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Novel therapeutic strategies for adult obese asthmatics

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Synopsis

Asthma is a complex syndrome that affects an estimated 26 million people in the United States but gaps exist in the recognition and management of asthmatic subgroups. In this manuscript, we propose alternative approaches for future treatments of adult obese asthmatics that do not respond to standard controller therapies of inhaled corticosteroids, bronchodilators, and anti-leukotriene drugs. We draw parallels between seemingly disparate therapeutics through their common signaling pathways. Specifically, we describe how metformin and statins can potentially improve airway inflammation and suggest supplements, for example L-arginine, which can be used in combination with conventional therapies. A move towards more targeted therapies for asthma subgroups is needed. These therapies address asthma and the comorbidities that accompany obesity and metabolic syndrome to provide the greatest therapeutic potential.

Keywords

Severe asthma; L-arginine; Nitric oxide; Metformin; Statins; Obesity

Introduction

The adult obese patient with worsening asthma despite appropriate controller drug therapy is extraordinarily complicated to manage and treat. For example, consider a 40 year old woman with a medical history notable for adult-onset, non-allergic asthma, obesity, diabetes mellitus, and sleep apnea whose course has been punctuated by several emergency

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department admissions in the past year. She already requires continuous oral prednisone and four drug therapy for her asthma. How should such a patient be evaluated and treated for the foreseeable future? While asthma is a complex syndrome that affects an estimated 26 million people in the United States, there are gaps in the recognition and management of asthmatic subgroups asthmatics. Extrapolating results from short-term, randomized clinical trials to a broad, heterogeneous population of asthmatics treated in community settings is fraught with difficulty and can result in repeated trial-and-error therapeutic interventions. We still lack the ability to recognize different asthma phenotypes, to adapt and integrate care when comorbidities exist, and adopt new treatments. While published guidelines, including the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report-3 (EPR-3) and the World Health Organization (WHO) Global Initiative for Asthma (GINA) present step-wise evaluation and therapeutic recommendations for chronic persistent asthma management, they do not outline coherent plans for the care of adult-onset, obese asthmatics.

In this manuscript, we propose alternative approaches that may prove to be future treatments for adult obese asthmatics that do not respond to the standard controller asthma therapies of inhaled corticosteroids, bronchodilators, and anti-leukotriene drugs. We draw parallels between seemingly disparate therapeutics through their common signaling pathways (Figure 1). Specifically, we describe how metformin and statins potentially improve airway inflammation through activation of adenosine monophosphate activated protein kinase (AMPK), a key regulator of cellular metabolism and energy production, and through their effects on nitric oxide (NO). In addition, we discuss nutritional supplements, such as L-arginine, omega-3 fatty acids, and other minerals and vitamins that are currently studied and may potentially be used in combination with conventional therapies.

Metformin, insulin resistance, and asthma

The metabolic syndrome with insulin resistance may characterize subsets of asthmatics more than we recognize. The relationship between obesity, insulin resistance and asthma has been clearly established, however the mechanisms by which they influence the pathogenesis of asthma is unclear¹. Metformin is a biguanidine class oral anti-diabetic drug used to treat type 2 diabetes and insulin resistance. Although metformin reduces glucose production in the liver through inhibition of gluconeogenesis, the precise mechanisms are unknown and it may have differing modalities in different cell types. Metformin may indirectly activate AMPK by increasing AMP:ATP ratios through mild but specific inhibition of the mitochondrial respiratory chain complex I in hepatocytes, skeletal muscle, endothelial cells, pancreatic B-cells and neurons². Peroxynitrite, generated by inhibition of complex I, activates AMPK through a c-Src and PI3K-dependent pathway in bovine aortic endothelial cells³. Metformin also directly activates AMPK the inhibitions of AMP deaminase in isolated skeletal muscle⁴. In the lung, metformin up-regulates AMPK expression and activity and diminishes pro-inflammatory cytokine secretion in human bronchial epithelial cells, downregulating IκK activity and inhibiting NF-κB⁵.

