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Dietary interventions in asthma

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ABSTRACT:

Asthma is a chronic inflammatory disorder of the airways. The inflammatory response in asthma is heterogeneous. Allergen specific responses lead to activation of the acquired immune system, via a predominantly IL-5 mediated, eosinophilic pathway. Stimuli such as viruses and bacteria activate the innate immune system, via a predominantly IL-8 mediated, neutrophilic pathway. Asthma has also been demonstrated to involve a systemic inflammatory component.

Glucocorticoids are the predominant pharmacological treatment used to control inflammation in asthma. However, compliance with medications can be compromised due to patient concerns about side effects. Hence dietary interventions that target the inflammatory response in asthma have great potential.

Various aspects of dietary intake are known to modulate inflammation. Saturated fatty acids can induce an inflammatory response via activation of pattern recognition receptors. Omega-3 fatty acids can be anti-inflammatory, *via* mechanisms such as modification of eicosanoid production. Antioxidants can have anti-inflammatory effects as they scavenge free radicals, preventing activation of transcription factors including NF- κ B. Chronic excess energy intake can lead to obesity, which augments inflammation due to the release of inflammatory mediators by adipose tissue. Here we review the role of these dietary components in asthma.

Key Words: asthma, antioxidants, fatty acids, obesity, inflammation

INTRODUCTION

Asthma is a respiratory disease characterised by variable airflow obstruction that is often reversible, mucus hypersecretion and airway hyperresponsiveness (AHR) [1]. Asthma involves an inappropriate triggering of the T helper (Th)2 immune response, leading to interleukin (IL)-5 mediated eosinophilic airway inflammation and the hallmark symptoms of asthma: wheeze, shortness of breath, cough, sputum production and chest tightness [2]. Inhaled allergens trigger this response, causing the release of histamine, leukotrienes (LT) and the Th2 cytokines IL-4, IL-5 and IL-13 [3]. IL-5 stimulates the infiltration and activation of eosinophils, which cause damage to respiratory epithelial tissue [3]. This dysregulated Th2 response leads to an eosinophilic pattern of airway inflammation in some individuals. There is also evidence of a neutrophilic pattern of airway inflammation, characterised by a persistence of asthma symptoms and AHR in the absence of airway eosinophilia [4]. Neutrophilic asthma is generally characterised by an older, non-atopic, predominantly female population who exhibit less airway reactivity and a later onset of disease [4]. Environmental exposures such as pollutants, ozone, viruses and bacterial endotoxins induce neutrophilic airway inflammation and airway obstruction [2]. Increased levels of toll-like receptor (TLR)4 and TLR2 in the sputum of those with neutrophilic asthma, compared with other asthma inflammatory phenotypes, indicate that the innate immune response is involved [5]. Lipopolysaccharide (LPS) may be involved in the aetiology of neutrophilic asthma, which activates TLRs, leading to the release of the proinflammatory mediators IL-8, tumour necrosis factor-alpha (TNF- α) and IL-1 β [5], which attract neutrophils to the site of inflammation in the airways [6].

An increase in systemic inflammation is also observed in asthma [7]. Recently, we demonstrated that plasma IL-6 and C-reactive protein (CRP) are elevated in adults with neutrophilic asthma compared with non-neutropilic asthma [8]. We have also demonstrated IL-6 is associated with poorer lung function and asthma control, and sputum neutrophilia [9]. An obese murine model demonstrated reduced AHR following administration of IL-6 antibodies [10], while IL-6 deficient mice exposed to

ozone have reduced airway neutrophils [11]. There is also evidence of increased systemic inflammation in children with asthma. Serum/ plasma levels of TNF- α , LTB₄, and thromboxane (TX)A₂ have been found to be 5.6, 7.2 and 11 times higher, respectively, in the alveolar macrophages of infants with wheeze compared to infants without wheeze [12]. Elevated circulating levels of TNF- α and TNF receptor-1 and receptor-2 have also been documented in children and adults with AHR, compared to those without AHR and found to negatively correlate with FEV₁ [13]. These studies suggest that systemic inflammatory mediators may be important to airway responses in both adults and children with asthma.

