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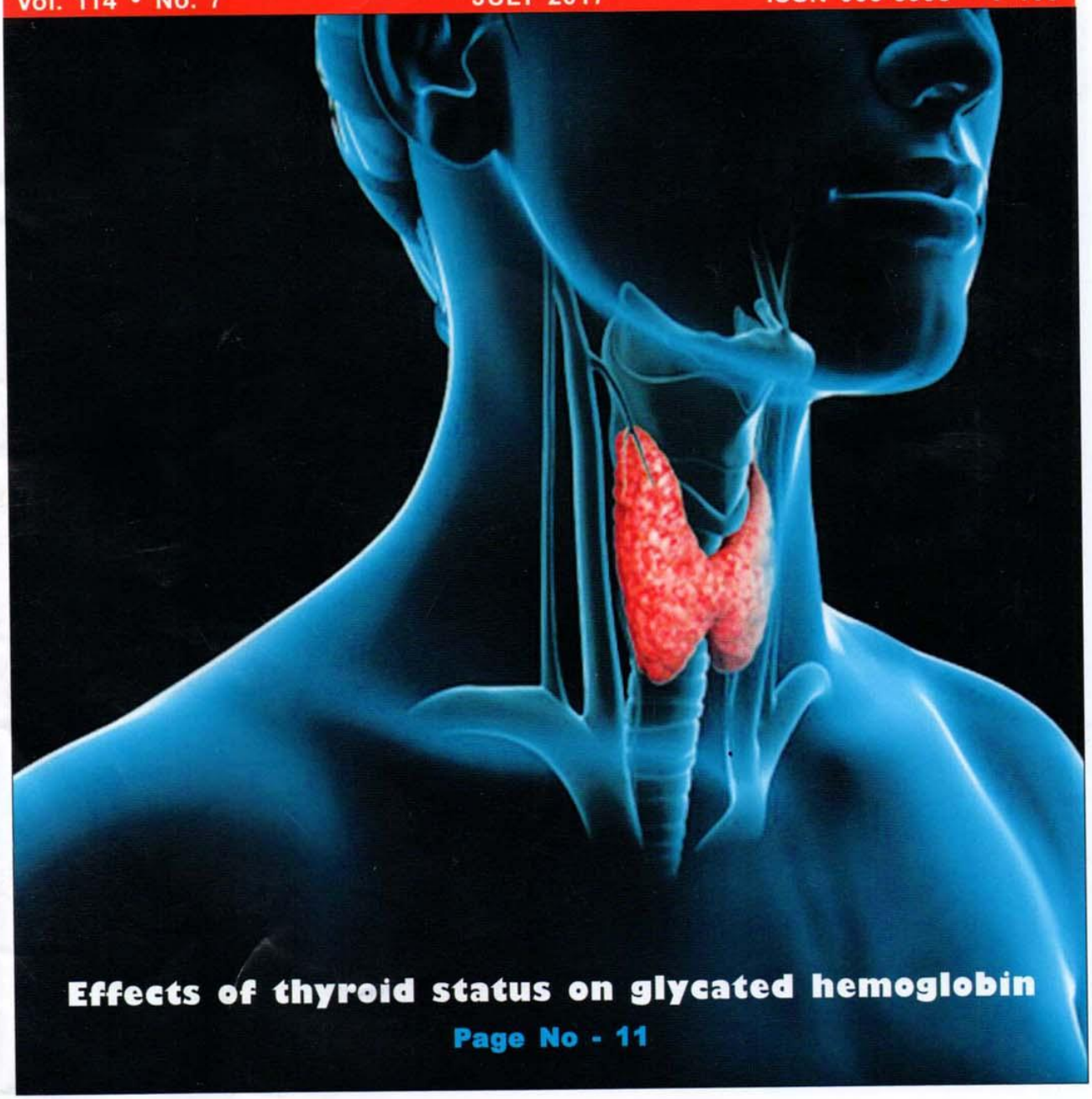

