ASTHMA AND METABOLIC SYNDROME - WHERE IS THE LINK?

Baharudin Ibrahim, Arwa Mohamed Amin Mostafa
School of Pharmaceutical Sciences, Universiti Sains Malaysia, Malaysia

Abstract: Asthma is a major burden on global health care system which is encumbering all regions in the world. Several risk factors can induce and exacerbate asthma. Recent compelling evidences have associated metabolic syndrome with the incidence of asthma. The abdominal obesity, hypertension and insulin resistance are metabolic syndrome criteria which are substantially involved in inducing and exacerbating asthma. Several mechanisms are involved in the association between metabolic syndrome and asthma. It could be due to mechanical reason, genetic factors, inflammatory effect, hormonal effect, insulin resistance and the effect of other co-morbidities associated with obesity. In this review, we discuss the mechanisms which link metabolic syndrome to asthma.

Keywords: Asthma, metabolic syndrome

Introduction

Asthma is a major global health issue which burdens people from all regions of the world. It was estimated that 334 million patients are suffering from asthma globally [1]. Using the Global Initiative for Asthma (GINA) definition, asthma is a chronic and heterogeneous airway inflammatory disease with symptoms that vary in time and intensity such as, wheeze, shortness of breath, chest tightness and cough [2]. Due to the airway hyper responsiveness of asthma, the symptoms can be instigated by stimuli such as exercise, allergen, change in weather or viral respiratory infection. An exacerbation of asthma may lead to long hospitalization and death. Asthma can be exacerbated by several risk factors such as type two diabetes mellitus (T2-DM), obesity or high body mass index (BMI), hypertension, gastroesophageal reflux and sleep-disorder breathing [3]. However, the presence of clustering conditions such as, metabolic syndrome has strong association with asthma [4, 5]. Rather than one disease, metabolic syndrome is a group of simultaneous disease conditions which include hypertension, abdominal obesity (central obesity), atherogenic dyslipidemia and insulin resistance or glucose intolerance [6]. According to the National Cholesterol Education Program's Adult Treatment Panel III report (NCEP ATP III), metabolic syndrome can be clinically diagnosed with the presence of at least three out of five criteria which are waist circumference more than 40 inch in men and 35 inch in women, blood pressure more than 130/85 mm Hg, fasting blood sugar more than 110 mg/dL, triglycerides (TG) more than 150 mg/dl and high density lipoprotein (HDL) less than 40 mg/dL in men and 50mg/dL in women [7, 8]. In metabolic syndrome, some types of cells suffer from function perturbation such as vascular endothelial cells, glandular epithelium, renal epithelial cells and potentially the airway epithelial and sub epithelial cells [5]. Such perturbations, make metabolic syndrome strong risk factor for cardiovascular diseases, stroke and diabetes. Adding to them, growing evidences have strengthened the association between asthma and metabolic syndrome [4, 9-11]. Here, we discuss the association of metabolic syndrome with asthma and the mechanisms linking this association.

Metabolic syndrome associated asthma, where is the link?

The association between metabolic syndrome and asthma was investigated in several population studies. In in the Korean health and genome study, the association between metabolic syndrome and asthma -like-symptoms was tested among 9942 adults who were 40 to 69 years of age [12]. Among asthma-like-symptoms, wheeze ($p=0.0006$), resting dyspnoea ($p=0.0062$) and post-exercise dyspnoea ($p=0.0001$) were significantly prevalent among subjects with metabolic syndrome compared to subjects without metabolic syndrome. Among the criteria of metabolic syndrome, abdominal obesity and elevated blood pressure were significantly associated with asthma-like syndrome. The metabolic syndrome and incidence of asthma study (The HUNT study) was one of the largest population based studies that asserted the association between metabolic syndrome and asthma (adjusted OR 1.57, 95% CI 1.31 - 1.87) [4]. In this study, 23,191 asthma-free subjects were categorized based on metabolic syndrome and followed-up for asthma incidence. Among metabolic syndrome components, high waist circumference (adjusted OR 1.62, 95% CI 1.36–1.94) and elevated glucose or diabetes (adjusted