Pharmacological management of asthma predominantly involves the use of inhaled corticosteroids (ICS) for prevention of symptoms, which are effective in reducing eosinophilic airway inflammation. However, there is emerging evidence that ICS are less effective in obese adults [14] and children [15]. Bronchodilators are also commonly used for relief of symptoms. Wood et al, have recently shown that the efficacy of β_2 -agonists, is reduced after a high fat meal [16]. Evidence suggests that dietary interventions to either reduce energy stores (reduce obesity) or reduce intake of saturated fat in targeted patients may improve responsiveness to current asthma therapy.

Asthma incidence has increased in western countries [17] and in those migrating from a developing to a westernised country [18], suggesting that features of a western lifestyle may be implicated in the development and progression of asthma. Epidemiological studies support this hypothesis; western-style fast food intake has been shown to increase asthma risk in children [19, 20], consumption of a diet high in 'western' foods versus 'asian' foods has been associated with increased asthma risk [21] and a diet high in fast foods, has been associated with increased childhood asthma prevalence [22]. Typical of westernisation is a dietary pattern consisting of a high intake of dietary fat, particularly saturated fat and an elevated omega-6:omega-3 ratio; a low antioxidant intake; and chronic metabolic surplus leading to obesity [23]. Conversely, Asian and Mediterranean dietary patterns are typically low in animal products and high in whole grains and vegetables [24]. This paper will discuss the

scientific and epidemiological evidence supporting the role of dietary intervention in both the management and prevention of asthma.

Dietary Fat and Asthma

As part of the normal response to a high fat meal, circulating fatty acids increase and are then utilised to meet the energy needs of the host. Excess fatty acids are incorporated into triacylglycerols, undergo lipogenesis and are stored [25]. However, fat intake exceeding the saturation point of both these pathways induces a lipotoxic state, causing activation of inflammatory pathways and oxidative stress, resulting in ‘postprandial metabolic inflammation’ [26]. This includes the release of NF- κ B and increased concentrations of IL-6 and CRP [16, 27]. These inflammatory changes occur within one hour postprandially and are sustained for at least three hours [16]. Therefore, constant exposure to a high fat diet results in a maladaptive response, leading to sustained systemic inflammation and oxidative stress. Both the quality and quantity of fat appear important in determining the postprandial inflammatory response. A number of studies have examined asthma risk in relation to the quantity of fat in the diet. For example, a 10% increase in dietary fat intake has been shown to increase the risk of asthma development by 70% in men [28]. In another study in school-aged children, increased percentage energy derived from fat intake was associated with an increased odds of current asthma [29]. Quantity of dietary fat intake has also been linked with increased odds of AHR [30] and asthma severity [31].

Saturated Fatty Acids and Asthma

Saturated fatty acids activate TLR4 and TLR2, resulting in the activation of NF- κ B and upregulation of the proinflammatory cytokines IL-6, IL-8 and TNF- α [32, 33]. Indeed, interventional studies show that in healthy populations a high saturated fatty acid intake is associated with increases in CRP, IL-6, TNF- α and NF- κ B activity [34, 35]. However, there is limited data in the asthmatic population.

Saturated fat intake increases the risk of current asthma in adolescents [36] and is associated with increased odds of AHR in young adults [30]. Self-reported dietary data in 638 Spanish schoolchildren demonstrates that intake of saturated fatty acids is associated with increased odds of current asthma [29]. Recently, Wood et al [16] found that a meal high in saturated fat was associated with suppressed bronchodilator response and increased sputum neutrophils and TLR4 micro (m)RNA in asthmatic adults. Additionally, in a cross-sectional population of asthmatic males, plasma saturated fatty acids were positively correlated with sputum neutrophils [9]. In contrast, other studies have found no association between saturated fatty acid intake and current asthma [37].

