Correlation between Coenzyme Q10 Level Long-Term Steroid Inhalation in Patients with Bronchial Asthma

Deny Perdana Putra[1], Arief Bakhtiar[2], Muhammad Amin[2]

[1]Department of Pulmonology, Faculty of Medicine, Universitas Airlangga, Surabaya 60285, Indonesia,
[2]Department of Pulmonology, Faculty of Medicine Universitas Airlangga, Dr. Soetomo Teaching Hospital, Surabaya 60285, Indonesia

Abstract

Background: The main therapy of asthma is inhaled steroids and is often used for long periods of time. Coenzyme Q10 is a potent antioxidant produced largely by mitochondria. Treatment of long-term oral steroids can cause mitochondrial damage which lowers the level of coenzyme Q10.

Objective: To analyze the relationship between coenzyme Q10 levels and long-term steroid inhalation in asthma patients.

Method: The study was conducted at Asthma Unit/COPD of Dr. Soetomo General Hospital Surabaya Indoensia, Pulmonology Unit of. Dr. M. Soewandhie General Hospital Surabaya Indonesia, and Pulmonology Unit of Universitas Airlangga Hospital Surabaya Indonesia. We measured coenzyme Q10 levels and the duration of inhaled steroid use in the subjects. The data were processed using computer statistics program. The correlation between coenzyme Q10 level and long-term steroid inhalation was analyzed using Pearson correlation test ($p < 0.05$).

Result: Coenzyme Q10 levels in all samples were normal and increasing. There was no low coenzyme Q10 level found in all samples. The result of Pearson's correlation test between coenzyme Q10 level with long-term steroid inhalation showed $r = -0.037$; $p = 0.848$ ($p > 0.05$).

Conclusion: There was no correlation between coenzyme Q10 level and long-term steroid inhalation found in this study.

Keywords: *Coenzyme Q10, Asthma, long-term steroid inhalation*

Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation [1]. To this day, asthma is still a problem in both developing and developed countries. Symptoms of asthma vary from the lightest, which do not disrupt activities, to the more permanent one that disrupt activities, including daily activities [2,3].

Corresponding author:
Arief Bakhtiar
Department of Pulmonology, Faculty of Medicine
Universitas Airlangga, Dr. Soetomo Teaching Hospital,
Surabaya 60285, Indonesia
Email: ariefbakhtiar001@yahoo.com

Approximately 300 million people around the world suffer from asthma. The average prevalence of asthma incidence in the world ranges from 1% to 18%. In Indonesia, according to basic health research data in 2007, the asthma prevalence was 4%. Basic health research data in 2013 showed that the prevalence of asthma at all ages was 4.5%. The highest prevalence was in Central Sulawesi (6.9%), followed by East Nusa Tenggara (7.3%) and Yogyakarta (6.9%). Asthma is included in the top ten causes of morbidity and mortality in Indonesia. The household health survey (SKRT) in 1986 showed that asthma is ranked fifth out of 10 causes of morbidity along with chronic bronchitis and emphysema [4].

Chronic inflammation in asthma leads to an imbalance of the pulmonary antioxidant system. This increases free radicals that will impact the hypersponsif and obstruction of the airway resulting in complaints triggering the formation of oxidant enzymes Nicotinamide adenine dinucleotide phospate (NADPH) oxidase, mieloperoksidase, eosinophil peroxidase and NO synthase[5]. ROS is released into the airway by the inflammatory cells that occur in the lungs [6,7].

Blood antioxidant levels, especially coenzyme Q10 are low in asthma patients compared to healthy people. This is due to the occurrence of oxygen-free radical processes derived from the lipid membranes in cells that accumulate in the bronchial mucosa. Coenzyme Q10 is a potential antioxidant that protects the body from free radicals and helps the supply of vitamin E (antioxidant and major cell membranes). Coenzyme Q10 plus tocopherol and vitamin C can reduce the need for steroid dose of bronchial asthma patients. This suggests a decrease in the inflammatory process of antioxidant supplementation. International guidelines recommend assessment of an APE or spirometry series to confirm the diagnosis of asthma, but spirometry can not provide clear information about the state or degree of airway inflammation at that time [8].

Low blood coenzyme levels in bronchial asthma and in individuals receiving long-term oral steroid therapy [6,9,10]. Oral administration of prednisolone steroid for a long periods can cause mitochondrial cell damage. Mitochondrial damage can cause an oxidant-antioxidant imbalance. Coenzyme Q10 is a powerful antioxidant in mitochondria. Mitochondrial damage will cause deficiency of coenzyme Q10 causing free radicals and aggravate inflammation [6]. Long-term administration of prednisolone oral steroids can affect mitochondrial damage [9].

