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**Author:** Thijs, W.
**Title:** Obesity-related risk factors for impaired lung function
**Issue Date:** 2018-03-07
Chapter 2

Association of lung function measurements and visceral fat in men with the metabolic syndrome.

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ABSTRACT

Background
Several studies have reported a positive relationship between lung function impairment and the metabolic syndrome. This is most usually explained by abdominal adiposity. We hypothesized that the main determinant of the association between lung function impairment and abdominal obesity is the presence of visceral fat.

Methods
The present study is a cross-sectional analysis of 98 non-diabetic men aged between 50–70 years with the metabolic syndrome. The amount of visceral and subcutaneous adipose tissue was determined by an MRI scan. The association between visceral fat and measures of lung function (FEV₁, FVC, exhaled and NO) was assessed using linear regression.

Results
98 participants were included in this analysis. There was a linear inverse association between visceral fat and both FEV₁ and FVC. None of the other different fat-related measurements (subcutaneous fat, waist circumference and BMI) or features of the metabolic syndrome were found to be associated with these lung function measurements.

Conclusion
In non diabetic subjects with the metabolic syndrome and a lung function that is within the normal range, visceral fat is negatively correlated with FEV₁ and FVC.
INTRODUCTION

Obesity is increasing and contributes to the overall burden of disease worldwide. The prevention of this chronic disease is one of the priorities of the World Health Organization. In population studies there is an association between reduced FEV1 and cardiovascular events. In addition, it is established that obesity is associated with reduced lung volumes.

In obese patients the distribution of fat appears to be an important contributing factor to morbidity and healthy survival. Especially an increase in visceral fat is associated with diabetes and the metabolic syndrome. Various studies have found an association between type 2 diabetes mellitus and impaired lung function. Furthermore, in large population based studies a positive relationship has been found between lung function impairment and features of the metabolic syndrome, predominantly abdominal adiposity.

Since subcutaneous fat and visceral fat differ in composition and function, and both contribute to abdominal obesity, it is relevant to establish the contribution of each to the association between abdominal obesity and lung function. Recently, it has become clear that adipocytes present in visceral fat produce more pro-inflammatory mediators than adipocytes present in subcutaneous fat. In view of the major role of inflammation in lung function impairment, visceral fat could contribute to decreased lung function in central obesity by a different mechanism than the mechanical factors that have been suggested to explain the association between abdominal obesity and decreased lung volumes.

We therefore hypothesized that in subjects with abdominal obesity the main determinant of lung function impairment is the presence of visceral fat. Therefore, it is important to gain insight in the association between visceral fat and lung function impairment. Since measurement of waist circumference does not allow us to estimate the amount of visceral fat, we used Magnetic Resonance Imaging (MRI), an imaging technique that allows the direct measurement of visceral and subcutaneous fat distribution.

We selected a male study group with the metabolic syndrome according to the International Diabetes Federation but without overt diabetes to minimize confounding by diabetes or gender (fat distribution and hormonal differences). The aim of the present study was to examine the association of visceral fat as measured by MRI and lung function in non-diabetic men with the metabolic syndrome.

MATERIALS AND METHODS

We conducted a cross-sectional analysis of 98 male subjects aged between 50–70 years with the metabolic syndrome (defined according to the International Diabetes Federation criteria but without diabetes). This study was an addendum to a trial study. The inclusion criteria for the participants were: a waist circumference > 94 cm and at least two other metabolic syndrome criteria: TG ≥1.7 mmol/L, HDL-chol: < 1.03 mmol/l, blood pressure ≥130 / ≥ 85 mm Hg. Exclusion criteria were the presence of type 2 diabetes, overt cardiovascular disease, use of statins or fibrates, and a BMI >40 kg/m². For this study we used the measurements taken at the end of the trial.
This study was an addendum to a double-blind placebo controlled randomized trial, testing the hypothesis that rosiglitazone 8 mg (4 mg bd) would prevent progression of atherosclerosis more than placebo in visceral obese male subjects with systemic inflammation. This was defined by hs-CRP levels higher than 1.8 mg/L and in their control patients with the metabolic syndrome and a hs-CRP lower than 1.8 mg/L.

