Difference in serum magnesium level among patients with stable chronic obstructive pulmonary disease (COPD) and exacerbated COPD

R Sanowara¹*, E N Keliat² and A Abidin²

¹Department of Internal Medicine Department, Faculty of Medicine, Universitas Sumatera Utara, RSUP H. Adam Malik, Medan, Indonesia
²Department of Pulmonology and Allergy-Immunology Division, Internal Medicine Department, Faculty of Medicine, Universitas Sumatera Utara, RSUP H. Adam Malik, Medan, Indonesia
*Corresponding author: oke_ricky@yahoo.com

Abstract. Stable COPD is marked with various degrees of inflammation throughout large and small airways also in the alveoli which cause mucus hypersecretion, narrowing of the airway, and alveoli damage. Exacerbation is an episode of elevated inflammation. The relation between inflammation response and magnesium has been observed with the increase of proinflammation cytokines in magnesium deficiency. A cross-sectional study of 34 patients who came to RSUP H. Adam Malik (17 stable COPD patients and 17 acute exacerbated COPD patients) was conducted to examine serum magnesium level and spirometry in stable condition. Mean serum magnesium level for stable COPD patients group was 2.09 ± 0.11 mEq/L. It was higher than in the exacerbated COPD patients group 1.69 ± 0.27 mEq/L. Mann–Whitney statistical analysis showed a significant difference in magnesium level between stable COPD and exacerbated COPD groups (p<0.05).

1. Introduction

Global Burden of Disease Study projected that COPD, which ranked sixth as a cause of death in 1990, will become the third leading cause of death worldwide by 2020; a newer projection estimated COPD would be the fourth leading cause of death in 2030¹.

Between January – December 2012, there were 110 cases of COPD in Haji Adam Malik General Hospital in Medan, with Case Fatality Rate (CFR) 10.9%².

The stable clinical state is by varying degrees of inflammation affecting the large and small airways as well as the alveoli, resulting in mucus hypersecretion, airway narrowing, and alveolar destruction, respectively. With this background of mild inflammation, there is a general belief that exacerbations are episodes where the inflammatory process is enhanced, although the processes involved and their effects are poorly understood³.

Several studies evidence close relations between magnesium and inflammatory response. Increased levels of proinflamatory cytokines (Interleukin 6, Tumor Necrosis Factor – α) have been reported in animals under magnesium deprivation for three weeks. Researchers also detected plasma Substance – P (SP) which is a well-known cytokine production stimulator, during the first week of magnesium deficiency. The secretion of these cytokines can be maximal at either five days (Interleukin – 4 and
Interleukin – 5) or seven days (Interleukin – 2, Interleukin – 10 and Interferon gamma) after magnesium deficiency.

Bronchospasm is a contributing factor in the inability to clear secretion. It may result in a reduced pulmonary gas exchange with consequences such as decreased quality of life and repeated hospitalization. Although the precise mechanism of this action is unknown, it suggested that magnesium plays a role in the maintenance of airway patency via relaxation of bronchial smooth muscle.

In Indonesia, the study about magnesium in chronic obstructive pulmonary disease patients has never been done before. This study was conducted to observe the difference in magnesium level between patients with stable and exacerbated chronic obstructive pulmonary disease.

2. Methods
A cross-sectional study was conducted on patients with chronic obstructive pulmonary disease in RSUP HAM Medan. The subjects of this study were stable and exacerbated chronic obstructive pulmonary disease patients whose age were 40 years or older. The exclusion criteria were: 1) pregnancy and lactation, 2) patients with chronic kidney disease, 3) thiazide diuretics and loop diuretics use, 4) malignancy, 5) alcoholism.

Early diagnosis of COPD was based on anamnesis and physical examination and later confirmed by spirometry when the patients were in stable condition. Routine blood and magnesium level were analyzed automatically by Abbott Architect ci4100 integrated system (USA). Spirometry was performed using precalibrated Spirovit Sp – 1, Schiller AG (Switzerland). Tabulating and analyzing data was with computer statistic program Statistical Package For Social Sciences (SPSS) version 24. The univariate analysis was performed on demographic and clinical characteristics and presented as atable. Saphiro – Wilk test was performed for data normality because the sample size was less than 50. Bivariate analysis was performed to determine if the serum magnesium level in patients with stable and exacerbated COPD were statistically different. Because the data for serum magnesium level was not normally distributed Mann – Whitney U test was with a confidence interval of 95%.