Polyunsaturated Fatty Acids and Asthma

The manipulation of dietary polyunsaturated fat modifies the pattern of inflammation by changing the composition of cellular membranes, leading to alterations in eicosanoid and prostaglandin synthesis [38]. Linoleic acid is an omega-6 polyunsaturated fatty acid (PUFA) that is converted to arachidonic acid in the body, and then to the proinflammatory eicosanoids LTB₄ and prostaglandin (PG)E₂ [38]. LTB₄ enhances natural killer activity, is a neutrophil chemoattractant and increases the production of the Th1 cytokines TNF- α , IL-2, IL-6 and interferon (IFN)- γ [38]. Since dietary intake of omega-6 is high in a Western diet, there is a high concentration of this proinflammatory class of fatty acids incorporated into cellular membranes [39]. Omega-3 fatty acids actively compete with omega-6 for incorporation into cellular membranes. Increased intake of omega-3 fatty acids reduces arachidonic acid (AA) content of cellular membranes, and increases eicosapentaenoic acid (EPA) and docosohexaenoic acid (DHA) content. The presence of omega-3 fatty acids inhibits the conversion of AA to PGE₂, resulting in the production of PGE₃ and LTB₅, which are far less biologically active [39]. As a result, omega-3 fatty acids are considered to be anti-inflammatory.

The effect of omega-6 fatty acids has been examined extensively in asthmatic populations. A number of studies have quantified omega-6 intake by dietary questionnaire and found no associated risk of current asthma [36, 40]. However, the majority of studies that directly quantified fatty acid concentration suggest omega-6 fatty acids modify asthma risk and severity. For example, in a population of 526 children aged 8-11 years, AA concentration of serum cholesterol esters was associated with increased odds of current asthma and wheeze, while the odds of frequent asthma attacks was increased by 5.5 fold in the highest compared with the lowest quartile of AA [41]. Woods *et al.* [37] found total plasma omega-6 concentration in adults was associated with bronchial reactivity, but not with asthma diagnosis or atopy. Conversely, in another study, increased linoleic acid (an omega-6 fatty acid) concentration in the erythrocyte membrane was associated with reduced odds of asthma [42].

Several studies have reported that intake of omega-3 fatty acids or fish is associated with improved lung function [43, 44] and decreased risk of asthma [45-51], AHR [47, 48] and wheeze [50]. Conversely, there are also studies which don't support, or only partially support, this hypothesis [44, 52-59]. Similarly, data examining the possible benefits of dietary omega-3 fatty acid supplementation in asthma are heterogeneous. There is little evidence to suggest that omega-3 fatty acids are beneficial in established asthma, as summarized by a 2002 Cochrane review [60]. However, several studies have reported fish consumption, rather than purified EPA/DHA, to be protective against the development of asthma, particularly in childhood [47-51, 61]. One recent study found introducing fish to infants between the ages of 6 and 12 months is associated with a lower prevalence of wheeze at 4 years of age, compared with those infants who were introduced to fish either before or after this age [62]. It is also possible that different forms of marine oils in the diet may have varying effects on immune responses, due to the presence of a variety of lipid mediators, as well as different quantities of omega-3 fatty acids. For example, in an animal model of allergic asthma, a marine extract from green lipped mussels, but not purified fish oil, was shown to reduce Th2 cytokine

responses, eosinophil influx, mucus hypersecretion and AHR [63]. In a human trial, daily supplementation with this same marine extract decreased daytime wheeze and exhaled hydrogen peroxide concentration in a randomized controlled trial [64]. These data support the hypothesis that whole foods, rather than individual nutrients, may be most beneficial.

Monounsaturated Fatty Acids and Asthma

In *in vivo* models demonstrate monounsaturated fatty acids (MUFA) inhibit TLR4 and TLR2 activation of NF- κ B [33]. However, interventional studies have shown no beneficial effect of MUFA on circulating inflammatory markers [65], suggesting that MUFA alone may in fact be neutral in terms of inflammation in humans. Few studies have examined the effect of MUFA specifically in relation to asthma. Huang and Pan [36] found an inverse association between reported MUFA intake and asthma risk in female adolescents. Scott *et al.* [9] recently found an inverse association between plasma MUFA and neutrophilic airway inflammation in asthmatic men. However, others have found no effect of MUFA on current asthma [40, 41, 66, 67], lung function [41], atopy [37] or wheeze [40].