Effects of thyroid status on glycated hemoglobin

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GENERAL

Nutraceuticals and Asthma

SANJAY AGRAWAL

Asthma comes from the Greek word for "panting" and has been described as a pathological condition for centuries. It is a chronic inflammatory disorder of the airways in which many immunological cells play a role, including mast cells and eosinophils. In susceptible individuals, this inflammation causes symptoms which are usually associated with widespread variable airflow obstruction that is often reversible, either spontaneously or with treatment, and causes an associated airway hyper responsiveness (AHR) to a variety of stimuli. The clinical features of asthma include dyspnea, wheezing and coughing. One of the marked risk factors of asthma associated with the westernized lifestyle is our changing diet and/or nutritional status. It has been hypothesized that the significant changes in our diet plays a dominant role in the etiology of asthma.[1]

Antioxidants

The airways are continuously exposed to oxidants, either generated endogenously by various metabolic reactions (e.g. from mitochondrial respiration or released from phagocytes) or derived from exogenous sources (e.g. air pollutants and cigarette smoke). Allergen-activated inflammatory cells from asthmatic patients produce more ROS than from healthy individuals. In addition, several inflammatory mediators including histamine, lipid mediators, cytokines, chemokines, ECP, and EPO are potential stimuli for ROS production in the airways, leading to asthma exacerbation. Deficiency of endogenous antioxidant defenses has been reported in asthma. Since a diet rich in vitamin A or carotenoids, vitamin C vitamin E, and flavonoids, has been associated with a decreased prevalence of asthma, understanding the relationship between dietary antioxidants and asthma-associated inflammatory responses has been a recent focus. Vitamin A and carotenoids a systemic review and meta-analysis by Allen et al. has shown that dietary vitamin A intake is significantly lower in asthmatic patients than in healthy subjects. Asthmatic children have a lower serum vitamin A concentration than healthy controls. Supplementation of the diet with Lycopene, a carotene found in tomatoes and carrots, has a protective effect against asthma development in a murine model. All-trans retinoic acid (ARTA), a derivative of vitamin A, inhibits airway inflammation in asthmatic rats. ARTA inhibits total cell counts and the proportion of inflammatory cells in BALF, suppresses the expression of NF-κB and intercellular adhering molecule-1 (ICAM-1), and increases the expression of iκB. Retinoid acid also down regulates the expression of Th1 and Th2 chemokines in monocytes, including macrophage-derived chemokine and IP-10, which are all important in the inflammatory process. Airway smooth muscle cell migration, which contributes to the airway remodeling in chronic asthma is also inhibited by ARTA. However, excessive intake of vitamin A exacerbates pulmonary hype responsiveness in murine asthma model, suggesting that excessive vitamin A may increase the risk and severity of asthma. Mechanistically, vitamin A may regulate bronchial hyper reactivity by altering the function and abundance of the muscarinic M(2) receptors in bronchial tissue. Moreover, Carotenoids may regulate activation of a variety of transcription factors. Treatment of cells exposed to oxidative stress with β-carotene suppresses oxidative stress-induced activation of NF-κB and production of IL-6, TNF, and inflammatory cytokines. Carotenoids may influence the process of apoptosis in healthy cells.[2] While the pro-apoptotic protein Bax is down regulated after induction of external stimuli, β-carotene is able to increase expression of the antiapoptotic protein Bcl-2 in normal cells. In addition, β-carotene exhibits a pro-apoptotic effect in colon and leukemic cancer cells, and this effect occurs by a redox-dependent mechanism linked with NF-κB activity. These dual roles of vitamin A, including Carotenoids, on apoptosis provide the capability of Carotenoids as an effective anti-inflammatory agent in various diseases.[3]

Vitamin C

Many observational studies have reported associations between reduced dietary/blood vitamin C levels and reduced lung functions. Asthmatic children undergoing an exacerbation have significant lower serum levels of vitamin C. There is a positive correlation between