Obese asthmatics are less responsive to typical asthma controller therapy possibly because of contributing factors such as an increased pro-inflammatory environment that blunt the

efficacy of treatment⁶, yet there have been studies that have shown no difference in induced sputum eosinophils, a biomarker of airway inflammation, between obese and lean asthmatics^{7,8}. However, in a study of obese and lean asthmatics by Desai et al, there were similarities in sputum eosinophil counts between the two groups, but an increase in interleukin-5 (IL5), a mediator of eosinophil activation, in the sputum and increased eosinophil accumulation in the submucosal layer of the obese asthmatic group⁹.

The results from a study utilizing a high fat-diet-induced obese mouse model (male C57BL/6/J) of allergic airway inflammation are in agreement with patient observations. While eosinophil numbers in the bronchoalveolar lavage (BAL) from allergen-challenged, obese mice were decreased compared to their lean counterparts, the levels of infiltrated eosinophils in the lung tissue were higher in the obese mice. Treatment of these allergen-challenged obese mice with metformin reduced tissue eosinophil infiltration and increased the number of cells in the BAL fluid suggest differing modes of regulation for eosinophil migration and function between obese and lean asthmatics, possibly through decreased NF- κ B activation¹⁰. Another mouse study utilizing lean BALB/C female mice demonstrated that metformin decreases eosinophilic inflammation, peribronchial fibrosis and mucin secretion coupled with increased ratios of activated phospho-AMPK to total AMPK and decreased oxidative stress as measured by the ratio of reduced to oxidized glutathione¹¹.

Metformin can also increase nitric oxide synthase 3 (NOS3, endothelial NOS, eNOS) production of NO and improve endothelial function through AMPK-dependent positive regulation of NOS3 activity and inhibition of NOS3 negative regulators. Treatment of endothelial cell lines and mice with metformin increases AMPK dependent NOS3 phosphorylation at the regulatory site Ser 1177/1179 and NO production¹²⁻¹⁴. NOS3 activity is negatively regulated through phosphorylation of Thr495 by protein kinase C- β (PKC β), which is up-regulated in human asthmatics and patients with insulin resistance¹⁵. Pharmacologic inhibition of PKC β in endothelial cells freshly isolated from diabetics decreases basal levels of Thr495 phosphorylated NOS3 and improved insulin-mediated signaling of NOS3. Overall NOS expression and activity is also reduced in murine models of allergic inflammation and human asthmatics¹⁶⁻¹⁸. Overexpression of NOS3 in a mouse model of allergic asthma attenuates airway inflammation and airway hyperresponsiveness; possibly acting through increased levels of S-nitrosothiols in the lung or decreased interferon- γ (IFN- γ), IL5 or IL10¹⁹. Further studies are necessary to uncover whether NOS3 could be regulated by metformin in models of asthma or asthmatics.

These findings suggest that introducing metformin in conjunction with standard asthma controller therapy could prove beneficial for outcomes in obese asthmatics by modulation of NOS3 activity or other AMPK-dependent metabolic signaling pathways.

Asthma, the mevalonate pathway, and the statin drugs

The statin class of drugs inhibits the enzyme hydroxymethylglutaryl (HMG)-CoA reductase (HMGCR), which is the rate limiting step in cholesterol and isoprenoid biosynthesis in the mevalonate (MVA) pathway²⁰. Isoprenoids include pyrophosphate lipid molecules (e.g. farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP)) that are necessary

for post-translational modification of numerous intracellular proteins including small G-proteins, or GTPases (e.g. Rho, Ras, and Rac). GTPases require prenyl tethering to the membrane in order to maintain proximity to the appropriate transmembrane receptors and signaling transduction machinery. Limiting the availability of the isoprenoid substrate reduces the total amount of GTPase available for activation, potentially dampening cytokine and chemokine signal transduction and the responses that lead to cellular hypertrophy and inflammation²¹.

Statins' effect on isoprenylated GTPases is a mechanism that may be of particular interest in targeting the obese asthmatic population because translational studies in obese (ob/ob, leptin -/-) mice exposed to allergen have indicated increased activity of the GTPase, RhoA, in airway epithelial cells and airway smooth muscle. Increased RhoA activity has been implicated in airway smooth muscle hyperreactivity and hypertrophy. Geranylgeranylpyrophosphate synthase (GGPPS) expression, the enzyme upstream of FPP and GGPP synthesis, is also increased in obese (ob/ob) mice. Because RhoA requires prenylation by GGPP for activation, the use of statins to manipulate the MVA pathway may have further implications for airway hyperreactivity and remodeling, two key features in asthma^{22,23}.

