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A Review on Consequences of Alcohol Consumption

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ABSTRACT: ***This message highlights current perspectives on the immunomodulatory effects of acute and chronic alcohol intake by reviewing recent research. Chronic and even acute, moderate alcohol use may enhance the host's susceptibility to bacterial and viral illnesses. Reduced inflammatory response, altered cytokine production, and aberrant reactive oxygen intermediate formation seem to be related to impaired host defense following alcohol consumption. Furthermore, both acute and chronic alcohol consumption impairs cellular immunity, especially antigen-specific immune response. Although ethanol may impact T lymphocyte activity directly, reduced antigen presentation cell function seems to be a major component in the ethanol-induced reduction in cell-mediated immunity. Furthermore, based on the higher immunoglobulin levels observed in chronic alcoholics, a preferential activation of Th2 versus Th1 immune response has been proposed. The functional abnormalities of T and B lymphocytes, natural killer cells, and monocytes/macrophages that result in the altered immune response seen after alcohol use are discussed in the context of the effects of chronic and acute alcohol consumption on host defense and immunity in humans, animal models, and in vitro systems.***

KEYWORDS: ***Alcohol, Consumption, Consequences, Immunity.***

1. INTRODUCTION

Innate (non-specific) and acquired (specific) immunity are two systems that healthy people use to defend themselves against microorganisms. Prior to exposure to microorganisms, phagocytes such as neutrophils and macrophages, natural killer (NK) cells, circulating chemicals such as complement, and macrophage-derived soluble mediators are all examples of innate immunity. Exposure to foreign substances (antigens) triggers acquired immunity, which includes an integrated system of host defense in which many cells and molecules work together. Acquired immunity includes humoral and cell-mediated immune responses, as well as specific antibodies and lymphocyte-derived cytokines, as a result of complex cross-talk between T and B lymphocytes, antigen-presenting cells (monocytes, macrophages, dendritic cells, B lymphocytes), and antigen-presenting cells (monocytes, macrophages, dendritic cells, B lymphocytes). Exogenous substances that alter any of these immune system components, however, may compromise this well-coordinated defensive mechanism against infections. One of the modulators of host defense has been identified as alcohol [1]–[3].

Immune impairment in persistent alcohol users has long been documented in medical literature. Chronic alcoholics are more susceptible to infections from a range of pathogens, have a worse capacity to fight infections, and are more likely to acquire malignancies, especially cancers of the head, neck, and upper gastrointestinal tract. While starvation, vitamin insufficiency, and severe liver cirrhosis may all contribute to immunological problems in chronic drinkers, alcohol is a powerful immune system modulator. Alcohol consumption seems to affect the immune system at different levels, according to growing data from human and animal research in vivo as well as in vitro investigations. Aside from the immunomodulatory effects of chronic alcohol use, new research suggests that acute, moderate alcohol consumption may also regulate the immune system. Acute and chronic alcohol consumption may have an impact on the immune system's innate and acquired immunological responses. After acute or chronic alcohol consumption, altered inflammatory

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neutrophil, leukocyte, and macrophage activities lead to a weakened host defense against microbial infections. Furthermore, alcohol abuse may harm both the humoral and cellular components of a person's immune system. Inappropriate immunological defense is caused by impaired B lymphocyte activities and elevated amounts of some kinds of immunoglobulins at the cost of others. Furthermore, impaired cellular immunological responses play a key role in increasing susceptibility to infections after acute or chronic alcohol use [4]–[6].

1.1. Effects of Chronic Alcohol Use on Inflammation and Host Defence:

1.1.1. Phagocytic cells and inflammation

Phagocytic cells, such as neutrophils and macrophages, play an important role in finding, eating, and destroying germs that enter the body during the inflammatory response. Chemotactic agents such as activated complement components (C5a), leukotrienes (LTB4), or other proteins belonging to the chemokine family are used to attract phagocytic cells from the circulation to the site of inflammation. Alcohol has a number of effects on this process. The adherence and migration of neutrophils and monocytes through the vascular endothelium at the site of infection, phagocytosis of the pathogen, and intracellular destruction of the pathogen by proteolytic enzymes in the phagolysosomes or by toxic oxygen-derived radicals are all part of the process of neutrophil and monocyte migration from the bloodstream. Chronic alcohol feeding of male Sprague–Dawley rats resulted in enhanced adhesion molecule (CD18) expression in neutrophils in experimental models.

