

# Correlation between increased interleukin-6 with insulin resistance in non-diabetic chronic obstructive pulmonary disease patients

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## ABSTRACT

Chronic obstructive pulmonary disease patients (COPD) have been linked to systemic inflammation. The presence of a systemic inflammatory response is characterized by increased activation and mobilization of inflammatory cells into the circulation. Systemic inflammation is characterized by an increase in proinflammatory cytokines including IL-6, TNF- $\alpha$ , and CRP. Increased IL-6 will cause insulin resistance and IL-6 is considered as a good predictive marker for insulin resistance. This research is an analytic cross sectional study. Affordable population is all COPD patients in the pulmonary polyclinic at the Sanglah Hospital and Network Hospitals in the period of May to October 2019 who have met the criteria as a research sample. The association between increased IL-6 and insulin resistance was tested using spearman analysis. The effect of confounding variables such as age, sex, nutritional status, smoking and steroid use, on the relationship of serum IL-6 and HOMA-IR index values were tested using partial correlation analysis. This study included 47 subjects, 42 male (89.3%) and 5 female (10.7%). Results of study, showed that there was no a significant correlation between IL-6 and HOMA-IR ( $r = -0.24$ ;  $p = 0.09$ ). Also, there is no influence of confounding variables on the relationship IL-6 and HOMA-IR. Age variables ( $r = -0.18$ ;  $p = 0.21$ ), gender ( $r = -0.18$ ;  $p = 0.21$ ), nutritional status ( $r = -0.14$ ;  $p = 0.32$ ), smoking ( $r = -0.17$ ;  $p = 0.26$ ), and steroid therapy ( $r = -0.18$ ;  $p = 0.22$ ). On the other hand, obesity status was strongly related to HOMA-IR ( $r = 0.64$ ;  $p = 0.001$ ). This study proves that there was no significant correlation found between the increase in serum IL-6 and the HOMA-IR index value. Nevertheless, obesity status is a factor that is very strongly associated with the HOMA-IR index value.

**Keywords:** COPD, IL-6, HOMA-IR, insulin resistance.

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## INTRODUCTION

COPD is one of the leading causes of morbidity and mortality worldwide. Exacerbations and comorbidities contribute to the severity of the disease in COPD patients. In developing countries, the prevalence of COPD has increased due to the increasing of smoking rate.

COPD has been linked to systemic inflammation that is characterized by increased activation and mobilization of

inflammatory cells into the circulation. Systemic inflammation is characterized by an increase in pro inflammatory cytokines including TNF, IL-6, IL-8, IL-18 and C-Reactive Protein (CRP) (Naik et al., 2014). IL-6 is a pro-inflammatory cytokine that is important in systemic inflammation in patients with COPD. Agusti et al. (2012), in a study stated that there is a relationship between increased IL-6 and poor clinical in patients with COPD.

One important metabolic linkage of chronic inflammatory activity is insulin resistance (Kiran et al., 2015). Insulin resistance is a condition where there is a failure of the target organ to respond to the hormone insulin so that a greater amount of insulin is needed to obtain a normal response from the target cell. From several studies, it is said that IL-6 is a good predictive marker for insulin resistance. In a study by Kiran et al. (2015), the prevalence of insulin resistance was found to be higher in patients with COPD compared to controls, which was 60% compared to 14.28%. Insulin resistance is a risk factor for the development of atherosclerotic heart disease and type 2 diabetes mellitus in the future in patients with COPD. Thus, insulin resistance causes a higher risk for metabolic and cardiovascular disease in patients with COPD despite being clinically stable.

There are several ways to measure insulin resistance, including oral glucose tolerance test (OGTT), fasting insulin levels, HOMA-IR index (Homeostasis Model Assessment-Insulin Resistance), fasting glucose / insulin ratio (Fasting Glucose / Insulin Ratio = FIGR), and the QUICKI (Quantitative Insulin Sensitivity Check Index). Measurement of fasting insulin levels, FIGR, QUICKI and HOMA-IR is more suitable for epidemiological research because it only requires one examination (Lee et al., 2006). The HOMA-IR index value used to determine insulin resistance status is 2.5 (Merja et al., 2015).

One of the key strategies for managing insulin resistance in COPD patients is to overcome the inflammatory response. Besides overcoming inflammation, insulin resistance therapy also consists of pharmacological and non-pharmacological therapies. Drugs that can reduce insulin resistance include metformin, thiazolidinediones (TZDs) and acarbose. Other therapies that can be used include interleukin-1 receptor antagonists, salicylates, anti-TNF- $\alpha$ , and anti-chemokine (Rehman and Akash, 2016). Non-pharmacological therapies include diet management, maintenance of muscle mass, physical exercise, and adequate sleep (Govers et al., 2015). This study is done to determine the relationship of increased IL-6 with insulin resistance in COPD patients without diabetes mellitus.