After the placebo-controlled trial was finished 110 patients were invited a visit the lung department and 98 patients agreed to a lung function analysis which was performed after informed consent. The addendum to the protocol was approved by the local review board (LUMC, 14-5-2007 Protocol P04.232).

**Measurements**

**Clinical assessments**

Clinical history, physical examination including blood pressure measurements, and anthropometry, and laboratory assessments were performed at the clinical research unit at the end of the trial. Blood pressure was recorded in supine position after 15 minutes rest. Blood pressure was defined as the mean value of 3 measurements taken with intervals of at least 2 minutes. Body weight and body length were measured. Waist circumference was measured in a horizontal plane between the lowest costal margin and the upper pelvic rim. Hip circumference is measured at the level of the major trochanters. Circumferences were recorded in centimetres.

Laboratory measurements included fasting glucose, triglyceride, total- and HDL-cholesterol and hs-CRP levels, measured at the department of clinical chemistry.

**MRI measurements**

Subjects were positioned in the magnet in a supine position. The body coil was used for obtaining the images. A sagittal single shot gradient echo sequence survey scan was used for the imaging of the vertebral column in the lumbar region. Subsequently, a second single shot gradient echo sequence in the transversal plane was used for obtaining three contiguous slices of 10 mm without angulations with the following parameters: echo time 3.7 ms (TE), repetition time 7.5 ms (TR), pulse angle 45°. Two signal averages were performed. The slices were centred at the intervertebral disk level between the fourth and fifth lumbar vertebra. The images were obtained with three breath holds of 6 s. The field of view was 500 mm. A voxel size of 1 mm × 1.3 mm × 10 mm was obtained. The measurements were taken at the end of the trial and images were assessed using the MASS software package allowing a semi-automated detection of subcutaneous and visceral adipose tissue area.

**Flow volume curve and reversibility**

Flow-volume curves were recorded, after the placebo controlled Rosiglitazone trial ended, by pneumotachograph to obtain the vital capacity (VC), expiratory rest volume (ERV), forced expiratory volume in 1 second (FEV₁) and the forced vital capacity (FVC). To test whether the obstruction is reversible to bronchodilators, FEV₁ and FVC (absolute values and percentage of predicted values) were measured before and 15 minutes after four single inhalations of 100 mcg albuterol administered through a large volume spacer.
Exhaled NO measurements were measured with a chemiluminescence analyzer (Aerocrine AB, Niox, Solna, Sweden) according to a standardized procedure. After inhaling NO-free air, the subjects performed a slow expiratory vital capacity maneuver with a constant expiratory flow of 50ml/s against a resistance of 10 cm H$_2$O using online visual monitoring. Exhaled NO concentrations were determined at a 3 second-plateau and expressed as parts per billion (ppb). If the chemiluminescence analyzer was not available exhaled nitric oxide was measured using a portable analyzer; the NIOX MINO (Aerocrine AB, Solna, Sweden) following the manufacturer’s instructions. Subjects performed a 10 s slow steady exhalation, which was assisted by visual and audio biofeedback systems located on the device. The two methods used give comparable results. Three successive recordings at 1-minute intervals were made and the mean exhaled NO was used. Exhaled NO was considered to be elevated above 25 ppb.