3. Results
During the study period from October 2016 – March 2017, 17 subjects from each exacerbated and stable COPD group were obtained for a total of 34 study subjects who met the inclusion criteria. Characteristics of the whole study subjects regardless of clinical status is in table 1. Characteristics of study subjects with respect to clinical status, stable COPD or exacerbated COPD is in table 2. Serum magnesium level mean and median with respect to clinical status, stable COPD and exacerbated COPD is in table 3. Boxplot diagram of serum magnesium levels in stable COPD and exacerbated COPD groups are in figure 1.

Of the total 34 subjects, 29 (85.3%) were male, and 5 (14.7%) were female. The mean age of the study participants was 60.7 (SD±7.39) years old. History of smoking was in 30 subjects (88.2%), and 4 (11.8%) without a history of smoking. Duration in which the subjects maintain the habit of smoking varied from 0 to 50 years with a median of 25.5 years. Subjects’ body weight was between 35 – 90 kilograms with a median of 55 kilograms. The height of the subjects varied between 140 – 171 cm with a median of 161 cm. Subjects’ body mass index (BMI) were between 15.7 – 45.9 kg/m² with median of 21.5 kg/m². Forced expiratory volume in 1 second (FEV1) was between 13.2 – 78% with a median of 39.5%. Mean Forced vital capacity (FVC) was 45.19 (SD±18.2)%. Serum magnesium level was between 0.92 – 2.28 mEq/L with a median of 1.96 mEq/L.

| Table 1. Characteristics of the study subjects regardless of clinical status. |
|-----------------------------------|-----------------|
| Sex                              | Characteristics |
| Male                             | n = 29 (85.3%)  |
| Female                           | n = 5 (14.7%)   |
The mean serum magnesium level for the stable COPD group was significantly different from that for the exacerbated COPD group, as confirmed by Mann–Whitney U test. The mean serum magnesium level for the stable COPD group was 2.09 ± 0.11 mEq/L, while for the exacerbated COPD group it was 1.69 ± 0.27 mEq/L. This difference was statistically significant (p < 0.05).

#### Table 2. Characteristics of the study subjects with respect to clinical status.

| Variable | Stable (N = 17) | Exacerbated (N = 17) | P  |
|----------|-----------------|----------------------|----|
| Sexa     |                 |                      |    |
| Male     | 14 (48.3%)      | 15 (51.7%)d          | 1.00 |
| Female   | 3 (60%)         | 2 (40%)              |    |
| Age (years)b | 58.88±5.93 | 62.52±8.4e          | 0.153 |
| History of Smokingc |              |                      |    |
| Current/Ex-smoker | 14 (46.7%) | 16 (53.3%)d          | 0.601 |
| Non-smoker | 3 (75%) | 1 (25%)              |    |
| Cigarette/dayc | 20 (0-32) | 20 (0-40)f          | 0.204 |
| Duration (years)b | 23.94±14.39 | 28.47±13.31e        | 0.348 |
| Body Weight (kg)c | 50 (40-90) | 55 (35-77)f         | 0.407 |
| Height (cm)b | 159.18±8.8 | 160.82±6.93e       | 0.549 |
| Body Mass Index (Kg/m²)c | 20.2 (15.7–45.9) | 21.5 (17.8–29.3)f | 0.458 |
| FEV1 (%)c | 42.8 (14.2–78) | 25.5 (13.2–72.5)f | 0.148 |
| FVC (%)b | 46.95±16.74 | 43.43±19.92e       | 0.581 |

aFisher exact test
bIndependent t-test
cMann Whitney U test
dNumerical Data, normal distribution: mean± SD
eNumerical Data, not normally distributed: median (minimum–maximum)

#### Table 3. Mean and median of serum magnesium level in stable and exacerbated COPD groups.

| Clinical Status | N   | Mean  | Std. Deviation | Median | Min  | Max  | P Valuea |
|-----------------|-----|-------|----------------|--------|------|------|----------|
| Stable          | 17  | 2.0918| 0.11555        | 2.1000 | 1.85 | 2.28 | 0.0001   |
| Exacerbated     | 17  | 1.6871| 0.26727        | 1.7100 | 0.92 | 2.00 |          |
| Total           | 34  | 1.8894| 0.28861        | 1.9650 | 0.92 | 2.28 |          |

aMann–Whitney U test
Figure 1. The diagram of serum magnesium level boxplot for stable COPD and exacerbated COPD groups.