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serum vitamin C levels and asthma development in children (OR=0.72 per mg/dl, 95% CI=0.55, 0.95). Furthermore, asthma patients have significantly lower vitamin C level in both the cellular and fluid-phase fraction in induced sputum [205]. Higher maternal intake of citrus fruits rich in vitamin C during pregnancy is significantly associated with a reduced risk of allergic inflammation in the offspring [206]. Administration of vitamin C in OVA-challenged mice decreases AHR, influx of inflammatory cells in BALF and attenuates lung inflammation. Similarly, high dose vitamin C supplementation significantly reduces eosinophilic infiltration in BALF and increases the Th1/ Th2 cytokine secretion ratio; thus, skewing the Th1/ Th2 balance toward non-allergic Th1 immune response in asthmatic mice. A randomized, placebo controlled, double-blinded crossover trial has shown that vitamin C supplementation (1500 mg/day) attenuates asthma symptoms. Moreover, exhaled nitric oxide, urinary leukotriene C4, D4, E4 and 9α, 1β-prostaglandin F2 after exercise are down regulated. On the contrary, there are also studies showing no significant effect of vitamin C supplementation on asthma symptoms. For example, in a randomized, placebo-controlled, double-blind parallel group trial three hundred asthma patients provided with 1 g/day vitamin C or placebo for 6 weeks do not show any improvements of asthma symptoms , therefore, there is insufficient evidence from randomised-controlled trials to support the use of vitamin C for asthma treatment. As its mechanism of action, vitamin C may regulate factors that can influence gene expression, apoptosis, and other cellular functions indicated in inflammation. In fact, vitamin C protects against cell death triggered by various stimuli, and major proportion of this protection is associated with its antioxidant ability.[4]

Vitamin E

The body of evidence from multiple studies suggests that a positive association between asthma outcomes and vitamin E intake or serum vitamin E levels. Asthmatic children have significantly lower serum levels of vitamin E than non-asthmatic children. A longitudinal birth cohort study has explored association between maternal plasma vitamin E, fetus and fetal lungs growth, and childhood asthma. The findings have shown that maternal vitamin E status has a positive effect on the growth of fetus and fetal lungs during early pregnancy and better asthma outcomes during childhood. Moreover, high maternal vitamin E intake during pregnancy also reduces the risk of infantile wheeze. Vitamin E intake is higher in control subjects than in asthma patients. However there is no relationship found between serum vitamin E level and asthma. On the other hand, administration of vitamin E for 6 weeks does not have an effect on asthma features and serum immunoglobulin levels in adults. Role of Vitamin E has been investigated in animal models of allergic asthma. Administration of Vitamin E to allergen-challenged mice reduces mitochondrial dysfunction, Th2 cytokines production, allergen-specific IgE, and expression of lipid mediators in lung leading to alleviation of asthmatic features. Expression of IL-5 mRNA and protein in lung, and plasma IgE level are reduced after OVA sensitization and challenge compared to wild type mice in vitamin E transfer protein knockout mice. Moreover, dietary supplementation with vitamin E affords variable degree of protection against ozone-induced enhanced airway response in allergen-sensitized guinea pigs. However, oral α-tocopherol has no protective effect on lung response in rat model of allergic asthma. There is no improvement in OVA induced AHR, the inflammatory cell infiltrate and histological changes. The observed opposite effects of vitamin E could be associated with the study design in an animal model of asthma. The effect of vitamin E deserves further evaluation.[5]

Vitamin D

Over the past several years, the role of vitamin D in immunomodulation has been studied and shown to have a significant impact on innate and adaptive immunity to infections, including the pathophysiology of allergic asthma. It has been proposed that the increase in allergy and asthma is a consequence of widespread vitamin D insufficiency which appears to be frequent in industrialized countries, reflecting the insufficient intake of diet-sourced vitamin D. The serum vitamin D level is associated with asthma in children as well as adults. A randomized, placebo controlled clinical study with 1024 children suffering from mild-to-moderate persistent asthma has shown that Vitamin D deficiency has associated with a higher rate of severe asthma . There is a significant positive correlation between forced vital capacity percent predicted and serum vitamin D level children with asthma. Moreover, 91.6% of these asthmatic children are not sufficient in serum vitamin D level. Low level of vitamin D in serum is also associated with

increased hyper responsiveness and reduced glucocorticoid response in adults with asthma. These studies have indicated that the low serum vitamin D level is related to reduced lung function and higher risk of asthma. Reduced the risk of asthma exacerbation triggered by acute respiratory tract infection is observed in a vitamin D supplementation. Higher consumption of vitamin D during pregnancy may reduce the risk of childhood wheeze and asthma.[6,7]

Flavonoids

Flavonoids interfere with oxidation of lipids and other molecules and this strong antioxidative property makes them protective against airway diseases linked to oxidative stress. In fact, several epidemiologic studies suggest the beneficial effects of flavonoids on asthma. A population-based case-control study has shown that apple consumption and red wine intake are inversely associated with asthma prevalence or severity, perhaps due to a protective effect of flavonoids.[8]