Statistical analyses
The data are presented as median and 25th and 75th percentile, or percentage. Triglycerides, exhaled nitric oxide and hs-CRP values were log transformed for statistical analysis due to their non-normal distribution. Linear regression was used to assess the association between lung function and the different features of fat and metabolic syndrome. Adjustments were made for age, pack years, hs-CRP, rosiglitazone, glucose, cholesterol and blood pressure. A restriction analysis that excluded participants with decreased lung function was performed. Results were considered significant at p<0.05 and the data were analyzed using the Statistical Package of Social Science (SPSS) version 20.0.
RESULTS

All analyses were conducted on 98 participants. We included 81 men with metabolic syndrome and CRP levels higher than 1.8 mg/L (of which 40 participants used Rosiglitazone) and 17 control patients with the metabolic syndrome and hs-CRP levels lower than 1.8 mg/L. The characteristics of the study population after the trial are presented in Table 2.1. Most patients were found to have no significant airway obstruction and no or little airway inflammation (as assessed by exhaled nitric oxide measurement), data presented in Table 2.2.

Table 2.1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All participants</th>
<th>Participants in Rosiglitazone arm trial</th>
<th>Participants in Placebo arm trial</th>
<th>Participants in control arm with lower Hs-CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 (57-64)</td>
<td>62 (57-64)</td>
<td>62 (59-65)</td>
<td>61 (57-64)</td>
</tr>
<tr>
<td>PY (years)</td>
<td>15 (0.3-29)</td>
<td>16 (2-30)</td>
<td>15 (1.5-27)</td>
<td>7 (0.2-1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.9 (26.4-30.7)</td>
<td>28.1 (26.5-30.7)</td>
<td>28.1 (26.1-30.8)</td>
<td>27.8 (26.3-30.8)</td>
</tr>
<tr>
<td>BP Systolic (mmHg)</td>
<td>139 (129-152)</td>
<td>137 (127-144)</td>
<td>134 (125-149)</td>
<td>149 (137-164)</td>
</tr>
<tr>
<td>BP Diastolic (mmHg)</td>
<td>82 (74-88)</td>
<td>79 (63-68)</td>
<td>80 (74-84)</td>
<td>92 (84-97)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>102 (96-109)</td>
<td>100 (94-112)</td>
<td>100 (96-108)</td>
<td>104 (101-109)</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.0 (4.6-5.3)</td>
<td>4.9 (4.4-5.3)</td>
<td>4.9 (4.6-5.4)</td>
<td>5.2 (4.7-5.4)</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.7 (0.8-2.1)</td>
<td>1.2 (0.8-1.8)</td>
<td>1.2 (0.8-2.1)</td>
<td>2.6 (1.5-3.5)</td>
</tr>
<tr>
<td>HDL-Cholesterol (mmol/l)</td>
<td>1.4 (1.1-1.6)</td>
<td>1.5 (1.2-1.7)</td>
<td>1.3 (1.1-1.5)</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Hs-CRP (mg/l)</td>
<td>1.4 (0.7-2.6)</td>
<td>1 (0.6-2.5)</td>
<td>2.2 (1.4-3.1)</td>
<td>0.9 (0.6-1.3)</td>
</tr>
<tr>
<td>Waist visceral fat (cm²)</td>
<td>343 (288-486)</td>
<td>338 (272-575)</td>
<td>328 (287-436)</td>
<td>386 (300-502)</td>
</tr>
<tr>
<td>Waist subcutaneous fat (cm²)</td>
<td>700 (610-885)</td>
<td>736 (623-911)</td>
<td>739 (596-914)</td>
<td>649 (520-807)</td>
</tr>
</tbody>
</table>

Values are median (25th, 75th percentiles). PY is pack years, BMI is body mass index and BP is blood pressure.