OR 1.43, 95% CI 1.01–2.04) were significant. Furthermore, Assad et al (2013) indicated that asthma is associated with three components of metabolic syndrome, the abdominal obesity, hypertension and elevated fasting glucose or diabetes in an un-adjusted models [13]. However, upon adjusting the models to BMI, it was found that BMI rather than metabolic syndrome is strongly associated with asthma in women. From the aforementioned studies, it is understandable that the abdominal obesity, insulin resistance (elevated glucose) and hypertension are the main risk factors that associate metabolic syndrome with asthma. Based on these risk factors, there are several suggestive mechanisms which explain the link between metabolic syndrome and asthma. It can be due to mechanical effect, genetic factors, epigenetic factors, inflammatory effect, mitochondrial dysfunction, hormonal effect and the effect of other co-morbidities [5, 11, 14].

Abdominal obesity or visceral obesity component of the metabolic syndrome is actually a leading factor for hypertension and insulin resistance [15, 16]. Therefore, visceral obesity plays pivotal role in the metabolic syndrome-asthma linkage. This link is bilateral. Accordingly, obese asthmatic patients are more likely to develop metabolic syndrome and vice versa [11]. The obesity associated asthma is distinctive phenotype of asthma (OAA) and it is more likely to have poorer therapeutic outcome than non-obese asthmatic [9, 14]. This appear in the mechanical, genetic, inflammatory and hormonal effects of obesity on asthma.

The mechanical effect of abdominal obesity on lung volumes is manifested in the exponential reduction of the functional residual capacity (FRC) and the expiratory reserve volume (ERV) with the increase of BMI [17, 18]. In other words, an increase of BMI would cause an increase in airway resistance [18]. Obesity is associated with several genetic variabilities that have substantial effect on asthma and its response to therapy. In fact, asthma and obesity have shared genetic factors [14]. For instance, the β2-adrenergic receptor gene (ADRβ2) and the glucocorticoid receptor gene (NR3C1) are related to asthma and obesity. The Gln27 polymorphism of the ADRβ2 gene was found significantly more frequent among obese patients compared to non-obese [19]. This polymorphism interferes with the response to β2-agonists in asthma [20]. The polymorphism of the NR3C1 gene was found to be significantly associated with bronchial asthma [14]. Besides, abdominal obesity is highly affected by the genetic variation in glucocorticoid receptors [21]. Obesity is known to cause chronic pro-inflammatory status in the human body which is characterized by the perturbation of pro-inflammatory mediators [14]. The increased levels of high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor alpha (TNF-α), interleukin (IL-6) and leptin were observed in obese-asthma patients [11, 14]. This pro-inflammatory status can lead to airway modulation, insulin resistance and hypertension. Obese asthmatic children had higher pro-inflammatory leptin and lower anti-inflammatory adiponectin compared to non-obese asthmatic children [22]. The increase of leptin with the decrease of adiponectin has key role in airway inflammation, lung dysfunction and the development of asthma [12, 23]. Besides, leptin can increase the levels of other pro-inflammatory mediators such as TNF-α and IL-6 [11]. It is worthy to note that leptin can cause renal and sympathetic effects leading to hypertension which is associated with asthma as well [12]. Hormonal-differences has its implication on obesity linked asthma. Obesity reduces progesterone levels [24]. Progesterone causes up-regulation of ADRβ2 receptor. Moreover, leptin present in higher concentration in women than men [14]. Thus, obese women are more likely to suffer from OAA than men.

Insulin resistance (glucose intolerance) a key element of metabolic syndrome leads to hyperinsulinemia which is an increased level of insulin due to the elevated glucose levels [5]. Hyperinsulinemia is associated with increased airway contractility, cell proliferation and fibrosis of the airway smooth muscle [25]. Indeed, increased insulin activates the PI3K/Akt pathway in the bronchial epithelial cells which leads to bronchoconstriction. Furthermore, metabolic syndrome is associated with increased asymmetric dimethyl arginine (ADMA) which impairs the arginine-nitric oxide metabolism and cell programing [26]. This causes an increase in arginine catabolism, as well as the formation of toxic reactive nitric oxide (peroxynitrite) which cause bronchoconstriction and mitochondrial dysfunction. This impairment was found in both metabolic syndrome and asthma as well.