Statins may also regulate L-arginine metabolism and NO production. In addition to being induced by Th2 cytokines, IL-4 and IL-13, arginase 1 or 2 expression can be induced via a RhoA/RhoKinase (ROCK) mediated pathway. Endothelial cell RhoA/ROCK can be indirectly activated by reactive oxygen and nitrogen species such as H₂O₂ and ONOO⁻, via protein kinase C. Insulin resistance and diabetes increases the production of these oxidative species through several sources, including uncoupled mitochondrial complex I, mitochondrial NOS (mtNOS), and NOS3.

RhoA-dependent activation of Rho kinase (ROCK) increases arginase 1 expression in aortas and livers of streptozotocin-induced diabetic rats. Arginase activity depletes intracellular and plasma L-arginine, further reducing endothelium-derived NO production and promoting additional NOS uncoupling. However, this effect on endothelial NO production is reversible with administration of statins, ROCK inhibitor Y-27632, or L-citrulline²⁴⁻²⁶. The inhibitory effect of simvastatin on arginase expression and activity has also been observed in the airways of mice, in a model of allergic inflammation, though its mechanism of action has not been determined, as statins also inhibit the expression of IL-13 in airway epithelial cells^{27,28}. Statin-dependent reduction in circulating ADMA further aids production of NO by the NOS enzymes and reduces NOS uncoupling. Thus, simvastatin (and potentially other statins) can function to improve dysfunctional NO metabolism in asthmatic, inflamed lungs.

Statins and AMPK collectively engage in crosstalk that regulates NOS3 activity. Treatment of human endothelial cells with statins result in time and dose dependent increases in phosphorylated AMPK, followed by AMPK-dependent phosphorylation of NOS3 at Ser1177²⁹. These results were confirmed in the aorta and myocardium of mice orally administered atorvastatin³⁰. Independent of statin administration, AMPK activation also inhibited HMCGR by phosphorylation of the Ser-871/Ser872 site in cultured rat hepatocytes and human endothelial cells^{31,32}.

Statins applied to murine models of allergen-induced airway inflammation reduce inflammatory cell influx, Th2 cytokine production, ADMA levels, airway hyperreactivity, and airway remodeling^{33–36}. Specific inhibition of geranylgeranyltransferase (GGTase) by GGTI-2133 reduces airway hyperreactivity, whereas FTase inhibition increases inflammation and airway hyperreactivity. This indicates that the effect of statins on airway smooth muscle is dependent upon reduced isoprenylation of RhoA by GGPP and the therapeutic effect of statins, at least in allergic airway disease, is through its effects on geranylgeranylation, ie RhoA, not farnesylation³⁷.

In our severe asthma clinics, we found that female-predominant severe asthmatics with a mean body mass index (BMI) of ≥ 30 benefited from statin treatment. Median statin use for one year added to standard inhaler treatment, was associated with a higher asthma control test (ACT) score indicating improved asthma symptoms³⁸. As this is the only study we are aware of that evaluates statin use in obese severe asthmatics, data are limited and clinical application is precluded absent randomized clinical trials to test this observation.

Although data are limited in the obese asthmatic, the above references support the biological plausibility for the role of MVA metabolism and statins in mitigating asthma in this subgroup. The nonatopic adult-onset asthmatic, especially an individual with the confounding characteristics of obesity and metabolic syndrome tend to be more severe and refractory to current therapies. These additional comorbidities contribute to systemic inflammation, insulin resistance and reduced lung function originating from inflammation and mechanical stress derived from increased visceral mass. Statins may address many of these comorbidities; statins reduce pro-inflammatory signaling by RhoA/ROCK, increase NO production and reduce the production of oxidative species by uncoupled NOS enzymes, and activate AMPK, reversing insulin resistance. Therefore, we believe that future experiments in animal models and clinical trials with adult-onset asthmatics with obesity should evaluate the potential therapeutic role of statins and/or statin with L-arginine combination treatment.