Table 2.2 Pulmonary function

<table>
<thead>
<tr>
<th></th>
<th>All participants</th>
<th>Participants in Rosiglitazone arm trial</th>
<th>Participants in Placebo arm trial</th>
<th>Participants in control arm with lower Hs-CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ post pred (%)</td>
<td>105 (96-118)</td>
<td>104 (92-114)</td>
<td>106 (97-127)</td>
<td>109 (91-124)</td>
</tr>
<tr>
<td>FVC post pred (%)</td>
<td>108 (95-118)</td>
<td>106 (94-113)</td>
<td>111 (98-121)</td>
<td>109 (93-117)</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>79 (73-84)</td>
<td>78 (73-83)</td>
<td>82 (73-85)</td>
<td>79 (73-83)</td>
</tr>
<tr>
<td>VC (%)</td>
<td>109 (96-118)</td>
<td>108 (96-115)</td>
<td>109 (100-121)</td>
<td>110 (97-123)</td>
</tr>
<tr>
<td>ERV (%)</td>
<td>88 (61-124)</td>
<td>85 (56-115)</td>
<td>97 (68-128)</td>
<td>94 (62-129)</td>
</tr>
<tr>
<td>NO (ppb)</td>
<td>16 (11-24)</td>
<td>15 (9-28)</td>
<td>17 (11-22)</td>
<td>15 (12-27)</td>
</tr>
</tbody>
</table>

Values are means, median (25th, 75th percentiles). FEV₁ is forced expiratory volume in 1 s, FVC is forced vital capacity post predicted, VC is vital capacity post predicted, ERV is expiratory reserve volume and NO is exhaled Nitric oxide.
In the linear regression no association was found between any of the features of the metabolic syndrome and FEV₁, FVC and exhaled nitric oxide. Rosiglitazone use was also not correlated with any of these lung function measurements. However, whereas BMI and features of the metabolic syndrome, including waist circumference, were not associated with FEV₁ and FVC there was a significant association between waist visceral fat, and FEV₁ (beta -0.023; 95% CI -0.041, -0.006); this means that an additional 200 cm² of visceral fat (the IQR within this study) is associated with a 4.6% decrease in FEV₁ predicted. There was also an association with FVC (beta -0.024; 95% CI -0.040, -0.008), but not between subcutaneous fat and FEV₁ and FVC (Figure 2.1 and 2.2).

After adjustment for waist subcutaneous fat, age, height, waist circumference, pack years, rosiglitazone use, hs-CRP, glucose, cholesterol, triglyceride and blood pressure the association between visceral fat and FEV₁ (beta -0.055; 95% CI -0.085, -0.025) and FVC (beta -0.040; 95% CI -0.067, -0.014) remained.

There was also a significant association between waist visceral fat and ERV (beta -0.108; 95% CI -0.157, -0.058) and waist subcutaneous fat and ERV (beta -0.070; 95% CI -0.108, -0.032). After adjustment for age, pack years, rosiglitazone use, hs-CRP, glucose, cholesterol and blood pressure the association between visceral fat and ERV (beta -0.116; 95% CI -0.181, -0.052) and subcutaneous fat and ERV (beta -0.059; 95% CI -0.105, -0.014) remained.

To assess whether the association between visceral fat and FEV₁ and FVC is explained by ERV we explored the association. ERV was associated with FEV₁ (beta 1.1; 95% CI 0.6, 1.6) and FVC (beta 1.4; 95% CI 0.8, 1.9). Eight participants had a FEV₁ below 80% excluding these participants did not alter these results.

**Figure 2.1:** The correlation between visceral fat (cm²), subcutaneous fat (cm²), waist circumference (cm), BMI (kg/m²) and FEV₁ (%).

The Pearson correlation: visceral fat (cm²) and FEV₁ (%) r = -0.180 p = 0.038, subcutaneous fat (cm²) and FEV₁ (%) r = 0.009 p = 0.463, waist circumference (cm) and FEV₁ (%) r = 0.037 p = 0.357, BMI (kg/m²) and FEV₁ (%) r = -0.027 p = 0.401.
Waist subcutaneous fat had a stronger association (beta 19.6; 95% CI 16.1, 23.2) with waist circumference than visceral fat (beta 13.6; 95% CI 11.1, 16.2). Whereas hs-CRP showed a weak negative association with FEV1, after correction for waist visceral fat this was no longer significant. No association was found between log hs-CRP and FVC and exhaled nitric oxide.

