Review Article

Asthma and obesity in the Middle East region: An overview

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Abstract:

This paper aims to cover the current status of asthma and obesity in the Middle East, as well as to introduce the various studies tying the two diseases; further expanding on the proposed mechanisms. Finally, the paper covers recent literature related to sphingolipids and its role in asthma, followed by recommendations and future directions. In preparation of this paper, we searched PubMed and Google Scholar, with no restrictions, using the following terms; asthma, obesity, Middle East, sphingolipids. We also used the reference list of retrieved articles to further expand on the pool of articles that were used for this review.

Keywords:

Asthma, obesity, Qatar, sphingolipids, Middle East

Globally, asthma presents as a major public health concern,[1,2] with a varying prevalence rate among children.[3] The International Study of Asthma and Allergies in Childhood in 2013 reported a global prevalence rate of 14.1% among children ages 13–14 years, and 11.7% among children ages 6–7 years.[4] Global prevalence rates of rhinoconjunctivitis and eczema, among children ages 13–14 years, were 14.6% and 7.3%, respectively. Among those 6–7 years of age, the prevalence rates were 8.5% and 7.9% for rhinoconjunctivitis and eczema, respectively.[4]

As for the Middle East region, in 2017, a systematic review in a sample which included more than a quarter million children across the region, reported that the Middle East has lower asthma rates than developed countries, as a total asthma rate of 7.57% was reported among 13–14 year old children, and 7.43% among 6–7 year old children.[5] The review also showed that the prevalence of asthma was higher among males. Baghdad, Iraq had the highest prevalence rate (22.3%), while Isfahan, Iran had the lowest (0.7%).[5] According to Waness *et al*. in a review of respiratory disorders in the Middle East, the region continues to suffer respiratory-related illnesses due to a wide array of factors and obstacles. Pulmonologists, pediatricians, and family physicians, as well as other specialists, continue to face challenges in the region due to several distinctive environmental and cultural factors.[6] As for asthma in specific, Behbehani *et al*. indicates that much can be done when it comes to controlling asthma in the region.[7]

Locally in Qatar, in 2006, Janahi *et al*. (n = 3283) reported a prevalence rate of 19.8% for asthma, 30.5% for allergic rhinitis, 22.5% for eczema, and 11.9% for chest infections, among school children ages 6–12 years.[8] Similar rates were reported in an earlier study in 2005 as well.[9] In the Gulf region, in 2017, a study from Saudi Arabia reported an asthma prevalence rate of 24% among children in Makkah, with more males being affected than females, in a sample of children below 5 years of age.[10] In 2000, a study in Kuwait showed that males predominance was also reported in a sample of 13–14 year old children, with an

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asthma prevalence of 16.8%.[11] In 2008, a prevalence rate of 15.6% was reported among 13–14-year-old children in another study from Kuwait as well.[12] In Oman, a study in 2003 reported a prevalence rate of 20.7% for asthma, 10.5% for allergic rhinitis, and 14.4% for eczema, among school children ages 13–14 years. Among 6–7-year-old children, the rates were as follows: asthma 10.5%, allergic rhinitis 7.4%, and eczema 7.5%.[13] In the United Arab Emirates (UAE) in 2013, asthma prevalence rate was reported at 13% among 12–16 year old children. Body mass index (BMI) was non significantly higher among asthmatics compared to nonasthmatics.[14]

Asthma is one of those diseases that modern research has failed to ascertain a causation factor or element that can be targeted for management and control purposes.[15,16] Genetics and environmental elements have been cited as contributing factors in the development of asthma.[9,17-22] In the Gulf region, a study by Bener *et al*. (n = 1432) reported exposure to outdoor air pollutants as a contributing factor to the development of asthma among school children.[23] Another local study conducted on a sample size of 3204 children showed that family history of asthma outweighed other factors such as environmental factors in contributing to childhood asthma.[9] Similar findings were reported in another study in the UAE with a sample size of 406 children, ages 6–18 years.[24] Another UAE study reported family history and UAE nationality as predictors of asthma among adolescents and adults.[25] In Iraq, a study on 644 children, ages 6–12 years, reported family history, prematurity, crowding, low birth weight, and low parental education as risk factors for asthma.[26]