Resveratrol

Resveratrol scavenges intracellular ROS by inducing and stabilizing antioxidant enzymes such as catalase, SOD, and glutathione peroxidase hemoxygenase. In addition to its reducing properties, resveratrol has been shown to attenuate inflammation via inhibition of prostaglandin production and to decrease the phosphorylation of ERK1/2, COX-2 activity, and activity of various transcription factors including NF-κB, STAT3, HIF-1α, and β-catenin. Resveratrol also inhibits protein kinases (e.g. src, PI3K, JNK, and Akt) and the production of inflammatory mediators (e.g. IFN-γ, TNF, COX-2, iNOS, CRP and various interleukins). Recent studies have reported that resveratrol activates sirtuin1 (SIRT1) which modulates apoptosis and has been shown to increase longevity in some experimental systems [242]. SIRT1 modulates poly (ADP-ribose) polymerase-1 (PARP-1) activity upon DNA damage. Activation of SIRT1 by resveratrol leads to a decrease in PARP-1 activity and promotes cell survival, which can attenuate the inflammatory reaction. We investigated the effects of resveratrol on human mast cell activation in comparison to the anti-allergic drug tranilast. The results show that resveratrol inhibits mast cell degranulation, cytokine, chemokine and leukotriene release, and is more efficacious than tranilast. [9,10]

Selenium

Selenium is an important molecule in both innate and adaptive immune responses. It stabilizes activated platelets by inhibiting platelet aggregation and secretion of adenine nucleotide, thus possibly blocking the release of arachidonic acid from platelet membrane. In asthma, platelets participate by acting as inflammatory cells, by releasing mediators, spasmogens and/ or by interacting with other inflammatory cell types [168]. Selenium affects the expression of endothelial cell adhesion molecules, E-selectin, P-selectin, ICAM-1, VCAM-1, and ELAM-1, which are crucial in the inflammatory process for recruitment of inflammatory cells into the target tissue.

Conclusion

The prevalence of asthma is becoming the mortality and morbidity pandemic of the 21st century. The cost of in quality of patient's lives and economic burden of treatment is continuing to grow at pace unmatched in our current health system. It is impossible to enter public classroom now without seeing a young sufferer of this condition and any trip to the emergency department will show how dangerous this disease can be. As the incidence and severity of the disease continues to rise, medical research is continuing to search new treatment strategies. While many treatments currently exists those reserve for the severest of conditions carry their own inherent risk which may match the severity of disease itself. It is for these reasons alone that health care professionals are now examining the traits of our ancestors in time when this epidemic was less severe to determine if their medicines and practices hold the answer for the next treatment strategy. By combining the scientific knowledge at the molecular and clinical level and the resources of past it might hold the answer to breathless pandemic of the 21st century.

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A limitation of our study was that we could not measure RBC turnover directly with investigation like Chromium 51 tagged RBC assay and used reticulocyte count for indirect estimation of RBC turnover. We also could not measure malondialdehyde level.

HbA1c is an important tool for monitoring of glycemic status in diabetic patients. Recently, ADA has proposed its use in diagnosis of diabetes and prediabetes.[6] 50% of our hypothyroid patient showed discrepant result for diagnosis of prediabetes using plasma glucose (fasting and after 75 g oral glucose load) and HbA1c level of ≥5.7 (39 mmol/mol). In contrast, 6.6% patient of hyperthyroid group and 2.2% among controls showed this discrepancy.

In the second part of the study (who were followed up), 17 out of 22 patients in hypothyroid group had HbA1c ≥5.7 at the baseline. Six of those 17 patients had values <5.7 at the end of the study. Findings of our study suggest that we should be cautious while interpreting HbA1c data in patients with hypothyroidism.

Conclusion

Baseline HbA1c levels were found to be significantly higher in hypothyroid patients compared to control individuals despite similar glucose levels. HbA1c reduced significantly with treatment in hypothyroid patients without a significant change in glucose levels. Significant baseline or post treatment change was not observed in hyperthyroid patients. Our study suggests that HbA1c data should be interpreted with caution in patients with hypothyroidism.

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