“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 ± 0.20, BMI was 29.33 ± 7.48 kg/m², and the abdominal circumference was 107.34 ± 18.87 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 ± 11.5 vs. 68.1 ± 11.6 years old, P = 0.04), were thinner (average BMI 25.5 ± 6.2 vs. 31.06 ± 7.3, P = 0.001), and had a lower abdominal circumference (97.7 ± 18.3 vs. 111.7 ± 17.5 cm, P = 0.001). No such difference was observed for years of smoking. Male PAD patients with COPD had a lower BMI (25.2 ± 5.6 vs. 29.9 ± 7.4, P = 0.016), and their abdominal circumference was smaller (96.1 ± 18.0 vs. 110.2 ± 16.5 cm, P = 0.004). Female PAD patients with COPD had a lower BMI (26.3 ± 8.2 vs. 33.1 ± 7.0, P = 0.045), but their abdominal circumference was not different from females without PAD (102.0 ± 19.7 vs. 114.0 ± 19.4 cm, P = 0.162). Patients with PAD had a worse lung disease (FEV1% 34 ± 8% vs. 45 ± 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 embol (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.
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 arterial 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 ≥ 0.90 and ≤ 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 ± 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 ± 0.2, the BMI was 29.3 ± 7.4 kg/m², and the abdominal circumference was 107.3 ± 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).

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 ± 0.1, while COPD patients without PAD had a mean ABI of 1.1 ± 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 ± 11.5 vs. 68.1 ± 11.6 years old) (P = 0.001), thinner (average BMI 25.5 ± 6.2 vs. 31.1 ± 7.3) (P = 0.001), and had a lower abdominal circumference (97.7 ± 18.3 vs. 111.7 ± 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 ± 8 vs. 45 ± 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 (χ² = 0.967, P = 0.326). Subgroup analysis found that male patients with COPD who had PAD had a lower BMI (25.2 ± 5.6 vs. 29.9 ± 7.4, P = 0.016), and their abdominal

| Table 1. Overall data of the 87 patients with COPD |
|-----------------|-----------------|-----------------|
| Ankle brachial index | 1.0 ± 0.2 |
| Body mass index (kg/m²) | 29.3 ± 7.4 |
| Abdominal circumference (cm) | 107.3 ± 18.8 |

| Table 2. Association between peripheral artery disease and clinical parameters |
|-----------------|-----------------|-----------------|
| No. of patients | Patients with PAD | Patients without PAD | P value |
| Age (yrs) | 68.1 ± 11.6 | 73.6 ± 11.5 | 0.001 |
| ABI | 0.8 ± 0.1 | 1.1 ± 0.1 | 0.01 |
| BMI (kg/m²) | 25.5 ± 6.2 | 31.1 ± 7.3 | 0.001 |
| AC (cm) | 97.7 ± 18.3 | 111.7 ± 17.5 | 0.001 |
| FEV1% | 34 ± 8 | 45 ± 16 | 0.01 |

ABI = ankle brachial index categories
AC = abdominal circumference

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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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References


Table 3. Gender effect on patients with peripheral artery disease

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

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

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### Capsule

**Peripheral education of the immune system by colonic commensal microbiota**

The instruction of the immune system to be tolerant of self, thereby preventing autoimmunity, is facilitated by the education of T cells in a specialized organ, the thymus, in which self-reactive cells are either eliminated or differentiated into tolerogenic Foxp3 regulatory T (Treg) cells. However, it is unknown whether T cells are also educated to be tolerant of foreign antigens, such as those from commensal bacteria, to prevent immunopathology such as inflammatory bowel disease. Lathrop et al. have shown that encounter with commensal microbiota results in the peripheral generation of Treg cells rather than pathogenic effectors. The authors observed that colonic Treg cells used T cell antigen receptors (TCRs) different from those used by Treg cells in other locations, implying an important role for local antigens in shaping the colonic Treg cell population. Many of the local antigens seemed to be derived from commensal bacteria, on the basis of the in vitro reactivity of common colon Treg TCRs. These TCRs did not facilitate thymic Treg cell development, implying that many colonic Treg cells arise instead by means of antigen-driven peripheral Treg cell development. Further analysis of two of these TCRs by the creation of retroviral bone marrow chimeras and a TCR transgenic line revealed that microbiota indigenous to a mouse colony was required for the generation of colonic Treg cells from otherwise naive T cells. If T cells expressing these TCRs fail to undergo Treg cell development and instead become effector cells, they have the potential to induce colitis, as evidenced by adoptive transfer studies. These results suggest that the efficient peripheral generation of antigen-specific populations of Treg cells in response to an individual’s microbiota provides important post-thymic education of the immune system to foreign antigens, thereby providing tolerance to commensal microbiota.

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Eitan Israeli

### Capsule

**The NLRC4 inflammasome receptors for bacterial flagellin and type III secretion apparatus**

Inflammasomes are large cytoplasmic complexes that sense microbial infections/danger molecules and induce caspase-1 activation-dependent cytokine production and macrophage inflammatory death. The inflammasome assembled by the NOD-like receptor (NLR) protein NLRC4 responds to bacterial flagellin and a conserved type III secretion system (TTSS) rod component. How the NLRC4 inflammasome detects the two bacterial products and the molecular mechanism of NLRC4 inflammasome activation are not understood. Zhao and collaborators have shown that NAIP5, a BIR-domain NLR protein required for *Legionella pneumophila* replication in mouse macrophages, is a universal component of the flagellin-NLRC4 pathway. NAIP5 directly and specifically interacted with flagellin, which determined the inflammasome-stimulation activities of different bacterial flagellins. NAIP5 engagement by flagellin promoted a physical NAIP5-NLRC4 association, rendering full reconstitution of a flagellin-responsive NLRC4 inflammasome in non-macrophage cells. The related NAIP2 functioned analogously to NAIP5, serving as a specific inflammasome receptor for TTSS rod proteins such as *Salmonella PrgJ* and *Burkholderia BsaK*. Genetic analysis of *Chromobacterium violaceum* infection revealed that the TTSS needle protein Cprl can stimulate NLRC4 inflammasome activation in human macrophages. Similarly, Cprl is specifically recognized by human NAIP, the sole NAIP family member in humans. The finding that NAIP proteins are inflammasome receptors for bacterial flagellin and TTSS apparatus components further predicts that the remaining NAIP family members may recognize other unidentified microbial products to activate NLRC4 inflammasome-mediated innate immunity.

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