4. Discussion

The role of magnesium in cellular biology is close to that of another bivalent ion, calcium. The requirement for magnesium developed in tandem with, and in competition to that of calcium. Magnesium can as nature’s physiologic calcium blocker. Bronchial smooth muscle requires the generation of electrochemical differences across the cell membrane for muscular contraction to occur. It is by modulating calcium influx in and out of the cell. Magnesium can block calcium channel, reduce the neuromuscular junction cholinergic transmission by reducing acetylcholine-induced depolarization sensitivity, mast cell, and T cell stabilization, also the stimulation of nitric oxide and prostacyclin. In this manner, low intracellular magnesium level may cause airway hyperresponsiveness.

Magnesium allegedly has direct anti-inflammatory properties, especially at clinically relevant concentration, by attenuating the neutrophil respiratory burst through its negative effects on calcium influx. The underlying mechanism for the inflammatory response to magnesium deficiency is not clearly elucidated. Events that considered trigger inflammatory response in magnesium deficiency are: cellular entry of calcium and priming of phagocytic cells, the opening of calcium channels and activation of N-methyl D-aspartate receptors, the release of neurotransmitters such as substance P, membrane oxidation and activation of nuclear factor kappa B.

In plasma, magnesium can be in three fractions; in an ultrafiltrate fraction consisting of ionized magnesium (70–80%), complex bound magnesium (1–2%), and in protein-bound fraction (20–30%). Ionized magnesium assay is more clinically relevant and superior to total magnesium examination because ionized magnesium is the one that possesses biological activity. The chemical property of magnesium makes ionized magnesium to be difficult and demanding, and existing ion–selective electrodes have suffered from a lack of selectivity and relatively long response times. Selectivity of ionized magnesium assay may suffer from specific interference (such as from calcium and natrium ion) and non–specific interference (silicon, detergent, and thiocyanate in smokers. In this study, we chose to examine total serum magnesium level because of feasibility reason; it is the routine and readily available examination in our hospital.

In this study, we found that serum magnesium level in the stable COPD group (2.09±0.11 mEq/L) was higher than serum magnesium level in exacerbating COPD group (1.69±0.27 mEq/L). Mann –
Whitney U test statistical analysis showed the difference in serum magnesium level between stable and exacerbated COPD groups were significant (p< 0.05).

A study by Azis et al in 2005 at St. Joseph’s Regional Medical Centre New Jersey found that serum magnesium level of patients with exacerbated COPD (0.77±0.10 mmol/L) was significantly lower than serum magnesium level of stable COPD patients (0.91±0.10 mmol/L). The study above by Azis et al serum magnesium levels of both the stable and exacerbated COPD group were in the hypomagnesemia range (normal range for serum magnesium level is between 1.4 – 2.1 mEq/L).

Another study by Singh et al in 2012 found that 34% of exacerbated COPD patients had hypomagnesemia. The study by Singh et al used 0.74 – 0.99 mmol/L as a reference value for normal serum magnesium level. While in our study only one subjects in the exacerbated COPD group whose serum magnesium level was in the hypomagnesemia range (2.94 %). Kshirsagar et al in 2014 found 72% exacerbated COPD patients had hypomagnesemia (Kshirsagar et al used <1.7 mg/dL as a reference value for hypomagnesemia). The parameter examined by Kshirsagar et al was ionized magnesium assay, not total serum magnesium. In the study by Kshirsagar et al, the ionized magnesium level of exacerbated COPD patients was significantly lower than those of the stable COPD group.

Assessment of magnesium status is biochemical. Total serum magnesium level is the most commonly requested test to assess magnesium status and is informative when the result is low, indicating hypomagnesemia. However, the test result of normal total serum magnesium level remained problematical because in patients suspected of magnesium deficiency serum concentration can be normal despite whole body deficiency. It is not surprising because only 1% or less of total body magnesium is in the blood; the bulk of magnesium is intracellular bound to numerous subcellular components, and these are the moieties which account for its biological role. In other words, normal serum magnesium (total or ionized) must be with caution. The practical, inexpensive, and commonly used serum magnesium test is potentially flawed, capable of identifying magnesium deficiency in some but not all patients with magnesium deficiency and negative body stores. A study by Ruljancic et al in 2007 compared magnesium levels of stable COPD patients with healthy non–smoker subjects and subjects with a history of smoking without COPD did not find significant differences of total serum magnesium level among the three groups. However, ionized magnesium in polymorphonuclear cells in the patients with stable COPD and subjects with a history of smoking without COPD were significantly lower than healthy non–smoker subjects. In the other hand, total calcium in polymorphonuclear cells of patients with stable COPD and subjects with smoking history without COPD were significantly higher than total calcium in polymorphonuclear cells of healthy non–smoker subjects. Higher total calcium / total magnesium ratio in patients with stable COPD and subjects with smoking history without COPD indicated relative magnesium deficiency compared to calcium level and suggest the conclusion of intensified calcium activity. The study above demonstrates the limitation of total serum magnesium assay. Magnesium loading test should be conducted to rule out the possibility of latent/chronic magnesium deficiency if kidney function was normal. Magnesium loading test is by administrating 30 mmol of elemental magnesium (sulfate or chloride) intravenously continued by analyzing 24-hour urinary secretion of elemental magnesium. In this test, urinary elemental magnesium secretion < 25 mmol/24 hours indicates latent magnesium deficiency.