Asthma and Obesity

Obesity is another major public health concern that has gone rampant across the globe, whether among adults or children.[27-31] In Qatar, Rizk *et al*. reported a metabolic syndrome prevalence rate of 3.0%, and an obesity/overweight rate of 31.3% among children ages 6–12 years.[32] Mandeya and Al-Oballi Kridli list social norms, dietary practices, sedentary lifestyle, and lack of physical activity, as risk factors for obesity and overweight among children in Qatar.[33] The authors attribute these risk factors to the higher financial status among the population which has led many more to utilize a modern western lifestyle.[33] The rates of overweight and obesity they found when comparing the various studies in Qatar was comparable to other Gulf countries.[33]

A study from UAE reported a prevalence rate of 44% for metabolic syndrome, and a mean BMI of 35.3 ± 6.1, among 260 young obese participants.[34] An earlier study from the UAE as well, conducted on a sample size of 4381 children, ages 5–17 years, reported a prevalence rate of 21.5% for being overweight and a 13.7% for being obese.[35] A more recent UAE study reported an overweight and obesity rates of 14.7% and 18.9%, respectively, among 1541 children, ages 6–19 years.[28] Nahhas *et al*. reported asthma to be associated with obesity in both genders, but stronger among females, in a sample of Saudi children ages 6–8 years.[36]

While the link between the two diseases, asthma and obesity remain to be debatable and subject to future scrutiny,[37-40] A plethora of studies have attempted to shed the light on the aforementioned. Among adults, a meta-analysis reported a dose-response relationship between asthma incidence and weight in both genders.[41] In a similar fashion, children with a BMI equivalent to the 85th percentile or greater were found to be at risk of developing asthma among 10 years old from both genders,[42] and 2–3-year-old boys.[43] Another study reported a positive correlation between obese children and asthma among 2–5 and 9–13 years old.[44] A meta-analysis which covered six studies reported that an increased risk of developing asthma among obese children when compared to nonobese children. In addition, a significant dose response was observed for BMI and asthma incidence.[45]

Michelson *et al*. showed that asthma severity was associated with a higher BMI, as well as higher levels of the inflammation marker C-reactive protein.[46] An earlier Brazilian study reported a positive association between asthma symptoms/severity and obesity, among children ages 13–14 years.[47] On the contrary, Ross *et al*. reported no difference between obese and nonobese asthmatic children, in regards to asthma severity, airway obstruction, and inflammation.[48] In a similar fashion, a negative association was found between BMI and asthma severity in another study.[49] Others investigated the relationship between weight and asthma in regards to indoor pollutant exposure and showed that obese or overweight children had more symptoms when exposed to fine particles compared to normal weight children.[19] A systematic review by Ali and Ulrik showed that asthma and obesity have similar or overlapping risk and causation elements such as genetic factors, physical activity, and nutrition.[50]

Pathophysiology

Not much is known in regards to the mechanisms behind obesity and asthma.[40] Ali and Ulrik listed epigenetic, hormonal, environmental, genetic, mechanical, and immunological factors as possible mechanism routes tying the two diseases.[50]

Lang reported that obesity is usually associated with factors that play a role in the development of asthma.

Such include obesity comorbidities, airway narrowing, and inflammation.[21,39] The latter induces an amplified response in the lungs due to the production of adipokines by fatty tissue.[51] Others reported that obese asthmatics have more comorbidities and lower lung functions when compared to normal weight asthmatics.[52] While von Mutius showed that BMI affects asthma either by mechanical or inflammatory means and not by allergic airway inflammation.[53] A significant association was found between obesity and asthma among children and adolescents in the NHANES study, where non atopic asthma had a stronger association when compared to atopic asthma.[54]

Two phenotypes have been reported as related to asthma and obesity: early onset and late onset.[55,56] Early onset is characterized by the following features: onset begins in an earlier age, increased atopy or allergens, airway epithelium production of cytokines including Th2 and weight loss reduces exacerbations.[55] The late onset type is characterized by the following features: mechanical restriction of tidal volume, increase in metabolic inflammation markers, decrease in eosinophilia and Th2, weight loss improves airway closure, corticosteroids decrease exacerbations, severity increases with weight gain, and weight loss reduces exacerbations.[55] Baffi *et al*. grouped the implications of excess adipose tissue among obese asthmatic patients into mechanical/physiological and immune/metabolic implications. The mechanical involves lung function and changes in airway, while the immune/metabolic implications involve immune and metabolic functions.[57] In the first type of asthma, obesity alters the allergic component, while in the second obesity alters the lungs itself.[56]