In addition to all the aforementioned mechanisms that link metabolic syndrome with asthma, there are several obesity related co-morbid conditions which can induce or exacerbate asthma condition such as sleep disorder breathing (SDB), gastroesophageal reflux disease (GERD), T2-DM, hypertension and dyslipidemia [14]. The SDB has been found significantly associated in asthma [27]. Similarly, GERD is associated with chest congestion, lung inflammation and cough which may cause asthma and bronchitis [28]. The association between hypertension and asthma is understandable with the effect of leptin on the renal and sympathetic activity [12]. Elevated serum triglycerides and low HDL were associated with wheezing in large population study of 85,555 Spanish adults [29]. T2-DM is highly associated with declined lung function [30]. Noteworthy, the impaired arginine-nitric oxide metabolism and mitochondrial dysfunction which link metabolic syndrome with asthma, are apparently manifested in T2-DM [31, 32].

Conclusion

It could be concluded that the association between asthma and metabolic syndrome is supported by growing body of evidences. This association is multifactorial rather than one direct linkage between the two conditions. Asthmatic patients suffering from metabolic syndrome should not be treated for asthma in isolation from their metabolic syndrome status to avoid poor therapeutic outcome. A personalized therapeutic regimen that includes weight management, asthma type phenotyping, as well as drug response phenotyping may have better outcome.

References

1. The Global Asthma Network (GAN) Steering Group. *The Global Asthma Report 2014*. 2014 [cited 2016 24/07/2016]; Available from: http://www.globalasthmareport.org/resources/ Global_Asthma_Report_ 2014.pdf.
2. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention 2016*. 2016 [cited 2016; Available from: www.ginasthma.org.
3. Shore, S.A., *Obesity and asthma: Possible mechanisms.* Journal of Allergy and Clinical Immunology, 2008. **121**(5): p. 1087-1093.
4. Brumpton, B.M., et al., *Metabolic syndrome and incidence of asthma in adults: the HUNT study.* Eur Respir J, 2013. **42**(6): p. 1495-502.
5. Agrawal, A., et al., *Emerging Interface between Metabolic Syndrome and Asthma.* American Journal of Respiratory Cell and Molecular Biology, 2011. **44**(3): p. 270-275.
6. Huang, P.L., *A comprehensive definition for metabolic syndrome.* Disease Models and Mechanisms, 2009. **2**(5-6): p. 231-237.
7. Grundy, S.M., et al., *Diagnosis and management of the metabolic syndrome an American Heart Association/National Heart, Lung, and Blood Institute scientific statement.* Circulation, 2005. **112**(17): p. 2735-2752.
8. Grundy, S.M., et al., *Definition of Metabolic Syndrome.* Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition, 2004. **109**(3): p. 433-438.
9. Garmendia, J.V., et al., *Metabolic syndrome and asthma.* Recent Pat Endocr Metab Immune Drug Discov, 2014. **8**(1): p. 60-6.
10. Agrawal, A. and Y.S. Prakash, *Obesity, Metabolic Syndrome, and Airway Disease: A Bioenergetic Problem?* Immunology and allergy clinics of North America, 2014. **34**(4): p. 785-796.
11. Serafino-Agrusa, L., M. Spatafora, and N. Scichilone, *Asthma and metabolic syndrome: Current knowledge and future perspectives.* World Journal of Clinical Cases : WJCC, 2015. **3**(3): p. 285-292.
12. Lee, E.J., et al., *Asthma-Like Symptoms are Increased in the Metabolic Syndrome.* Journal of Asthma, 2009. **46**(4): p. 339-342.
13. Assad, N., et al., *Body Mass Index Is a Stronger Predictor than the Metabolic Syndrome for Future Asthma in Women. The Longitudinal CARDIA Study.* American Journal of Respiratory and Critical Care Medicine, 2013. **188**(3): p. 319-326.
14. Ali, Z. and C.S. Ulrik, *Obesity and asthma: A coincidence or a causal relationship? A systematic review.* Respiratory Medicine, 2013. **107**(9): p. 1287-1300.
15. Mathieu, P., et al., *Visceral Obesity: The Link Among Inflammation, Hypertension, and Cardiovascular Disease.* Hypertension, 2009. **53**(4): p. 577-584.
16. Kahn, S.E., R.L. Hull, and K.M. Utzschneider, *Mechanisms linking obesity to insulin resistance and type 2 diabetes.* Nature, 2006. **444**(7121): p. 840-846.
17. Pelosi, P., et al., *The effects of body mass on lung volumes, respiratory mechanics, and gas exchange during general anesthesia.* Anesthesia & Analgesia, 1998. **87**(3): p. 654-660.
18. Jones, R.L. and M.-M.U. Nzekwu, *THe effects of body mass index on lung volumes*.* Chest, 2006. **130**(3): p. 827-833.
19. Ishiyama-Shigemoto, S., et al., *Association of polymorphisms in the beta2-adrenergic receptor gene with obesity, hypertriglyceridaemia, and diabetes mellitus.* Diabetologia, 1999. **42**(1): p. 98-101.