The main therapy of bronchial asthma is anti-inflammatory inhaled steroid. Many people with asthma require inhaled steroid therapy in a long time to be able to control their asthma. Inhaled steroids can affect the systemic if used continuously and in a long time, causing it to affect blood coenzyme Q10 levels. To date, there has been no study examining the correlation between coenzyme Q10 levels and long-term inhaled steroids in patients with bronchial asthma. Therefore, we are interested in conducting this study to examine the correlation between coenzyme Q10 and long-term inhaled steroids in people with bronchial asthma.

Method

The subject of this study consisted of patients with bronchial asthma that met the inclusion and exclusion criteria. The inclusion criteria included patients with stable asthma treated in pulmonology and asthma unit/COPD on a regular basis, aged of above 21 and treated with inhaled steroid in a long period of time. The exclusion criteria excluded patients with asthma exacerbations attack, patients with other respiratory disorders (pneumonia, COPD, or other chronic respiratory diseases), patients with systemic disorders (heart disorders, parkinsonism, malignancy, diabetes, hypertension, HIV, dyslipidemia and renal failure), patients consuming certain medication (class of statin, beta blocker, diuretic, glucophage, haloperidol), and patients consuming ubiquinone preparations on a regular basis. Subjects that were willing to be enrolled in this study were asked to fill the informed consent .

This is a cross-sectional observational analytic study conducted at Asthma Unit/COPD of Dr. Soetomo Teaching Hospital Surabaya Indonesia, pulmonology unit of Dr. M. Soewandhie General Hopsital Surabaya Indonesia and Universitas Airlangga Hospital Surabaya Indonesia. The amount of subjects was determined by identifying them based on the criteria and identifying their use of inhaled steroid for 30 months or more according to anamnesis, medical records, and the records of medication taken. We obtained 29 subjects.

We conducted this stuyd by collecting the data of the subjects' characteristics including age, body weight, height, BMI, FEV1 pred, FEV1/FVC pred, ACT score, long-term use of steroids, coenzyme Q10, sex, occupation, controller, reliever, asthma degree, type of asthma. Measurement of serum coenzyme Q10 level using Agilent tool with HPHPLC method.

The data were collected based on data obtained during the study that met the subject criteria. The data obtained were processed manually and were presented in the form of tables and graphs. The data were processed using computer statistics program SPSS version 23.0 (SPSS, Inc., Chicago, IL). Prior to statistical test, shapiro wilk test were performed. If the test result of shapiro wilk was $p<0.05$ then statistical test of coenzyme Q10 and long-term steroid inhalation was analyzed using spearman rank test ($p <0.05$). If otherwise, the statistical

test used was pearson correlation test.

Result

Demographic Data

Tabel 1. Mean and Demography

Variable	Mean±SD (n=29)
Age (year)	50.55±7.52
Weight (kg)	58.31±11.25
Height (cm)	154.69±6.51
BMI	24.34±4.26
FEV1 pred (%)	99.90±36.94
FEV1/FVC pred (%)	64.48±13.67
ACT Score	19.48±4.75
Steroid Period (Month)	44.38±11.55
Coenzyme Q10	1.38±0.54

The result of identification of 29 subjects showed that the mean of the subjects' age was 50.55 ± 7.52 years old, with the youngest subject being 32 years old and the oldest 64. All subjects who were willing to be involved in this study were over 21 years old. The mean of the subjects' weight was 58.31 ± 11.25 kg, while for the height was 154.69 ± 6.51 cm. According to the value of body height and weight, the obtained Body mass indedx (BMI) value was 24.34 ± 4.26 kg/m2 with BMI value range of 17.00-32.00 kg/m2. The result of asthma control test score (ACT) subject showed the score of 19.48 ± 4.75 (Table 1).

Tabel 2. Distribution of Demography Data Frequency

Variable	categori	% (n=29)
Sex	Male Female	6.90 93.10
Occupation	Housewife Teacher Lecturer Taylor Private Employee Navy Soldiers	58.60 13.80 3.40 3.40 17.20 3.40
Controller	seretide® symbicort®	37.90 62.10
Reliever	berotec® ventolin®	82.80 17.20
The degree of Asthma	Mild Moderate Severe	3.45 93.10 3.45
Asthma Control Level	Uncontrolled Partly Controlled Controlled	41.40 37.90 20.70

The next subject characteristics were based on the frequency distribution of subject demographic data. The majority of subjects were female (93.10%). Most subjects also used controllers with Symbicort type (62.10%) and reliever with berotec type (82.80%). The majority of subjects had asthma in the moderate category (93.10%) and most subjects had uncontrolled asthma (41.40%; table 2). Subjects used steroid medications for 44.38 ± 11.55 months. The shortest span was 31 months and the longest was 72 months. The mean of coenzyme Q10 profile in the sample was 1.38 ± 0.54 mg/L with the lowest value being 0.51 mg/L and the highest 2.53 mg/L (Table 1).

