Advances in Relationship Between Alcohol Consumption and Skin Diseases

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Abstract: Throughout history, alcohol consumption has been an integral part of human culture. Alcohol consumption, alcoholism in particular, influences the onset and progression of liver diseases, neurological disorders, and multiple types of cancer. However, the role of alcohol consumption in influencing skin diseases has often been overlooked. In this review, we present the progress of research investigating the effects and potential mechanisms of action of alcohol consumption on acne, rosacea, psoriasis, atopic dermatitis, melanoma, and non-melanoma skin cancer.

Keywords: ethanol, acne, rosacea, psoriasis, atopic dermatitis, skin tumor

Introduction

Ethanol is a small molecule that is soluble in lipids and water. Therefore, alcohol intake affects nearly every tissue in the body, and the time to recover from resultant tissue damage depends on the amount and duration of alcohol consumption. While the impact of alcohol consumption on the skin is relatively minor compared with that on the liver, gastrointestinal tract, and nervous system, it still should not be overlooked, given that the skin is the largest organ of the human body.

Ethanol ingested orally is oxidized to acetaldehyde by alcohol dehydrogenase and, ultimately, converted into acetic acid. Alcohol and its metabolites may trigger and aggravate certain skin diseases.

The influence of alcohol on skin diseases potentially involves the following mechanisms:

The skin-gut axis: Alcohol intake can influence the gut microbiota, and many patients with skin diseases, such as rosacea, have concomitant gastrointestinal diseases, including small intestinal bacterial overgrowth and Helicobacter pylori infection;

Stimulation of skin inflammation: Alcohol stimulates the production of inflammatory cytokines in keratinocytes and promotes the proliferation of lymphocytes, which exacerbates inflammatory skin diseases such as psoriasis;

Promotion of vascular permeability: Alcohol increases microvascular permeability, which may be a direct cause of skin flushing after consumption. An increase in vascular permeability also induces tissue inflammation in the skin; and

Damage caused by metabolites: During the metabolic process, alcohol produces acetaldehyde and generates reactive oxygen species, which affect the normal biological function of DNA through oxidative stress and epigenetic effects. This may result in damage to the immune system or even carcinogenesis.

This paper reviews recent progress in research investigating the relationship between alcohol consumption and several common skin diseases, including acne, rosacea, psoriasis, atopic dermatitis, and skin tumors.

Non-Neoplastic Skin Diseases

Acne

Acne is one of the most common skin conditions in humans. Although acne usually affects adolescents, it is common in adults. It typically manifests as comedones, papules, pustules, nodules, or cysts on the face, chest, back, and other parts of the body.
with high concentrations of sebaceous glands. Despite the large body of research addressing acne, the pathogenesis of the disease remains poorly understood. The prevailing viewpoint is that acne is mainly associated with high sebum secretion, abnormal keratinization of the sebaceous glands, and aberrant growth of epidermal microorganisms. It is believed to be a multifactorial disease originating from the pilosebaceous unit.\(^7\)

Alcohol consumption appears to be a risk factor for acne. Many cross-sectional studies conducted among European and Asian populations have found that individuals consuming alcohol exhibit a significantly higher risk for developing acne compared with abstainers.\(^8\)–\(^11\) The effects of alcohol consumption on adolescent acne, a common acne subtype, have been inconsistent in the literature. A large-scale community-based study conducted in six cities in China revealed that alcohol consumption was associated with adolescent acne, where 41% of drinkers suffered from acne.\(^12\) However, another study involving 1277 schoolchildren in Lithuania reported an absence of associations between acne and alcohol consumption.\(^13\) Such inconsistencies may be explained by differences in cultural conventions, regulations governing alcohol consumption in adolescents, and the frequency of alcohol consumption among different regions. As for adult acne, Shen et al study provided the prevalence in adults (over 25 years old).\(^12\) They found the prevalence of acne was 5.5% in heavy drinkers, 5.8% in mild to moderate drinkers, and 5.5% in non-drinkers, suggesting that alcohol consumption does not appear to be a risk factor for adult acne. Nevertheless, a cross-sectional study involving 3888 subjects, whose age range is 17–71, found that alcohol consumption was associated with acne severity, particularly mild acne.\(^14\) It reported that alcohol consumption is a risk factor for mild acne compared to more severe acne with the odds ratio of 1.484. These inconsistent results suggest that the role of alcohol consumption in adult acne should be studied in age stratification and whether it is persistent or late-onset acne.

The mechanisms by which alcohol elevates the risk of acne remain unclear but may involve its effect on epidermal microorganisms.\(^15\) Certain acne-related microorganisms possess alcohol dehydrogenase, which converts excess alcohol into toxic acetaldehyde, which in turn may play a role in the pathophysiology of acne.