Numerous studies commented on the management/treatment options of obese asthmatic patients which revolve around avoiding triggers, treating comorbidities, and pharmacotherapy.[55,57-60] These studies agree that obese asthmatics are less responsive to therapy than others.[57-60] Others have reported on the management approaches of the obesity aspect for obese asthma patients which are mainly lifestyle oriented and include weight loss strategies, physical activity on regular basis, dietary approaches, and reduction of sedentary lifestyle patterns.[55,58,61] Furthermore, several studies have shown the effectiveness of behavior modification attempts in inducing weight loss among obese non asthmatic children.[62,63] A randomized clinical trial conducted on 8–17 years old obese asthmatic children showed improvements in static lung function and asthma control after a 10 week diet-induced weight loss regimen.[61] Others have reported on the positive role that physical activity plays in reducing both asthma severity and incidence.[15,64] However, the overall picture in regards to the role of physical activity on pediatric asthma remains subject to further scrutiny.[58,65-67] In all, Rastogi *et al*. suggested that the most influential factor that aids in reducing obesity-related asthma morbidity comes through focusing on the obesity aspect of the illness, both onset and progression.[68]

Based on the preceding, it becomes of dire need that novel therapeutic/management options be discovered and sustained by future research. One of the possible promising routes is managing a better understanding of the role of sphingolipids.[69-71]

Role of Sphingolipids

Sphingolipids are an integral part of cell membranes with various functions[69,72] including molecule signaling,[73-75] regulation of cell growth and death, migration,[74] and role in inflammation.[74,76] Sphingolipids have been reported to play a role in the pathogenesis of asthma[18] by inducing airway remodeling, smooth muscle contractility,[77] and changes in inflammatory cell functioning.[77,78] The mechanism that these lipids influence inflammation can occur through different routes.[69]

Furthermore, the orosomucoid-like (ORMDL) proteins have been reported to play a role in the sphingolipid pathway involving the synthesis and homeostasis of sphingolipids.[18,73-75] They are responsible for regulating the enzyme serine palmitoyl CoA transferase (SPT) which initiates the production of sphingolipids.[22,75] In addition, they play a role in controlling the amount of ceramide inside cells.[16,79] Research by Worgall *et al*. showed that decrease in SPT induces airway hyperreactivity without inflammation, a decrease in lung sphingolipids, and alteration of magnesium lung homeostasis.[80] Russo *et al*. reported that the synthesis of sphingolipids becomes interrupted in adipose tissue as a result of the influx of fatty acid.[71] Worgall reported that ORMDL3 is tied to asthma by its inhibition of the synthesis of sphingolipids.[81]

ORMDL3 is of particular interest as several studies have associated genetic variances of ORMDL3 with asthma.[18,22,82-86] More specifically, the genetic variant in the 17q21 haploblock, which modifies the expression of ORMDL3, has been shown to be linked to increased risk of developing asthma.[75,82,87-89] Others confirmed the role of locus 17q21 but in relation to genes other than the ORMDL3.[90] Moreover, 17q12-21 polymorphisms have been linked to asthma in numerous studies.[91-95] Within the 17q21 region, several studies reported single-nucleotide polymorphism (SNP) rs2872507, which modulates the ORMDL3 gene expression, to be significantly correlated with asthma.[16,96,97] Others reported the same, but in relation to SNP rs8067378,[82] and rs7216389.[82,98]

While the above has been studied in relation to asthma, not much has been done in relation to obesity-induced asthma. That being said, further work would need to focus on studying ORMDL3, sphingolipids, in relation to obesity-induced asthma in specific. Future directions revolve around the following themes: (a) the degradation of ORMDL, as well as the mechanisms involving the expression of ORMDL on asthma[75,99] (b) identifying a direct link between ORMDL3 to SPT activity[22] (c) tailored therapeutic and prevention strategies based on one's genotype and environmental exposure.[100]

Conclusion

In all, the emerging evidence of the involvement of sphingolipids in both, the initiation and maintenance of inflammation, may open the door to new therapeutic approaches involving novel agents.[69,70,76,101] The same applies to the role of decreased *de novo* synthesis of sphingolipids described by Worgall *et al*.[80] As the number of asthma/obesity cases continues to rise, so does the dire need for more efforts directed toward creating new approaches of management. The literature cited here involving sphingolipids seems to be promising. On the population level, intensifying health education efforts in regards to nutrition and physical activity seem to be crucial to curb the pandemic phenomenon of obesity.

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Conflicts of interest
There are no conflicts of interest.

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