Antioxidants and Asthma

Reactive oxygen species (ROS) are produced as part of normal cellular activities, such as respiration, and have an important role in cellular signalling and homeostasis. ROS are highly reactive, with excessive formation causing cellular damage to DNA, proteins, lipids and polysaccharides. Excess ROS in the airways induce airway inflammation [68], AHR [68, 69] and mucin secretion [68]. This creates a positive feedback loop, whereby airway inflammatory cells further contribute to increased oxidative stress in the airways. Antigen challenge in allergic individuals results in the spontaneous production of ROS by airway eosinophils [70]. Furthermore, circulating eosinophils, neutrophils and monocytes from asthmatics have a greater production of ROS compared with cells from non-asthmatics [71]. Therefore, both the airway and systemic inflammatory changes occurring in asthma appear to contribute to oxidative stress, resulting in antioxidant depletion and consequently an

oxidant-antioxidant imbalance. Asthmatics appear to have low antioxidant levels in the airways compared with healthy subjects, independent of an adequate antioxidant intake [72]. Antioxidant intake appears to protect against asthma development [73], likely due to its role in maintaining oxidant-antioxidant balance, thus preventing oxidative damage. Children with asthma have a lower total antioxidant capacity (TAC), while malondialdehyde (MDA, a marker of lipid peroxidation) has been correlated with exhaled nitric oxide (eNO) concentration [74], thus suggesting oxidative stress and allergic airway inflammation modify antioxidant activity in asthmatic children.

Exogenous antioxidants, including ascorbic acid, carotenoids, flavonoids and tocopherols, assist in maintaining cellular equilibrium and preventing cellular damage by neutralising ROS. Dietary fruits and vegetables are the primary source of exogenous antioxidants, and the decline in fruit and vegetable intake in Western society, resulting in a shift in oxidant-antioxidant balance, has been hypothesised to have contributed to the recent rise in asthma prevalence [75]. Indeed, intake of whole fruits and vegetables has been linked with respiratory outcomes and asthma development. For example, children who reported eating fruit more than once a day had a forced expiratory volume in 1 second (FEV₁) that was 79mL higher than children who reported never eating fruit [76]. Over a seven year period, adults who had the greatest reduction to their fresh fruit intake had a decline in FEV₁ of 107mL when compared with adults who maintained their fruit intake [77]. In a recent 3 month randomised controlled trial in adults with asthma, a high fruit and vegetable intake (≥ 5 serves of vegetables and ≥ 2 serves of fruit per day) was shown to decrease the risk of asthma exacerbation by 2.2 fold, compared to a low fruit and vegetable intake (≤ 2 serves of vegetables and ≤ 1 serve of fruit per day). An increase in plasma CRP was also reported in the low fruit and vegetable group [78].

Carotenoids and Asthma

Carotenoids, which are primarily found in fruit and vegetables, have potent antioxidant properties. Two large epidemiological studies have shown that higher plasma carotenoid levels slow age-related lung function decline [79, 80]. In addition, a number of cross-sectional studies have demonstrated that self-reported dietary intake of carotenoids is linked with better respiratory function in both adults and children [81, 82]. β -carotene and α -carotene have been linked with a 15% and 10% reduced risk of asthma development in children, respectively [83, 84]. In adults with asthma, Wood *et al.* [85] demonstrated that a ten day low antioxidant diet resulted in a significant reduction in plasma carotenoid concentrations, associated with an increase in sputum neutrophil concentration and a significant deterioration in FEV₁, forced vital capacity (FVC) and asthma control. Hazlewood *et al.* [86] supplemented OVA-sensitised mice with tomato extract, rich in lycopene, for 14 days and demonstrated a significant reduction in eosinophil, IL-5 and IL-4 influx into the airways. Retinol, which can be derived from β -carotene, has also been investigated in a small number of studies [87-89]. A randomised controlled trial in chronically malnourished pregnant women found the offspring of mothers supplemented with Vitamin A had a 46mL higher FEV₁ and FVC at age 9-13 years, compared with the offspring of mothers who received the placebo [87].

Vitamin C and Asthma

Vitamin C acts as an electron donor to ROS and is the most abundant antioxidant in the airway lining fluid [90]. Vitamin C may reduce the risk of asthma development in both adults [91] and children [84] and increased intake has been associated with better lung function [88]. Low vitamin C levels have been associated with increased bronchial reactivity to methacholine [30]. There is evidence to suggest that subjects regularly exposed to ozone may particularly benefit from vitamin C intake [92, 93]. Indeed, guinea pigs treated with vitamin C for 26 days have a reduced influx of eosinophils and neutrophils into the airways after OVA-challenge [94]. A randomised cross-over trial in children demonstrated that a six week supplementation with either vitamin C, zinc or omega-3 fish oil, was

associated with improvements in asthma control, FEV₁ and FEV₁/FVC, and a reduction in sputum eosinophils [95]. Despite numerous studies suggesting potential benefit of vitamin C in relation to airway responses, a recent Cochrane review concluded that there was insufficient evidence to recommend a specific role for vitamin C in the treatment of asthma, largely due to a lack of methodologically strong and large-scale randomised controlled trials [96].