L-arginine and asthma

L-Arginine is a substrate in protein synthesis, a molecular component for the conversion of ammonia to urea in the urea cycle and the substrate in a number of diverse enzymatic pathways, including the synthesis of nitric oxide (NO), creatine, agmatine, ornithine, glutamate, proline, polyamine and dimethylarginines, including asymmetric dimethylarginine (ADMA).

Dietary supplementation of amino acid formulations is common practice among healthy individuals and those with chronic illnesses. The semi-essential amino acid, L-arginine has been reported to confer beneficial effects in various small studies of surgery, trauma, and infectious and non-infectious inflammation. Direct infusion of L-arginine to the peripheral or pulmonary arterial beds, has been tested in acute and chronic disease states, including coronary heart disease, pre-eclampsia and myocardial infarction, because of its bronchodilator and vasodilator actions^{39–41}. L-arginine can also be used as a primary therapeutic in sickle cell disease patients with acute chest syndrome, where deficiency in

NOS3-derived NO contributes to red cell sickling and vasoconstriction⁴² augmenting NO production and improving outcomes in this disease.

Factors that regulate the output of NO in the airway, endothelium and adipose tissues of asthmatics include the concentration of L-arginine, the metabolic precursor of NO, and asymmetric dimethylarginine (ADMA), an endogenous NOS inhibitor. NO is primarily derived from the oxidative deamination of L-arginine and O₂ into NO and L-citrulline by the NOS family of enzymes. This family includes NOS1 (neuronal NOS, nNOS), NOS2 (inducible NOS, iNOS) and NOS3 (endothelial NOS, eNOS). NOS is also present in mitochondria and referred to as mtNOS but is a variant of NOS1⁴³. Depletion of L-arginine can cause the NOS isoforms to produce superoxide ($\bullet\text{O}_2^-$) in a process referred to as “uncoupling” that results in the transfer of an electron from NADPH to oxygen instead of L-arginine^{44,45}. NO and superoxide ($\bullet\text{O}_2^-$) can combine to form peroxynitrite (ONOO⁻). Thus, reduced L-arginine availability to NOS enzymes can have the double effect of reducing NO output and producing oxidative and nitrosative species.

Initial studies using DNA microarray analysis in mouse models of allergen-induced inflammation identified the arginase enzymes as potential “asthma signature genes.” Arginase 1 and arginase 2 catalyze the hydrolysis of L-arginine to ornithine and urea. Increased arginase activity in asthmatics and particularly obese asthmatics is important both, for the downstream products of arginase activity, including proline and polyamines which contribute to airway remodeling and cellular proliferation, and its capacity to regulate the availability of L-arginine to the NOS enzymes by substrate depletion. Analysis of lung tissue of asthmatic subjects confirmed that increased arginase 1 expression correlated with additional effects of increased serum arginase activity and decreased plasma L-arginine compared to controls^{17,46}. Further analysis based on patient subpopulation revealed that serum arginase 1 level in nonatopic asthmatics was further amplified compared to atopic asthmatics.

Animal models of allergic airway inflammation have shown that inhibition of arginase ameliorated lung inflammation, reduced airway and peribronchial eosinophilia, and decreased production of Th2 pro-inflammatory cytokines, IL-4 and IL-13, and eotaxins. Arginase inhibition reduced characteristics of airway remodeling, including goblet cell hyperplasia, airway smooth muscle proliferation, and subepithelial collagen accumulation. Airway hyperreactivity and airway maximal contraction were also reduced⁴⁷⁻⁵⁰. In lieu of arginase inhibition, supplementation with oral or aerosolized L-arginine produced comparable results indicating that the driving force for these improvements was maintaining adequate levels of L-arginine⁵¹.

Increased arginase activity in the obese, nonatopic asthmatic subpopulation may be derived from sources beyond the lung. Obese subjects have heightened expression of arginase 1 (4.5 fold) in circulating mononuclear cells compared to normal weight subjects⁵². Exposure to high levels of insulin causes endothelial cells to have increased arginase II activity that leads to the uncoupling of NOS3 and increased inflammatory cell adhesion via soluble intercellular cellular adhesion molecule 1 (sICAM). Abrogation of these effects can be achieved through arginase inhibition⁵³. Hyperglycemic rats have increased arginase 1 and

arginase 2 expression in muscle arteriole beds which inhibit the vasodilation resulting from increased flow. Inhibition of arginase reverses the arteriole flow impedance⁵⁴. In these models, the beneficial effects of arginase inhibition include mitigation of hypertension, insulin resistance and systemic inflammation.

