABI higher than 1.4. Interestingly, the association between high ABI and mortality was similar to that of low ABI and mortality, highlighting a U-shaped association between this non-invasive measure of peripheral artery disease and mortality risk [11].

In our study none of the COPD patients reached an ABI higher than 1.4, so we focused on the group of patients with low ABI (< 0.9) – assuming that these patients have "hidden" atherosclerosis that was not still clinically evident.

The obesity paradox phenomenon among patients with COPD is not new and has been described before [19]. It means that patients who are overweight have better survival rates than those of normal weight [19, 20]. The reasons underlying

the obesity paradox have not been elucidated. A study of 2392 patients who underwent major vascular surgery found that indeed patients who were classified as being underweight were at increased risk for mortality. In that study, patients with worse COPD were thinner and had a higher mortality rate [21].

## LIMITATIONS

The small sample size and the short follow-up time are not enough to make definite conclusions, and future research should involve larger populations of patients with COPD and for a longer time.

## CONCLUSIONS

COPD patients with atherosclerosis tended to be thinner and older and had less visceral obesity and worse lung disease. Still, there are unknown mechanisms that may link weight, atherosclerosis with survival, and these mechanisms should be sought in the future.

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