**Rosacea**

Rosacea is a chronic inflammatory skin disease characterized by recurrent flushing, a burning sensation, and skin manifestations such as papules, pustules, and rhinophyma concentrated around the center of the face. Congenital and adaptive immune response dysfunction, vascular and nervous system dysregulation, and inflammatory responses are the suggested causes of the pathogenesis of rosacea.\(^16\)

Whether alcohol consumption aggravates rosacea remains controversial. Two epidemiological studies separately conducted in the United States and the United Kingdom suggested that alcohol consumption exacerbates rosacea, with increased alcohol intake being significantly associated with an increased risk of rosacea.\(^17\),\(^18\) The pertinent mechanisms by which alcohol consumption aggravates rosacea may involve alcohol-induced capillary dilation, an increase in inflammatory factors, and changes in the gut microbiome.\(^19\)–\(^21\) Ethanol ingested through alcohol consumption can be oxidized by the gut microbiota leading to an increase in the concentration of acetaldehyde, the most toxic product of ethanol metabolism, which in turn affects microbiota homeostasis. A study has reported that patients with rosacea exhibited a significantly higher incidence of small intestinal bacterial overgrowth compared with the control group.\(^22\) Some case-control studies have reported a lack of significant correlation between alcohol consumption and rosacea.\(^23\) However, given the presence of differences in clinical and pathological manifestations among the various subtypes of rosacea, investigating the role of alcohol consumption in different subtypes is required. For instance, Second et al found that alcohol consumption was only associated with the phymatous subtype.\(^24\) Further research is required to elucidate the exact mechanisms.

**Psoriasis**

Psoriasis is a complex chronic immune-mediated skin disorder that affects approximately 2% of the global population.\(^25\) It often occurs with comorbidities such as depression and cardiovascular diseases. Psoriasis is believed to be co-mediated by genetic and environmental factors, with the former including the HLA-C*06:02 risk allele, and the latter including infection, stress, smoking, and obesity. Pathogenic mechanisms of the disease involve the participation of key cytokines, such as interleukin (IL)-17 and IL-23.\(^26\)
Early cross-sectional and case-control studies have reported that alcohol consumption increases the risk of psoriasis.27,28 A possible explanation is that excessive alcohol consumption due to long-term drinking causes immune system impairment and an increased risk of infection. Alcohol induces the generation of pro-inflammatory cytokines in various cell types and promotes lymphocyte proliferation and activation. In addition, alcohol and its metabolites can induce keratinocyte proliferation by increasing the transcription levels of its characteristic genes, such as α5 integrin, cyclin D1, and keratinocyte growth factor receptor.29 However, a recent large cohort study from Taiwan found that alcohol consumption was not significantly associated with the development of psoriasis.30 A systematic literature review that screened 911 studies investigating psoriasis and alcohol consumption reported a lack of evidence supporting alcohol consumption as a risk factor for psoriasis.31 In view of the limitations of observational studies, Wei et al performed a Mendelian randomization study using data from two genome-wide association study databases and confirmed the absence of a causal relationship between alcohol consumption and psoriasis.32 Recent findings have been inconsistent with previous studies. Therefore, experimental exploration at the molecular level is required.

Atopic Dermatitis
Atopic dermatitis is a chronic, relapsing inflammatory skin disease, characterized mainly by severe pruritus and eczematous skin changes such as papules, exudation, and crusting. Adult atopic dermatitis is often comorbid with other allergic conditions such as asthma and allergic rhinitis. Its pathogenesis is associated with skin barrier damage skewing toward the T-helper type 2 (Th2) response in the immune system. The disease is also believed to be jointly induced by genetic and environmental factors.33

Current research investigating alcohol consumption and atopic dermatitis can be divided into two major categories: the risk for atopic dermatitis in the offspring of mothers who consumed alcohol during pregnancy, and the risk for atopic dermatitis among individuals who consume alcohol regularly. A meta-analysis of three neonatal cohort studies and one cross-sectional study revealed that alcohol consumption during pregnancy was significantly associated with atopic dermatitis among offspring.34 Some studies have found a dose-dependent relationship between alcohol consumption and the risk for atopic dermatitis.35 Neonates born from a normal pregnancy exhibit a skewed Th2 response that persists for several months until the Th1/Th2 balance is re-established. Excessive maternal alcohol intake during pregnancy may further promote Th2 skewing and thereby increase the risk for infantile atopic dermatitis.36 Another possible explanation is the increase in plasma immunoglobulin (Ig)E levels after alcohol consumption.37 Previous research has found a dose-dependent relationship between maternal alcohol consumption during pregnancy and IgE levels in umbilical cord blood.38 In terms of the second category, the meta-analysis from Halling-Overgaard AS have indicated no consistent association between atopic dermatitis and alcohol use in adolescents and adults after analyzing eight observational studies.34 However, a recent cross-sectional study in Dutch general population found that moderate to severe atopic dermatitis was associated with alcohol consumption of > 2 drinks per day and had no association with ≤ 2 alcoholic drinks per day.39 This might provide us with clues that the relationship between alcohol consumption and atopic dermatitis should be investigated at different disease severity and alcohol consumption levels.