In an ongoing phase II study (#NCT01841281), we are examining a subset of adult severe asthmatics, who are predominantly overweight/obese and female. The go-to biomarkers that are indicative of asthma do not necessarily apply for this obese, late-onset population, as this subset is nonatopic (low circulating IgE) and exhibit low exhaled NO which inversely correlates with BMI and deceptively low sputum eosinophilia⁵⁵. Shifts in NO metabolism are indicative of the vascular dysfunction relating to obesity and the changes in exhaled NO may represent corresponding changes in the lung⁹. We hypothesize that this subset of asthmatics will respond favorably to L-arginine supplementation in addition to their standard therapy because in obese asthmatics, the age of asthma onset appears to dictate how they respond to controller therapies, whether their obesity is causative or a comorbid condition.

ADMA and phosphodiesterase inhibition

NO production by the NOS enzymes can be inhibited by endogenous competitive inhibitor, asymmetric dimethylarginine (ADMA), which can uncouple NOS enzymes, producing superoxide. ADMA is derived from the posttranslational modification of L-arginine by protein-arginine methyltransferase (PRMT) type 1⁵⁶. The lung is a major source of protein bound asymmetrical dimethylarginine with > 3 fold higher levels of bound ADMA compared to heart, kidney or liver tissue, and an estimated 1.4% of arginine residues present in lung proteins asymmetrically dimethylated⁵⁷. Proteolytic degradation of these proteins releases methylarginines to the free amino acid pool^{58,59} where they can be enzymatically converted into L-citrulline and dimethylamine by the dimethylarginine dimethylaminohydrolase (DDAH) enzymes or excreted in the urine⁶⁰.

The lung arginine:ADMA ratio is significantly altered in asthmatics compared to non-asthmatics, with sputum ADMA inversely correlating to exhaled NO⁶¹. Increased plasma ADMA has been observed in numerous disease states, including pulmonary arteriole hypertension (PAH), chronic obstructive pulmonary disease (COPD), cardiovascular disease, and diabetes mellitus⁶¹⁻⁶³. The subgroup consisting of obese, nonatopic asthmatics, independent of other confounding metabolic risk factors, may have significantly increased levels of plasma ADMA and reduced L-arginine:ADMA ratio due to obesity alone⁶⁴. Other potentiating factors such as insulin resistance, even in normotensive individuals, also correlate with increased ADMA^{65,66}.

Mouse models of allergic airway inflammation have given further insight into the role of ADMA metabolism in disease. Allergen exposed mice, like human asthmatics, have significantly increased levels of ADMA in their serum and BALF⁶⁷ and further examination revealed increased synthesis of ADMA in alveolar epithelial cells and macrophages and reduced expression of ADMA catabolic enzyme, DDAH2 in airway epithelial cells compared to control mice⁶⁷. Altering ADMA degradation by overexpressing DDAH1

reduced markers of inflammation including eosinophilia, Th2 cytokines IL-4 and IL-13, arginase, and IgE⁶⁸.

DDAH2 expression is regulated by intracellular cAMP concentration via protein kinase A (PKA)-dependent phosphorylation of the transcription factor, cAMP response element-binding (CREB) protein. PKA activation is mediated by cAMP binding to PKA-regulatory subunits, resulting in the release of active PKA, which can phosphorylate numerous targets, including CREB which require phosphorylation to facilitate binding to the CRE domains upstream of the human DDAH2 gene. Inhibiting cAMP to AMP conversion through the use of phosphodiesterase (PDE) 3/4 inhibitors, increases catabolism of the endogenous NOS inhibitor, ADMA, and increasing NOS3 activity in endothelium and alveolar macrophages^{69,70}. Activation of PKA by PDE4 inhibitors may also target RhoA pathways. PKA-dependent RhoA phosphorylation inhibits RhoA activation and phosphorylation of guanine nucleotide dissociation inhibitor (GDI) by PKA enhances GDI binding to RhoA, deactivating it⁷¹. As the Rho/ROCK pathway also regulates expression of arginase, this pathway may further alleviate the depletion of L-arginine and NOS uncoupling^{26,72}.