Correlation between Coenziem Q10 Long Steroid Inhalation Use Period

According to the result of Pearson correlation test between coenzyme Q10 with long-term steroid inhalation usage showed r = -0.037 and p = 0.848, indicating no significant relationship between coenzyme Q10 and long-term steroid inhalation. Pearson correlation test result showed that coenzyme Q10 with long seretide® inhalation usage was r = 0.380 and p = 0.912 which means that there was no significant relationship between coenzyme Q10 and long seretide® inhalation. Pearson correlation test results showed that coenzyme Q10 with long-term symbicort inhalation usage was r = -0.194 and p = 0.441, suggesting no significant relationship between coenzyme Q10 and long-term symbicort inhalation.

Figure 1 shows that the data spreads irregularly which means there is no significant relationship between the two variables. However, the results of the Pearson correlation coefficient with minus value and the tendency of the scatter plot image indicate that the longer the use of inhaled steroids increase the tendency of lower coenzyme Q10.

Discussion

To this day there is no literature or research that assess coenzyme Q10 on the use of long-term inhaled steroids. Coenzyme Q10 levels are low on the use of long-term oral steroids. The cause of low levels of coenzyme Q10 is mitochondrial damage. The damaged mitochondria can be established definitively through tissue biopsy but are too invasive. The non invasive way used to assess mitochondrial damage is by measuring the levels of coenzyme Q10 which is a natural antioxidant synthesized in mitochondria [11,12].

In this study there is no low coenzyme Q10 level and therefore we expected the function and structure of the mitochondria in this study sample are within normal limits. Mitochondrial damage can be caused by various diseases including heart problems, Parkinson's, malignancy, diabetes, hypertension, HIV, dyslipidemia and kidney failure and patients with those problem have been excluded from this study. We have also excluded drugs that can cause low levels of coenzyme Q10 including beta blockers, diuretics, statins, glucophage and haloperidol and asthma sufferers who consume ubiquinone supplementation have also been excluded. By conducting this study we hope to understand whether or not the use of steroids in the long term can cause low levels of coenzyme Q10 and then to use the knowledge to improve the management of bronchial asthma.

The systemic side-effects that are expected for long-term use of steroid inhalation are not proven. This may be due to the duration of inhaled steroid use that was not long enough. In this study we used a 30-month baseline, following oral prednisolone steroidal studies given for 16, 24, and 30 months [9]. With the assumption that the longest period was 30 months, the benchmark duration of steroid inhalation in this study is then more than 30 months. Systemic side effects of steroid inhalation use in asthma were related to adrenal gland disorders, osteoporosis and skin thickening. A study discusses high doses of inhaled steroids that may have adverse systemic effects. In this study we use steroid dose in accordance with the recommended GINA based on step-up and step-down therapy theory, causing the systemic side effects to be suppressed [12]. Systemic effects that can cause mitochondrial damage do not occur and therefore the coenzyme Q10 levels are not low.

The use of long-term symbicort® steroids showed the trend of lower coenzyme Q10 when compared to long-term seretide® use. Budesonid turbuhaler deposited in the lungs was 2.2 times larger than the MDI fluticason and 3.4 times larger than the fluticason discus. The systemic availability of budesonid turbuhaler was also higher than that of fluticason discus and MDI [13]. Budesonid turbuhaler that was 4 times larger was deposited in the lung and spread to systemic when compared with fluticason discus [14]. Coenzyme Q10 is affected by its endogenous production, its use by the body's cells and the intake of food. Endogenous production is strongly influenced by cell mitochondria. Its use is strongly influenced by oxidative stress levels.

Some food and beverage products containing coenzyme Q10 such as meat (deer, pig's heart, beef heart, beef liver, pork liver, beef, pork, chicken and egg), dietary fat (repeseed oil, tuna, and grilled frozen fish), cereals (wholemeal bread and wholemeal bread), vegetables (whole grains, cauliflower, nuts, and carrots), fruit (blackcurrant, lingonberry, strawberries, oranges, apples), and some dairy products (yogurt, emental cheese, edam cheese, and milk with 1.5% fat) [15].