## MATERIALS AND METHODS

This study used a cross sectional analytic design. This research was conducted at the pulmonary polyclinic at Sanglah Central General Hospital and Network Hospital, starting from May to October 2019. The study sample was all COPD patients without diabetes mellitus in the pulmonary polyclinic at Sanglah Hospital and Network Hospital and met the criteria inclusion. The total used sample was 47 peoples who were determined by consecutive sampling. Serum IL-6 and HOMA-IR were examined at Prodia Laboratory Denpasar, Bali. Human Interleukin 6 Immunoassay (Quantikine) reagen is used for IL-6 examination. HOMA-IR was measured by fasting blood sugar x fasting insulin divided by 405. Fasting blood sugar use glucose HK (GLUC2) reagent and fasting insulin use immulite 2000 reagent. Data about obesity status, smoking and steroid therapy are collected using questionnaires.

Data was analysed using the Statistical Package for Social Science (SPSS) version 26. Analyses included spearman correlation dan partial correlation. A  $p < 0.05$  was considered significant.

## RESULTS

The research subjects consisted of 42 men (89.3%) and 5 women (10.7%) as shown in Table 1. Research subjects had an average age of  $65.36 \pm 8.29$  years with an age range between 46-81 years. A total of 22 subjects (46.8%) had normal nutritional status and 10 subjects (21.2%) had pre-obese nutritional status. A total of 35 subjects exposed to firewood (74.5%) were included as risk factors for COPD. It was found from results that the median serum IL-6 level was 5.5 pg/ml with a median HOMA-IR value of 1.0 as shown in Table 2.

In this study, bivariate analysis was performed on serum IL-6 and HOMA-IR variables. To determine the normality of data distribution, the Kolmogorov-Smirnov (KS) test was performed. KS test results show that the HOMA-IR is not normally distributed ( $p < 0.05$ ). The correlation test results found no correlation between the two variables with a significance value of 0.09 and a correlation coefficient of -0.24 as shown in Table 3.

In this study, a partial correlation analysis was performed to determine the effect of confounding variables such as age, sex, nutritional status, smoking and steroid use on the correlation of serum IL-6 and HOMA-IR index values. Table 4 shows the results of the partial correlation analysis.

Based on Table 4, it can be seen that there is no influence of confounding variables on the correlation between IL-6 and HOMA-IR.

In this study, a correlation analysis of factors related to HOMA-IR was conducted to assess the effect of these factors on the value of the HOMA-IR index (Table 5). It shows that the obesity status correlates very strongly with HOMA-IR with a significance value of 0.001 and a correlation coefficient of 0.64.

## DISCUSSION

There are 47 samples used, most were male. Historically, COPD is more common in men than in women; it is related to smoking and environment exposure (Sharon et al., 2015). The mean of age was 65.36 years. An epidemiological study in COPD patients in China shows that the prevalence of COPD increases with age. The risk of COPD in populations 70 years of age or older increases 9.94 times compared to the 40-year population (Yumin and Rongchang, 2013). This study obtained a median BMI was  $21.5 \text{ kg/m}^2$  with nutritional status classified as underweight 19.1%, normal 46.8%, overweight 12.7% and pre-obese 21.2%. Singh and Saxena (2010) reported that obesity is a risk factor for insulin resistance. In a study conducted by Bolton et al

**Table 1.** Sociodemographic characteristics of research subjects.

| Characteristics                     | n = 47           |
|-------------------------------------|------------------|
| Age (year), mean $\pm$ SD           | 65.36 $\pm$ 8.29 |
| Gender, n (%)                       |                  |
| Male                                | 42 (89.3)        |
| Female                              | 5 (10.7)         |
| Body Mass Index (BMI), median (IQR) | 21.5             |
| Nutritional status, n (%)           |                  |
| Underweight (<18.5)                 | 9 (19.1)         |
| Normal (18.5-22.9)                  | 22 (46.8)        |
| Overweight (23-24.9)                | 6 (12.7)         |
| Pre-Obese (25-29.9)                 | 10 (21.2)        |
| Occupation, n (%)                   |                  |
| Farmer                              | 12 (25.5)        |
| Construction workers                | 10 (21.3)        |
| Other                               | 25 (53.2)        |

Other = driver, housewife, private employee, government employee, sculptor.

**Table 2.** Clinical characteristics of research subjects.

| Characteristics                   | n = 47     |
|-----------------------------------|------------|
| Former smoker (sticks), n (%)     |            |
| Mild (1-10)                       | 7 (14.9)   |
| Moderate (11-24)                  | 26 (55.3)  |
| Severe (>24)                      | 2 (4.3)    |
| Do not smoke                      | 12 (25.5)  |
| Degree of obstruction, n (%)      |            |
| Mild                              | 8 (17.0)   |
| Moderate                          | 20 (42.6)  |
| Severe                            | 15 (31.9)  |
| Very severe                       | 4 (8.5)    |
| Outdoor pollution, n (%)          |            |
| Firewood                          | 35 (74.5)  |
| Passive smoker                    | 4 (8.5)    |
| Other                             | 8 (17.0)   |
| Steroid inhalation therapy, n (%) |            |
| < 1 year                          | 34 (72.3)  |
| 1 year                            | 4 (8.5)    |
| 2 year                            | 3 (6.4)    |
| > 2 year                          | 2 (4.3)    |
| Do not use                        | 4 (8.5)    |
| IL-6 (pg/ml), median (IQR)        | 5.5 (7.3)  |
| HOMA-IR, median (IQR)             | 1.0 (1.80) |