20. Hall, I.P., et al., *Association of Glu 27 beta 2-adrenoceptor polymorphism with lower airway reactivity in asthmatic subjects.* Lancet, 1995. **345**(8959): p. 1213-4.
21. Rosmond, R., et al., *A Glucocorticoid Receptor Gene Marker Is Associated with Abdominal Obesity, Leptin, and Dysregulation of the Hypothalamic-Pituitary-Adrenal Axis.* Obesity Research, 2000. **8**(3): p. 211-218.
22. Abdul Wahab, A., et al., *Serum Leptin and Adiponectin Levels in Obese and Nonobese Asthmatic School Children in relation to Asthma Control.* Journal of Allergy, 2013. **2013**: p. 654104.
23. Dixon, A.E., et al., *An official American Thoracic Society Workshop report: obesity and asthma.* Proceedings of the American Thoracic Society, 2010. **7**(5): p. 325-335.
24. Sood, A., *Sex Differences: Implications for the Obesity-Asthma Association.* Exercise and sport sciences reviews, 2011. **39**(1): p. 48-56.
25. Singh, S., et al., *Insulin and the Lung: Connecting Asthma and Metabolic Syndrome.* Journal of Allergy, 2013. **2013**: p. 627384.
26. Mabalirajan, U. and B. Ghosh, *Mitochondrial Dysfunction in Metabolic Syndrome and Asthma.* Journal of Allergy, 2013. **2013**: p. 340476.
27. Li, L., et al., *Sleep-disordered breathing and asthma: evidence from a large multicentric epidemiological study in China.* Respiratory Research, 2015. **16**(1): p. 1-10.
28. Gaude, G.S., *Pulmonary manifestations of gastroesophageal reflux disease.* Annals of Thoracic Medicine, 2009. **4**(3): p. 115-123.
29. Fenger, R.V., et al., *The relationship of serum triglycerides, serum HDL, and obesity to the risk of wheezing in 85,555 adults.* Respir Med, 2013. **107**(6): p. 816-24.
30. Ehrlich, S.F., et al., *Patients Diagnosed With Diabetes Are at Increased Risk for Asthma, Chronic Obstructive Pulmonary Disease, Pulmonary Fibrosis, and Pneumonia but Not Lung Cancer.* Diabetes Care, 2010. **33**(1): p. 55-60.
31. Kövamees, O., A. Shemyakin, and J. Pernow, *Amino acid metabolism reflecting arginase activity is increased in patients with type 2 diabetes and associated with endothelial dysfunction.* Diabetes and Vascular Disease Research, 2016.
32. Cheng, Z. and F.A. Almeida, *Mitochondrial alteration in type 2 diabetes and obesity: An epigenetic link.* Cell Cycle, 2014. **13**(6): p. 890-897.