Neoplastic Skin Diseases
Melanoma
Melanoma, also referred to as malignant melanoma, is a highly malignant tumor arising from melanocytes. It predominantly affects the skin but can also be found in mucous membranes and internal organs. The incidence of melanoma has risen steadily over the past few decades.40 The incidence of melanoma is attributed to genetic and phenotypic characteristics and environmental exposure. For example, fair-skinned individuals are at a higher risk for developing melanoma.41 Exposure to ultraviolet radiation is the most critical environmental factor for the development of melanoma.42 Both excessive sun exposure and ultraviolet tanning equipment are considered carcinogenic.43,44 Additionally, the impact of dietary factors, such as coffee,45 alcohol,46 and smoking,47 in modulating the risk pathways for melanoma has been of considerable interest.
Many studies have investigated the relationship between alcohol consumption and melanoma, with their outcomes subjected to secondary analysis in several meta-analyses.\textsuperscript{40,48,49} Gandini et al’s meta-study, which included 20 independent studies, indicated that alcohol consumption increases the risk of developing melanoma, with the amount of alcohol intake positively correlated with risk.\textsuperscript{40} This is consistent with the results of several other meta-analyses.\textsuperscript{48,49} In addition, it appears that different types of alcohol exhibit different effects. A prospective cohort study observed that individuals with a preference for white wine or liquor exhibited a higher risk for developing melanoma compared with abstainers (52% and 65%, respectively).\textsuperscript{50} The relationship between alcohol consumption and melanoma may involve the participation of the alcohol-related gene \textit{ALDH2} in the pathogenesis of melanoma. Aldehyde dehydrogenase (ALDH2) is an alcohol-metabolizing enzyme with allelic variations that may affect alcohol detoxification. Researchers investigating the correlation between \textit{ALDH2} polymorphism and melanoma have found that the wild-type \textit{ALDH2} allele had strong positive correlations with melanoma incidence and mortality.\textsuperscript{51} An experimental animal study revealed that melanoma progression and tumor angiogenesis, under the influence of ethanol, is mediated by the upregulation of vascular endothelial growth factor and its receptor Flt-1.\textsuperscript{52} Another study found that long-term alcohol consumption inhibited memory T cell proliferation, accelerated interferon-gamma decay in CD8 T cells and increased the percentage of myeloid-derived suppressor cells in the peripheral blood and spleen, which may be associated with melanoma onset, progression, and metastasis.\textsuperscript{53}

\section*{Non-Melanoma Skin Cancer}
Non-melanoma skin cancer primarily includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BCC is the most common skin malignancy in humans. Although BCC is characterized by indolent growth and a low mortality rate, its incidence has been rising steadily. Environmental factors, such as ultraviolet radiation exposure, are one of its risk factors.\textsuperscript{54} SCC is a malignant tumor arising from keratinocytes or skin appendages (eg, endocrine glands or the pilosebaceous unit). It accounts for 20\% of all skin cancers, and its lifetime prevalence has progressively increased.\textsuperscript{55} Sun exposure, human papillomavirus infection, and actinic keratosis are risk factors for SCC of the skin.\textsuperscript{56}

Similar to melanoma, the risk of developing non-melanoma skin cancer is increased by alcohol consumption, with the amount of alcohol intake being positively correlated with risk.\textsuperscript{50} Three prospective cohort studies investigating BCC of the skin found that the amount of alcohol consumed was correlated with the risk of BCC in both male and female patients.\textsuperscript{57} The correlations between white wine and liquor and an increased risk of BCC were consistent, whereas beer and red wine exhibited no association with BCC. Alcohol consumption was also associated with a higher incidence of aggressive subtypes of BCC compared with non-aggressive BCC.\textsuperscript{58} Such subtypes are characterized by rapid infiltration and progression and are often difficult to manage. Alcohol consumption was also associated with an increased risk of SCC of the skin. One study reported that each additional drink (12.8 g alcohol) per day was associated with a 22\% increased risk of SCC of the skin.\textsuperscript{59} The salient mechanisms involve the potential role of acetaldehyde and the immunosuppressive effects of alcohol. Acetaldehyde is the primary metabolite of alcohol. It can function as a photosensitizer and generate reactive oxygen species and related intermediates when exposed to ultraviolet radiation. This process further induces oxidative DNA injury, strengthens the binding of acetaldehyde to DNA, and causes skin carcinogenicity through epigenetic effects.\textsuperscript{60} Alcohol possesses immunosuppressive effects and is capable of aiding mutated cells in evading the immune surveillance of the body, thereby increasing the likelihood of cancer development.\textsuperscript{61}

\section*{Conclusion}
Findings regarding whether alcohol consumption triggers or exacerbates non-neoplastic skin diseases are inconsistent. Hence, further studies are necessary to determine relationship between alcohol consumption and non-neoplastic skin diseases and the precise mechanisms of action. For neoplastic skin diseases, it is apparent that alcohol consumption triggers and exacerbates skin tumors, with the relationships being dose dependent. Considering the potential risks involved, reduction or avoidance of alcohol consumption should be advocated to reduce the occurrence of neoplastic skin diseases.
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39. Liu and Chen