Vitamin E and Asthma

Vitamin E prevents autoxidation of lipids and converts ROS to less active forms [23]. Vitamin E includes four tocopherols and four tocotrienols, and is associated with improved asthma control [97], reduced wheeze [98, 99] and better lung function [82]. A higher maternal intake of vitamin E reduces asthma risk in offspring at five years of age [99] and wheeze at age two years [100]. Furthermore, vitamin E intake is associated with lower serum Ig(Immunoglobulin)E concentration and lower allergic sensitisation [101]. This is supported by murine models, demonstrating an attenuated IgE-mediated immune response after vitamin E supplementation [102, 103]. After intranasal OVA-challenge, Wagner *et al.* [104] demonstrated a 74% reduction in airway eosinophils and significant reductions in the nasal expression of IL-5 and IL-13, in rats treated with γ -tocopherol for four days. Nonetheless, a randomized control trial of vitamin E supplementation for asthma in adults, showed no evidence of clinical benefit [105].

Obesity and Asthma

Obesity is a risk factor for asthma, with obesity doubling the risk of asthma development in adults [106], and increasing risk of asthma in school aged children by 1.5 times [107]. Obese asthmatic adults experience more severe asthma symptoms, increased emergency room visits and hospitalisations, and poorer lung function, compared with asthmatics within the healthy weight range [108, 109]. Similarly, obese children experience more severe asthma, as supported by two recent analyses of large cohorts which reported an association between increased BMI and/ or adiposity in

children and increased asthma symptoms, asthma exacerbations and emergency department presentations [110, 111]. In adults, abdominal obesity is associated with a greater risk of non-allergic, but not allergic, asthma [112] and the association appears to be stronger in females [113, 114]. In children, the association between obesity and asthma appears to exist in both the absence and presence of allergy, however, evidence suggests the obese-asthma association may be stronger in allergic children [115]. While there is clear evidence supporting an association between obesity and asthma outcomes, evidence suggesting mechanisms is less clear. Various hypotheses have been proposed including mechanical effects [116, 117], inflammation [9, 118] and hormones [119, 120].

Mechanical Effects of Obesity

Obesity is associated with increased breathlessness independent of asthma, believed to be the result of adipose tissue within the android and thoracic regions exerting a direct effect on the chest wall and downward movement of the diaphragm [116].

Inflammatory Effects of Obesity

Both obesity and asthma involve a low-grade systemic inflammation, and it has been suggested that obesity-induced inflammation may drive the development and progression of asthma in susceptible individuals. It is clear that the typical Th2 inflammatory response is not responsible, as several studies have found no association between obesity and eosinophilic airway inflammation [121, 122] or eNO [111, 122] in adults or children. Higher levels of systemic leukocytes, neutrophils and platelets have been documented in obese asthmatic children compared with those of a healthy weight [123], although there is no evidence of altered airway inflammation [124]. Evidence of an inverse association between obesity and both sputum eosinophilia [125] and eNO [125, 126] in adults suggests obesity may actually produce a shift away from the Th2 response in adult asthma. Neutrophilic inflammation is Th1 driven and has also been recently examined as a potential driver of

the obese-asthma phenotype. Scott *et al.*[9] found a positive association between BMI and airway neutrophilia and BMI in females, and others have since found a similar association between BMI and neutrophils in adults, both in the airways [127] and circulation [127, 128].