**Table 3.** Results of analysis of the correlation of IL-6 with HOMA-IR.

| Variable | HOMA-IR                     |         |
|----------|-----------------------------|---------|
|          | Correlation coefficient (r) | p-value |
| IL-6     | -0.24                       | 0.09    |

(2007), from 56 subjects with COPD patients, the mean BMI was 25.7 kg/m<sup>2</sup>. In this study, around 25.5% worked as farmers and 21.3% worked as construction workers who routinely performed activities without using personal protective equipment. Around 74.5% of the samples were exposed to firewood smoke. Exposure to firewood (outdoor pollution) is one of the risk factors for COPD.

COPD has been linked to systemic inflammation with its various comorbidities. The systemic inflammatory response is characterized by an increase in proinflammatory cytokines including IL-6. Research conducted by Bolton et al (2007), mean serum IL-6 levels in stable COPD patients at 2.75 pg/ml while in healthy subjects 1.43 pg/ml. In this study there was also an increase in the mean CRP values (2034.7 ng/ml) and TNF- $\alpha$  (2.25 pg/ml). One of the metabolic problems that occur due to chronic inflammation is insulin resistance. Insulin resistance can be measured by assessing the HOMA-IR index. The HOMA-IR index value of 2.5 has a sensitivity of more than 70% and a specificity of more than 60% for insulin resistance (Merja et al., 2015). In this study, the median serum IL-6 level was 5.5 pg/ml and the HOMA-IR index was 1.0. There was an increase in serum IL-6 levels while the HOMA-IR index value was lower than the cut off value set at 2.5. The median value of serum IL-6 levels in this study was almost close to the results of a study conducted by Krommidas et al. (2009) which was 6.9 pg/ml on stable COPD conditions.

IL-6 is a pleiotropic cytokine that has different effects on different cells. IL-6 can be produced by many types of cells including T cells, B cells, polymorphonuclear cells, endothelial cells, skeletal muscle cells and adipose tissue. Increased IL-6 in circulation can be caused by several factors including muscle contraction and adipose tissue dysfunction in obesity (Scheller et al., 2011).

Spearman correlation analysis on IL-6 and HOMA-IR variables showed no significant. The results of the analysis of confounding variables including age, sex, nutritional status, smoking and steroid therapy, no effect was found on IL-6 and HOMA-IR. In this study also conducted an analysis of factors related to HOMA-IR which includes obesity status, smoking and steroid therapy. Obesity status correlated very strongly with HOMA-IR with a significance value of 0.001 and a correlation coefficient of 0.64. This is in accordance with research conducted by Bolton et al. (2007), from 56 subjects with COPD patients, there was a strong correlation between obesity status and HOMA-IR with a significance value <0.001 and a correlation coefficient of

**Table 4.** Results of IL-6 and HOMA-IR partial correlation analysis with confounding variables.

| Confounding variables | Correlation coefficient (r) | p-value |
|-----------------------|-----------------------------|---------|
| Age                   | -0.18                       | 0.21    |
| Gender                | -0.18                       | 0.21    |
| Nutritional status    | -0.14                       | 0.32    |
| Smoking               | -0.17                       | 0.26    |
| Steroid use           | -0.18                       | 0.22    |

**Table 5.** Results of factors analysis related to HOMA-IR.

| Factors         | HOMA-IR                     |         |
|-----------------|-----------------------------|---------|
|                 | Correlation coefficient (r) | p-value |
| Obesity status  | 0.64                        | 0.001*  |
| Steroid therapy | -0.16                       | 0.27    |
| Smoke           | 0.23                        | 0.11    |

\*Significant.

0.50.

In the current study, an increase in serum IL-6 levels did not always result in an increase in HOMA-IR values. The subjects used in this study were stable COPD patients. Serum IL-6 levels in stable COPD patients are lower when compared with COPD that has exacerbations (Barnes and Celli, 2009). This is consistent with research conducted by Hurst et al (2006) that during exacerbations there is an increase in serum IL-6 by 47% compared to when conditions are stable. In addition, almost all subjects of this study had received inhaled steroid therapy so that serum IL-6 levels did not reflect the actual inflammatory state. This resulted in serum IL-6 levels in the subjects not yet causing insulin resistance. But in this study, there is factor that causes insulin resistance, namely obesity status. Obesity status correlates very strongly with HOMA-IR index values. So that COPD patients with obese nutritional status can lead to insulin resistance.

## CONCLUSION

There is no significant correlation was found between the increase in serum IL-6 and the HOMA-IR index value. Nevertheless, obesity status is a factor that is proven to be very strongly associated with the HOMA-IR index value.

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