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Assessment of Oxidative Mechanisms and Vitamin A Among Patients with Chronic Otitis Media

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ABSTRACT

Chronic otitis media (COM) represents a significant health concern, manifested by persistent fluid collection behind the tympanic membrane without acute infection symptoms. This research aimed to explore the roles of oxidative stress and the anti oxidative defense mechanism in patients with COM, distinguishing between those with and without cholesteatoma. This investigation encompassed 100 individuals diagnosed with COM, divided into two groups depending on the presence of cholesteatoma: 50 patients with cholesteatoma and 50 patients without cholesteatoma. Serum and diseased ear tissue samples were collected preoperatively and audiometric evaluations were conducted for all participants. The study measured serum levels of oxidative stress markers, including malondialdehyde (MDA) and antioxidant enzymes such as super oxide dismutase (SOD), catalase (CAT) and glutathione per oxidate (GPx), along with vitamin A, employing HPLC techniques. In this study, participants encompassed a gender-inclusive cohort ranging in age from 20-40 years. The comparative analysis of baseline characteristics revealed no significant differences between the two study groups. Notably, markers of oxidative stress and vitamin A concentrations were found to be substantially elevated in the group diagnosed without cholesteatoma. Oxidative stress, induced by ROS, is crucial in COM development. Serum markers can effectively assess oxidative stress in COM, yet may not fully indicate disease severity. Vitamin A's impact on COM incidence is indirect, but its antioxidant ability could be vital in managing the disease's pathophysiology. A larger, detailed study on Vitamin A intake is essential to clarify its role.

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Key Words
Otitis media, oxidative stress, vitamin A, cholesteatoma

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INTRODUCTION

Chronic otitis media (COM) is defined by the persistent rupture of the tympanic membrane and inflammation of the mucosal lining within the middle ear cavity and the air-filled spaces of the petrous part of the temporal bone, enduring for more than three months. A distinctive feature of COM, when accompanied by cholesteatoma, is the presence of a proliferative mass composed of keratinizing squamous epithelium within the middle ear and/or mastoid cavity. Historically, COM pathology was believed to be confined to the mucoperiosteum. Pathological changes exceeding this boundary can precipitate severe complications, including meningitis, osteitis and the degradation of bone[1,2]. In physiological equilibrium, reactive oxygen species (ROS) play a pivotal role as pathogenic agents in various diseases. While certain forms of reactive oxygen are indispensable for human existence, they can also exert detrimental effects on bodily tissues. The generation of ROS during biochemical and metabolic reactions, involving entities such as lipid peroxides, hydrogen peroxide, hydroxyl free radicals and a plethora of other derivatives, can cause widespread tissue damage. Oxidative enzymes like myeloperoxidase (MPO) and nitric oxide (NO) are among the contributors to this process. Free oxygen radicals (FORs) are essential for metabolic activities and the immune response, being produced by defense cells like macrophage, neutrophils and monocytes during their fight against antigens. An excess of FORs, however, leads to tissue injury, disrupting the normal reparative mechanisms and prolonging inflammatory responses. Antioxidants mitigate this risk by converting free radicals into less harmful entities and preventing the formation of new radicals, thus safeguarding tissues, lipids, proteins and DNA from damage that could culminate in cell death[3-5]. A disruption in the balance between reactive oxygen species (ROS) and the antioxidant defense system can hinder wound healing and promote sustained inflammation, contributing to the pathogenesis of cholesteatoma in COM. Enzymes such as glutathione peroxides, catalase and super oxide dismutase are critical, playing an indispensable role in combating free radical damage through the antioxidant defense system[5]. This investigation focused on the levels of antioxidant enzymes, including catalase (CAT), super oxide dismutase (SOD), glutathione peroxides (GHPx), malondialdehyde (MDA) and vitamin A, in serum samples of COM patients, both with and without cholesteatoma, revealing evidence of mucosal inflammation in the middle ear.