PDE4 inhibitors tested in murine models of chronic allergic airway inflammation, reduce airway eosinophilia, inflammatory cell recruitment, matrix metalloprotease (MMP)-9 activity, fibroblast migration and hypercontractility and subepithelial collagen deposition^{73,74}. For patient use, second generation PDE4 inhibitors for treatment of COPD have completed multiple randomized clinical trials, noting improvement in prebronchodilator FEV1 with limited side effects including nausea, diarrhea, headaches and weight loss. In combination with other asthma control therapies, the use of PDE4 inhibitors to treat severe, obese asthmatics, especially those with measurably heightened plasma ADMA levels may provide therapeutic benefits.

The potential treatment options reviewed in this section are united by the common principle that decreasing NOS uncoupling has significant clinical benefit in the subgroup of obese, nonatopic asthmatics in which the compounding factors of obesity, endothelial dysfunction, metabolic syndrome, and lung inflammation all contribute to perpetuating NOS dysfunction. These treatments approach the issue of deficient NO production from numerous directions. Supplementation with L-arginine bolsters the L-arginine:ADMA ratio, effectively outcompeting the NOS inhibitor molecule based on enzyme saturation and directly addressing the issue of limited substrate uncoupling NOS enzymes. Arginase inhibition indirectly produces the same effect, increasing both intracellular and plasma L-arginine availability and increasing the L-arginine:ADMA ratio. Finally, inhibition of PDE4 increases ADMA catabolism by decreasing cAMP turnover and subsequently increasing expression of DDAH2. The uncoupling of NOS by ADMA and/or substrate depletion results in the production of oxidative and nitrosative species in the airways, inflammatory cells, endothelial cells and adipose tissue, contributing to the progression of disease.

Vitamins and omega-3 polyunsaturated fatty acids: Other potential consideration in asthma and obesity

The bioavailability of fat soluble vitamins A, D and E in asthmatic patients has not been intensely explored but it can have an impact on obese asthmatic patients as body fat likely acts as a reservoir for storage of fat soluble vitamins. Although more research must be done to evaluate the adequate status of these vitamins in obese asthmatic patients, a summary of these vitamins and omega-3 polyunsaturated fatty acids and their impact on asthma is included.

Recent epidemiological studies point to an inverse relationship between vitamin A levels and severity of asthma^{75,76}. Vitamin A affects a broad array of immune responses through retinoic acid (RA), its major oxidative metabolite. Previous data indicates that vitamin A deficiency can impair immune function, whereas excess RA induces inflammatory disorders. Vitamin A or RA limits the differentiation of naïve T cells to T helper cell (Th)1 by reducing IL-12, INF- γ , and NF- κ B signaling, resulting in the increase of Th2 mediated processes. RA can oppose Th17 cell commitment by increasing TGF- β signaling and reducing the expression of IL-6 receptor, while excess vitamin A results in the induction of different subsets of Foxp3+ regulatory T (Treg) cells and their mediated processes⁷⁷. RA has also been shown to inhibit eosinophilic and basophilic differentiation and regulate IgA and IgG production in response to T cell-dependent antigens. Results from studies in mice and rodents suggest strongly that adequate vitamin A status is the key for maintaining a balance of well-regulated T-cell differentiation and function.

The clinicaltrials.gov website cites more than twenty-five asthma studies that are ongoing with vitamin D. Vitamin D supplementation and asthma has been studied for years and the conflicting findings are likely due to differences in study design, sample size, and method for assessing Vitamin D status through measuring levels of 25-hydroxyvitamin D (25(OH)D)^{78,79}. Potential beneficial effects of 1,25-dihydroxyvitamin D (1,25(OH)₂D₃ (calcitriol) synthesized by bronchial epithelial cells include increasing antimicrobial peptide production by facilitating toll-like receptor (TLR) signaling, regulation of the inflammatory response, airway remodeling, and respiratory muscle function. Circulating 25(OH)D can suppress IL-17 and IL-4 mediated expression of IL-13 and shift the Th1/Th2 balance towards Th2 dominance. These controversial functions may be due to the direct effect of Vitamin D on CD4+ T-cells by promoting an IL-10 secreting population of Treg cells⁷⁹. In addition, supplementation of calcitriol has been associated with decreases in body fat mass and improved insulin sensitivity in obese people⁸⁰. Despite supplementation of Vitamin D, large populations remain vitamin D deficient. This could apply to the adult obese asthmatic population, since the bioavailability seems to be decreased with increased body fat mass.