Bronchial asthma has varying levels of oxidative stress, causing the need for coenzyme Q10 to increase. This can be accomplished from endogenous formation derived from mitochondria and adequate nutritional intake. Endogenous synthesis is more influential on the adequacy of coenzyme Q10 levels compared with exogenous nutrient intake. The normal requirement of coenzyme Q10 is 30-150 mg per day and can increase as the needs increase. When the mitochondria as a coenzyme producer of Q10 is damaged, the coenzyme content of Q10 will be low [15]. Some levels of coenzyme Q10 are found to be higher than the normal range. Coenzyme Q10 levels may increase with increasing BMI.48. This is due to the fat-soluble nature of coenzyme Q10 [11,12].

Conclusion

There was no correlation between coenzyme Q10 and long-term steroid inhalation.

Ethical Clearance: This research involves participants in the process using a questionnaire that was accordant with the ethical research principle based on the regulation of research ethic regulation. The present study was carried out in accordance with the research principles. This study implemented the basic principle ethics of respect, beneficence, non-maleficence, and justice.

Conflict of Interest: The authors have not found any conflict of interest related to this research so far.

Source of Funding: All of the cost and fees related with this research are paid by the authors only with no sponsorship nor external funds.

Acknowledgement: This article was published as the graduation requirement of post-graduate study program at Universitas Airlangga Surabaya, Indonesia under the title "*Hubungan antara Kadar Koenzim Q10 dan Inhalasi Steroid Jangka Waktu Lama pada Penderita Asma Bronkial*" in http://repository.unair.ac.id/*70360*.

Reference

1. Yudhawati R, Krisdanti DPA. Imunopatogenesis Asma. J Respirasi. 2019 Apr;3(1):26.
2. Kudo M, Ishigatsubo Y, Aoki I. Pathology of asthma. Front Microbiol. 2013;4.
3. Miftahussurur M, Nusi IA, Graham DY, Yamaoka Y. Helicobacter, Hygiene, Atopy, and Asthma. Front Microbiol. 2017 Jun;8.
4. DKR I. Laporan hasil riset kesehatan dasar (Riskesdas) Indonesia tahun 2007. Badan Penelitian dan Pengembangan Kesehatan; 2008.
5. De Jager L, Deneyer M, Buyl R, Roelandt S, Pacqueu R, Devroey D. Cross-sectional study on patient-physician aggression in Belgium: Physician characteristics and aggression types. BMJ Open [Internet]. 2019;9(12). Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85077073956&doi=10.1136%2Fbmjopen-2018-025942&partnerID=40&md5=49c7edcfa645eb1f7b8b782b90349352
6. Gazdik F, Gvozdjakova A, Nadvornikova R, Repicka L, Jahnova E, Kucharska J, et al. Decreased levels of coenzyme Q10 in patients with bronchial asthma. Allergy. 2002 Sep;57(9):811–4.
7. Yudhawati R, Prasetiyo YD. Imunopatogenesis Penyakit Paru Obstruktif Kronik. J Respirasi. 2019 Apr;4(1):19.
8. Smith A, Cowan J, Filsell S, McLachlan C, Monti-Sheehan, Jackson P. Diagnosing Asthma. Am J Respir Crit Care Med. 2004;169(4).
9. Mitsui T, Azuma H, Nagasawa M, Iuchi T, Akaike M, Odomi M, et al. Chronic corticosteroid administration causes mitochondrial dysfunction in skeletal muscle. J Neurol. 2002 Jul;249(8):1004–9.
10. Tajima K, Obata Y, Tamaki H, Yoshida M, Chen Y-T, Scanlan MJ, et al. Expression of cancer/testis (CT) antigens in lung cancer. Lung Cancer. 2003 Oct;42(1):23–33.
11. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J. 2012;5(1):9–19.
12. Boe J, Skoogh BE. Is long-term treatment with inhaled steroids in adults hazardous? Eur Respiratory Soc; 1992.
13. Thorsson L, Edsbäcker S, Källén A, Löfdahl

C-G. Pharmacokinetics and systemic activity of fluticasone via Diskus® and pMDI, and of budesonide via Turbuhaler®. Br J Clin Pharmacol. 2001 Dec;52(5):529–38.

14. Agertoft L, Pedersen S. Lung Deposition and Systemic Availability of Fluticasone Diskus and Budesonide Turbuhaler in Children. Am J Respir Crit Care Med. 2003 Oct;168(7):779–82.
15. Boreková M, Hojerová J, Koprda V, Bauerová K. Nourishing and health benefits of coenzyme Q10 - A review. Czech J Food Sci. 2008;26(4):229–41.