MATERIALS AND METHODS

This research employed a meticulous analytical and comparative approach to ascertain the diagnosis of COM in 100 patients. The cohort was bifurcated based on the presence of cholesteatoma, resulting in 35 patients diagnosed with COM with cholesteatoma (29 females and 21 males) and an equal number presenting COM without cholesteatoma (23 females and 27 males). Diagnostic evaluations included pure tone audiometry and temporal bone computed tomography (CT), with the latter identifying granulation tissue in the middle ear and mastoid cells through soft tissue density indicators. Notably, none of the participants were undergoing antioxidant vitamin therapy, including Vitamin A, nor had a history of systemic diseases, acute infections, smoking, or alcohol consumption. Blood samples were collected under aseptic conditions after an overnight fast and processed via centrifugation at 3,000 RPM for 10 minutes to separate the serum for subsequent analyses. The serum was analyzed to quantify levels of antioxidant enzymes (CAT, GPx and SOD) and other markers such as MDA and vitamin E, with the samples earmarked for these specific tests preserved at-40°C until analysis. Surgical intervention in the form of a mastoidectomy was performed on all patients, during which tissue samples from affected middle ear or mastoid areas were harvested and stored at-40°C for future examination, categorized by cholesteatoma type. Vitamin A quantification was performed via high-performance liquid chromatography (HPLC). The statistical analysis of collected data was executed using SPSS software version 21.0. Gender distribution within the study groups was analyzed via a Pearson chi-squared test, with findings reported in frequencies and percentages. Continuous variables across the cohorts were compared using the independent sample t-test, presenting the outcomes as mean±standard deviation.

RESULTS AND DISCUSSIONS

Our participant pool was carefully selected to include individuals from a gender-diverse spectrum, spanning from 20-40 years of age. Through meticulous comparative analysis of baseline characteristics, our findings indicate no statistically significant variances between the two focal study cohorts, as summarized in (Table 1). Upon delving deeper into our

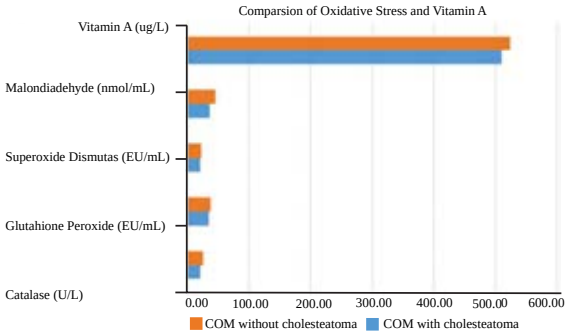

Fig. 1: Comparison of mean Oxidative stress and vitamin A

Table 1: Baseline variables of study groups with COM

Parameter	COM with cholesteatoma (n = 50)	COM without cholesteatoma (n = 50)	p-value
Age in years (Mean±SD)	30.5±11.8	35.5±10.4	0.37
Males	29	23	0.31
Females	21	27	
BMI, in kg/m2 (Mean±SD)	24.3±4.2	26.2±4.4	0.79

Table 2: Oxidative stress and vitamin A in study groups

Parameter	COM with cholesteatoma (n = 50)	COM without cholesteatoma (n = 50)	p-value
Catalase (U/L)	20.10±3.20	25.30±4.90	<0.05
Glutathione Peroxidase (EU/mL)	34.60±2.80	36.90±3.10	<0.05
Superoxide Dismutase (EU/mL)	20.20±2.10	21.40±1.90	<0.05
Malondialdehyde (nmol/mL)	35.80±2.30	44.60±2.60	<0.05
Vitamin A (ug/L)	510.50±160.30	525.70±165.50	<0.05