Whereas vitamin A and D exert most of their effects through the binding of nuclear receptors and regulating of gene transcription, vitamin C and E act as potent antioxidants.. Deficiencies in vitamin C and other plasma antioxidants are associated with lung disease and case-control and cross-sectional studies suggest that vitamin C supplementation may decrease asthma severity and exacerbation frequency through antioxidant mechanisms⁸¹. Vitamin E supplementation in asthmatics has been shown to help stabilize lung epithelia

membranes and protect against ozone-induced membrane injury by interrupting lipid peroxidation⁸². Increased levels of vitamin E are associated with less allergic skin sensitization, lower IgE secretion and suppressed neutrophil recruitment. Vitamin E supplementation in animal studies improves vasodilation and decreases oxidation of LDL through increased antioxidants levels in the vasculature. However, randomized controlled clinical trials of supplemental vitamin E in asthmatics have not consistently demonstrated that higher intake of vitamin E reduces asthma events⁸³.

Several clinical studies have been designed to test the hypothesis that diets supplemented with the omega-3 polyunsaturated fatty acids (n-3 PUFA), eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA), the major component of fish oil, ameliorates the development of asthma or improve asthma outcomes⁸⁴. It is noteworthy in the context of asthma, in the obese patient subgroup, intervention trials with n-3 PUFA show beneficial effects in patients with type 2 diabetes and cardiovascular disease^{85,86}. EPA impacts inflammatory signaling by competitively inhibiting enzymatic pathways that convert arachidonic acid (AA) to potent pro-inflammatory 4-series leukotrienes (LT) and 2-series prostaglandins (PG), mediated by 5-lipoxygenase (5-LO) and cyclo-oxygenase (COX). EPA may also inhibit IgE production through COX⁸⁷. In addition, EPA is metabolized to less inflammatory 5-series LTs and 3-series PGs and potent anti-inflammatory mediators, resolvins of the E-series (RvE1 and Rv3). The effects of DHA are distinct from EPA; DHA can decrease transcription of AA metabolizing enzymes, such as COX-2, by inhibiting NF- κ B activation. DHA can also be converted into anti-inflammatory mediators, including the resolvins of the D-series (RvD1, RvD2, RvD3, and RvD4), docosatrienes, and protectins⁸⁸. Results of the studies testing effects of n-3 PUFA on asthma pathogenesis over the past twenty years have been conflicting and at least one meta-analysis determined that n-3 PUFA does not affect asthma outcomes⁸⁴. However, there is a consensus that the total number of subjects in these trials is insufficient to make firm conclusions about the effects of the supplements.

Future Considerations / Summary

Controller drug therapies for asthma may partly or wholly ineffective in adult obese, nonatopic asthma patients, leaving them poorly controlled and exposed to adverse drug side effects, such as relative adrenal insufficiency, osteoporosis, and more frequent respiratory viral infections. One approach to therapy does not fit all and physicians must demonstrate a willingness to try several treatment alternatives. We recommend that asthmatic patients not appropriately responding to controller drug therapy be reevaluated. Adult obese, non-allergic asthmatics may have concomitant conditions that potentiate systemic inflammation; in turn, they may respond to treatment targeted at these associated conditions. Patients with the metabolic syndrome, hypercholesterolemia, and diabetes treated with either metformin or the statin drugs may find benefit for their asthma as well as their metabolic derangements. While firm recommendations cannot be made until further studies are performed, these medications, L-arginine, omega-3 fatty acids and other nutritional supplements are exciting considerations for future treatment of asthma. A move towards more targeted therapies for asthma subgroups is needed, and biologically, these therapies account for and treat the comorbidities associated with the obese, nonatopic asthmatic.