Effects of Obesity-Related Hormones

Adipokines, hormones released by adipose tissue, may have a role in driving the association between obesity and asthma as they are biologically active and their receptors are widely distributed throughout the body, including the lungs. Leptin and resistin are increased in obesity and also in asthma, independent of BMI [129-132]. They have pro-inflammatory effects, including activation of NF- κ B [133, 134], upregulation of TNF α levels [135, 136] and enhancement of neutrophil function [133, 137]. In animal models it has been shown that exogenous leptin administration enhances airway inflammation [138] and AHR [139]. Adiponectin, on the other hand, generally acts as an anti-inflammatory hormone and is reduced in obesity [140], most likely due to the production of TNF- α and IL-6 by adipose tissue-resident macrophages, which inhibits adipocyte production of adiponectin [141]. Adiponectin negatively regulates TLR signaling pathways [142], inhibits NF- κ B activity [142, 143] and suppresses proinflammatory cytokine production, including TNF α [144] and IL-6 [145]. In an allergic mouse model, exogenous adiponectin reduced AHR and inflammatory responses to an ovalbumin challenge, including a suppression of airway neutrophils [146]. Adiponectin levels have been shown to be reduced in asthma in some studies [147, 148] and reduced in subjects with low lung function [149]. Interestingly, some studies reporting that the relationship between adipokines and asthma only occurs in women [130, 147].

Weight Loss Interventions in Obese Asthma

Weight loss in obese asthma is associated with improved lung function, asthma severity and quality of life, and reduced asthma symptoms and medication usage [150-152]. A recent randomised weight

loss intervention in overweight and obese asthmatic adults found that a 5-10% weight loss was associated with a clinically significant improvement in asthma control and asthma-related quality of life [153], suggesting that a small weight loss may assist in the clinical management of this population. Only one randomised controlled weight loss trial has been conducted in adults with asthma, resulting in significant improvements in lung function and significantly fewer asthma exacerbations in the year following the intervention [152]. Few studies have examined the effects of weight loss on inflammation in asthma. Scott *et al.*[153] demonstrated that weight loss from the gynoid and arm regions is associated with reduced neutrophilic inflammation in asthmatic females. Dixon *et al.*[154] found an increase in bronchoalveolar lavage (BAL) lymphocytes, an increase in peripheral blood lymphocyte function, and a reduction in AHR in asthmatic adults who underwent surgically-induced weight loss. One recent uncontrolled weight loss study in obese adolescents, with and without asthma, reported significant improvements to plasma leptin, adiponectin and CRP, following 12 months of interdisciplinary therapy [150].

Summary

Weight loss interventions in asthma, via either dietary restriction or bariatric surgery, have clearly demonstrated that weight reduction improves lung function and symptoms. High quality randomised controlled trials are needed to understand the mechanisms driving this association; however, the efficacy of intervention is clear. With regard to antioxidants and fatty acids, there are a large number of studies, both epidemiological and mechanistic, that demonstrate a relationship between these nutrients and both immune responses and clinical asthma outcomes. However, the results of intervention trials are heterogeneous, with both positive and negative studies being reported [16, 60, 64, 78, 86, 87, 96]. The most convincing data is from studies that have used manipulation of whole foods such as fruit and vegetables, those examining populations at an increased risk of oxidative stress, and studies that objectively measure antioxidant status. Progress in the field is limited by the

paucity of this high quality, adequately powered, randomised controlled trials. Such trials are difficult to conduct due to the practical constraints and complexity of modifying dietary intake of whole foods and inducing weight loss in obese populations. However, considering the available evidence, it appears likely that this is the path to progress the field; as such trials are needed to obtain definitive evidence regarding the role of different dietary patterns or components.

Abbreviations

AA: Arachidonic acid;

AHR: Airway hyperresponsiveness;

BAL: Bronchoalveolar lavage;

BMI: Body mass index;

CRP: C-reactive protein;

DHA: Docosahexaenoic acid;

eNO: Exhaled nitric oxide;

EPA: Eicosapentaenoic acid;

FEV₁: Forced expiratory volume in one second;

FVC: Forced vital capacity;

ICS: Inhaled corticosteroid;

IFN: Interferon;

IgE: Immunoglobulin E;

IL: Interleukin;

LPS: Lipopolysaccharide;

LT: Leukotriene;

MDA: Malondialdehyde;

mRNA: Micro RNA;

MUFA: Monounsaturated fatty acid;

PG: Prostaglandin;

PUFA: Polyunsaturated fatty acid;

ROS: Reactive oxygen species;

TAC: Total antioxidant capacity;

Th: T helper;

TLR: Toll-like receptor;

TNF- α : Tumor necrosis factor-alpha;

TX: Thromboxane

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