investigations, markers indicative of oxidative stress alongside concentrations of vitamin A were observed to be notably heightened within the subset of individuals diagnosed without cholesteatoma, as illustrated in the detailed data presented in (Table 2 and Fig. 1). The chronicity of otitis media (OM) is intricately tied to a time line encompassing treatment strategies, the course of illness and potential complications. This condition remains significant in ontological practice due to various contributing factors such as recurrent upper respiratory tract infections, immunosuppressive disorders, allergies, malnutrition, hypertrophy of nasopharyngeal lymphatic tissue and craniofacial anomalies. Recent insights attribute the chronic nature of OM and associated tissue damage to the presence of reactive oxygen species (ROS)[6]. ROS production occurs endogenously during oxygen consumption-related physiological processes. The excessive synthesis of ROS chemically modifies proteins, carbohydrates, nucleoside, and lipids, leading to tissue damage and potentially contributing to the pathogenesis of several diseases. Non-enzymatic antioxidants in the body include glutathione, vitamin E (tocopherol), vitamin C (ascorbic acid), vitamin A (beta-carotene), albumin, bilirubin and uric acid[7]. Among the most crucial antioxidant enzymes are super oxide dismutase (SOD), glutathione peroxides (GHPx) and catalase (CAT). Oxidative stress arises from imbalances between antioxidant levels and oxidant production, resulting in phospholipid per oxidation and damage to essential components like lipids, lipoprotein, proteins and DNA[8].

Martanegara *et al*. noted that the majority (64.72%) of cases fell within the 21-30 age bracket[9]. Pratama *et al*., in a study at Sanglah General Hospital, reported varying percentages of chronic suppurative otitis media (CSOM) cases across different age groups[10]. Similarly, Gaurano and Johaarjy observed that cholesteatoma primarily affected individuals aged between 20 and 35[11]. In the current study, a similar age distribution was observed, with the highest incidence of CSOM occurring in individuals aged 25-35 years. This age group appears particularly susceptible, likely due to their active lifestyles and potentially reduced focus on hygiene, sanitation and overall health[9]. Yilmaz *et al*.[12] demonstrated elevated serum levels of malondialdehyde (MDA) preoperatively but lower levels of super oxide dismutase (SOD), glutathione peroxides (GHPx), retinol, beta-carotene, alpha-tocopherol, lycopene and ascorbic acid in children with ventilation tubes due to adenoidectomy and otitis media with effusion. They highlighted the normalization of antioxidant levels postoperatively and emphasized the necessity of antioxidant therapy in such patients. Garcia Callejo *et al*.[6] found significantly higher MDA levels in the effusion fluid of OM patients compared to middle ear fluid in patients with otitis media with effusion (OME). Baysal *et al*.[13] reported a reduced total antioxidant capacity and increased oxidative stress index in OM patients, with or without cholesteatoma.

This study compared oxidative balance between patients with and without cholesteatoma, finding significantly higher levels of MDA, SOD, GHPx and CAT in COM patients without cholesteatoma. These findings suggest that evaluating serum oxidative stress alone, without assessing tissue values, may suffice for evaluating oxidative stress in COM patients. Moreover, the severity of the disease does not directly correlate with oxidative stress levels, indicating that oxidative stress may not accurately reflect disease severity. Vitamin A serves as an exogenous antioxidant, inhibiting and neutralizing oxidation reactions[14]. Baysal et al. identified a significant increase in serum oxidant status and oxidative stress index among CSOM patients, highlighting the impact of dietary changes on vitamin levels and the role of vitamin A in cell differentiation and epithelial proliferation[15]. Additionally, vitamin E, as a fat-soluble antioxidant, effectively inhibits peroxyl radicals and halts the oxidation of polyunsaturated fatty acids (PUFA). According to Greaves *et al*., vitamin A complements the antioxidant properties of vitamin E, particularly at low oxygen concentrations. The study by Arulselvan *et al*. suggested that vitamin A deficiency may manifest as otitis media[16,17].

CONCLUSION

Oxidative stress, propelled by ROS, plays a critical role in the etiology of COM, irrespective of the presence of cholesteatoma. The measurement of serum oxidative stress markers, excluding tissue-level

assessments, could be sufficient for gauging oxidative stress in patients with COM. Nonetheless, these oxidative stress indicators may not accurately mirror the disease's severity. On another note, Vitamin A levels appear to have no direct influence on the incidence of COM and cholesteatoma. However, given its capacity to neutralize ROS, Vitamin A might possess a significant function in the pathophysiological mechanisms of these conditions. To draw a definitive conclusion, a study with a larger cohort and detailed information on the daily intake of Vitamin A by patients is required to elucidate its role more comprehensively.

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