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KEY POINTS

1. In the future, treatment regimens for obese, adult asthmatics may include several interventions that interfere with pathways common to several metabolic and nutritional disorders.
2. The diabetic drug, metformin, could decrease inflammatory mediators of asthma by improving insulin sensitivity and altering adenosine monophosphate activated protein kinase (AMPK).
3. The cholesterol lowering class of medications, statins, could have beneficial effects on both airway inflammation and structural remodeling in asthma.
4. L-arginine supplementation may benefit a subset of severe asthmatic patients with impaired nitric oxide synthase function in the lung.

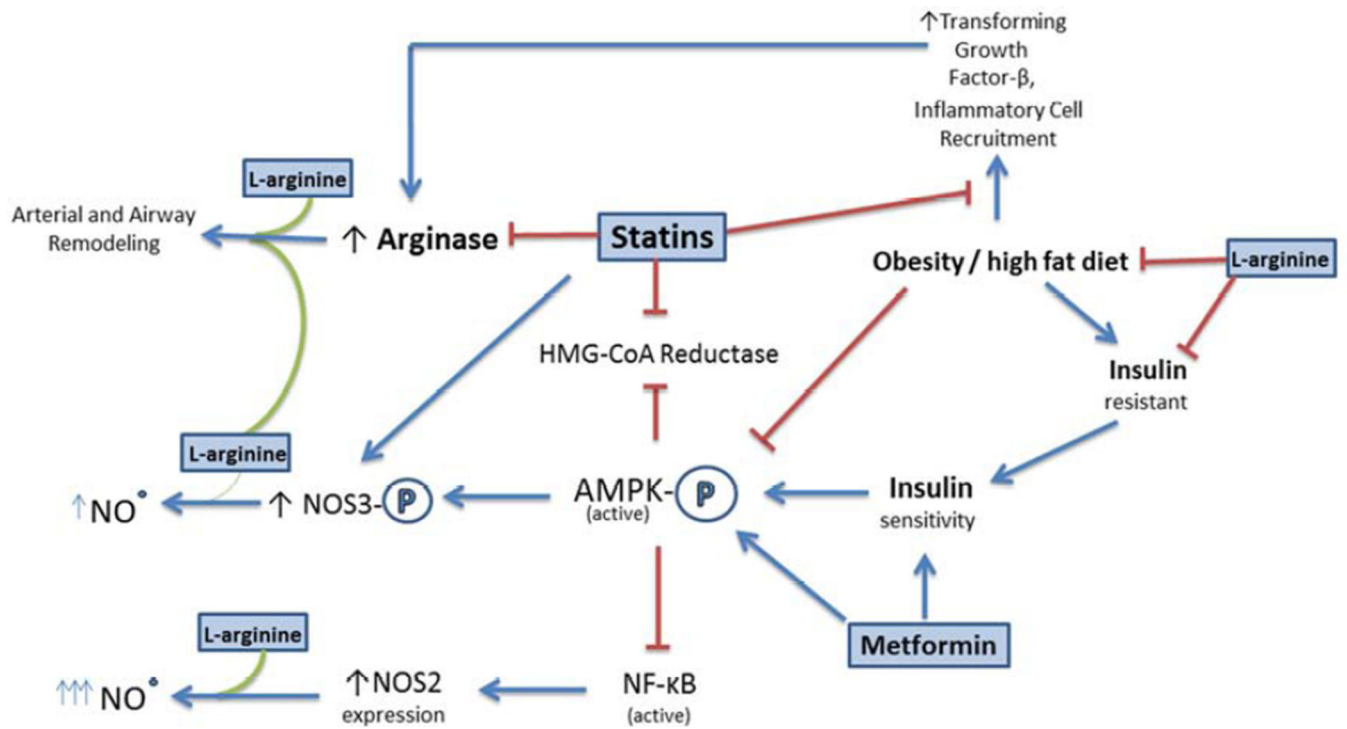


Figure 1.

Potential therapeutics for obese, adult asthmatics described in this review modulate pathways common to several metabolic and nutritional disorders. This allows for the treatment of several comorbidities by targeting their common dysfunction as opposed to individual symptoms. Direct targets include AMPK, which regulates numerous cellular metabolic pathways involved in energy storage and NOS3, which modulates vascular and bronchial smooth muscle tone.