Surya Prakash Bhatt et al in 2008 study 100 COPD patients and found that serum magnesium level is an independent predictor of frequent readmission due to acute exacerbation of chronic obstructive pulmonary disease. Serum magnesium of the patients who needed frequent admission to hospital (more than 3 times a year) was 1.77 ± 0.19 mEq/L, whereas serum magnesium level of patients who need less than three visits to the hospital per year was 1.86 ± 0.24 mEq/L. Bhatt et al also found that 90% of the subjects were either ex-smoker (33%) or current smoker (57%). The result of our study is by Bhatt et al; patients with exacerbating COPD had serum magnesium level than the patients with stable COPD.
5. Conclusion
Serum magnesium level in subjects with the stable chronic obstructive pulmonary disease was higher than serum magnesium level in the subjects with exacerbated chronic obstructive pulmonary disease. Mann – Whitney U test statistical analysis showed that the difference in serum magnesium levels between the subjects with stable and exacerbating COPD was statistically significant (p< 0.05).

References
[1] Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015 Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease
[2] Sidabutar P, Rasmalah and Hiswani 2013 Karakteristik penderita penyakit paru obstruksi kronik (PPOK) yang dirawat inap di RSUP H. Adam Malik Medan tahun 2012 [Skripsi] (FKM USU)
[3] White A J, Gompertz S and Stockley R A 2003 Chronic obstructive pulmonary disease 6: the aetiology of exacerbations of chronic obstructive pulmonary disease Thorax 58 73-80
[4] Tam M, Gomez S, Gonzales – Gross M and Marcos A 2003 Possible roles of magnesium on the immune system Eur. J. Clin. Nutr. 57 1193–7
[5] Aziz H S, Blamoun A I, Shubair M K, Ismail M M F, DeBari V A and Anees – Khan M 2005 Serum magnesium levels and acute exacerbation of chronic obstructive pulmonary disease: A retrospective study Ann. Clin. Lab. Sci. 35(4) 423–7
[6] Edwards L 2014 Three aspects in the treatment of acute exacerbations of chronic obstructive pulmonary disease: the rôle of nebulised magnesium, the risks of oxygen and the utility of the CRB-65 score [Thesis] (Cardiff University)
[7] Emelyanov A, Fedoseev G and Barnes P J 1999 Reduced intracellular magnesium concentrations in asthmatic patients Eur. Respir. J. 13 38–40
[8] Kshirsagar K R, Lomate S A, Aundhakar S C, Patil R, Jain V, Agarwal S and Patil N 2015 Serum magnesium level in acute exacerbation of chronic obstructive pulmonary disease [Thesis] (Krhisna Institute of Medical Sciences)
[9] Mazur A, Maier J A M, Rock E, Gueux E, Nowacki W and Rayssiguier Y 2007 Magnesium and the inflammatory response: potential physiopathological implications Arch. Biochem. Biophys. 458 48-56
[10] Saris N L, Mervaala E, Karppanen H, Khawaja J A and Lewenstam A 2000 Magnesium: an update on physiological, clinical, and analytical aspects J. Clinica Chimica Acta 294
[11] Singh J P, Kohli S, Devi A and Mahajan S 2012 Serum magnesium in COPD patients attending a tertiary hospital – a cross sectional study J. K. Sci. 14(4) 185-90
[12] Ismail A A A and Ismail N A 2016 Magnesium: a mineral essential for health yet generally underestimated or even ignored J. Nutr. Food Sci. 6(4)
[13] Ruljancic N, Popovic – Grie S, Rumenjak V, Sokolic S, Malic A, Mihanovic M and Cepelak I 2007 COPD: magnesium in the plasma and polymorphonuclear cells of patients during a stable phase Int. J. Chron. Obstruct. Pulmo. Dis. 4 41-7
[14] Bhatt S P, Khandelwal P, Nanda S, Stoltzfus J C and Fioravanti G T 2008 Serum magnesium is an independent predictor frequent readmission due to acute exacerbation of chronic obstructive pulmonary disease Respir. Med. 102(7) 999–1003