DISCUSSION
The results of this study show that in men at an early stage of the metabolic syndrome (without overt diabetes) and a normal lung function there is a significant linear inverse relation between visceral, but not subcutaneous fat, and FEV1 and FVC. In contrast, there was no correlation between subcutaneous fat (or other fat measurements) and FEV1 and FVC. Exhaled nitric oxide was not correlated with the metabolic syndrome and the fat measurements. This indicates that in non diabetic subjects with the metabolic syndrome, visceral fat appears to be a more sensitive parameter to assess the association between obesity and lung function impairment than subcutaneous fat or waist circumference.

Our results are in line with those published by Leone et al and by Lam et al, who reported a positive relationship between lung function impairment and metabolic syndrome, which was explained mainly by abdominal obesity and was independent of the body mass index.
We did not find such an association with abdominal obesity, which might be because our study focused on subjects with a high waist circumference and the other studies were population-based studies. We did find a significant association with visceral fat, which may be explained by the fact that waist circumference is predominantly an index of abdominal subcutaneous fat, and not of visceral fat. Indeed, in our study the relation between subcutaneous fat and waist circumference was stronger than the association between visceral fat and waist circumference.

How do we interpret the present findings? Obesity may limit lung expansion due to the mechanical pressure of the abdomen and cause restriction. Although we cannot formally exclude that the association between visceral fat and lung function impairment is also explained by mechanical factors, it is important to note that in this small selected group no relation with waist circumference or BMI was found. Therefore, visceral fat appears to be a more selective marker in the relationship of abdominal obesity and lung function impairment.

This higher selectivity may be explained by the observation that adipocytes present in visceral fat are a more important source of pro-inflammatory mediators than adipocytes present in subcutaneous fat. In some studies, visceral fat was found to be correlated with levels of CRP, which is mainly liver derived. Although this indicates that increased inflammation resulting from an increase in visceral fat may contribute to lung function impairment, it needs to be noted that we did not find a correlation between markers of inflammation (exhaled NO and hs-CRP) and visceral fat. However, we did not measure other (adipocyte-derived) pro-inflammatory mediators such as leptin that may be related to visceral fat.

Our study was subject to some limitations. Firstly, the majority of subjects were recruited after finishing a randomized controlled trial with Rosiglitazone, and therefore half of the subjects received Rosiglitazone 8 mg during a year previous to our lung function measurements. However, it is unlikely that this treatment affected the outcome of the present study, since similar results were found after statistical adjustment for use of Rosiglitazone. Secondly, whereas the patients that participated in the Rosaglitazone trial all had a Hs-CRP > 1.8 mg/L, an additional group was studied with metabolic syndrome but a Hs-CRP < 1.8 mg/L. Furthermore, we used the measurements taken after the trial which were closer to each other. This resulted in a study group with heterogeneous CRP levels. This is unlikely to have influenced our results because these were identical after adjustment for Hs-CRP. Finally, due to the cross-sectional design of our study no follow-up lung-function data or parameters of the metabolic syndrome were available.

The observed association between visceral fat and lung function measurement impairment was found despite the fact that the study subjects all had increased waist circumference (and therefore likely increased visceral fat) and a lung function that was within a normal range. Further studies are needed to clarify the link between visceral fat, inflammation and lung function impairment and should include study groups with a larger range of visceral fat and lung function. We hypothesize that in such groups the observed association may even be stronger. In addition, measurements of a range of adipocyte-derived pro-inflammatory mediators such as leptin would contribute to our understanding.
In conclusion, we have shown an association between lung function impairment and visceral fat in non diabetic men with the metabolic syndrome and a normal range of lung function. The observation that such an association with lung function impairment was not found with other parameters of obesity indicates that visceral fat is a more sensitive parameter to assess the association between abdominal obesity (a component of the metabolic syndrome) and lung function impairment.
2. Association of lung function measurements and visceral fat in men with the metabolic syndrome.

REFERENCE LIST


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