Furthermore, supernates from Kupffer cells (liver resident macrophages) were shown to increase chemotaxis of normal neutrophils in the same chronic alcohol-consumption rat paradigm, most likely through chemokines like interleukin-8 (IL-8) and macrophage inflammatory protein-2 (MIP-2). These findings imply that increased IL-8, MIP-2, or other chemokines generated in the liver by Kupffer cells may contribute to neutrophil infiltration in alcoholic hepatitis. Increased levels of systemic IL-8 were also seen in the blood of individuals with acute alcoholic hepatitis, which seemed to be linked to liver neutrophil infiltration. Even a single bolus dose of ethanol enhanced neutrophil chemotaxis to formilpeptide (FMLP) and FMLP receptor expression in rats for 3–24 hours following treatment. After acute alcohol consumption, Kupffer cells exhibited reduced chemotactic activity and FMLP receptor expression in the same rat.

These findings indicate that ethanol administration, both acute and chronic, may selectively activate or inhibit different phagocytic cell activities. However, human studies that demonstrate reduced chemotaxis of neutrophil leukocytes from chronic alcoholics in vitro contradict the aforementioned results in animal models. In chronic drinkers, impaired neutrophil function is thought to contribute to an increased vulnerability to infections. As a result, further research is required to determine if alcohol has a selective impact on CC- or CXC-chemokines, which are implicated in the site-specific activation of neutrophils, monocytes, and T and B lymphocytes involved in inflammation. Alcohol also affects phagocytic monocytes and macrophages, in addition to neutrophils. Patients with alcoholic cirrhosis have been shown to have impaired monocyte phagocytic function. Even acute alcohol addiction has been demonstrated in vitro to decrease monocyte phagocytic functions, antimicrobial activity, and expression of FcR-type II, which is important in antibody-coated particle phagocytosis [7]–[10].

In mice, both short-term and long-term alcohol use reduced peritoneal macrophage phagocytosis. Rat macrophage phagocytosis through Fc- and C3b- receptors was decreased without a reduction in the number of surface receptors expressed in another experimental model of persistent drinking. As a result, decreased macrophage phagocytic activities, as well

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as aberrant neutrophil leukocyte adherence and chemotaxis, are likely to contribute to local antimicrobial defense following alcohol use.

1.1.2. Reactive oxygen intermediates:

The production of active oxygen radicals, which are results of the oxidative burst, is a critical component in microbial death. Thus, following alcohol exposure, increased generation of oxygen radicals such as superoxide anion and hydrogen peroxide may be a mechanism weakening antibacterial immune defense. The generation of superoxide anion and hydrogen peroxide was reduced in alveolar macrophages from rats given ethanol either abruptly or continuously. Inducible nitric oxide synthase, the enzyme responsible for the production of nitric oxide in alveolar macrophages and neutrophils in response to bacterial stimulation, may be inhibited by ethanol.

In a recent research in rats, both acute and chronic alcohol therapy reduced alveolar macrophage nitric oxide production, suggesting that decreased reactive oxygen radical formation by ethanol-exposed macrophages may contribute to the compromised antimicrobial defense following alcohol use. Overproduction of reactive oxygen radicals, on the other hand, has been suggested as a possible patho-mechanism for alcohol-induced liver injury. Infusing rats with ethanol for 1, 3, or 5 hours increased not only the hepatic output of superoxide anions, but also inducible superoxide generation. Kupffer cells, not endothelial cells or hepatocytes, were shown to be the biological source of this ethanol-induced superoxide anion. These findings suggest that ethanol's negative impact on reactive oxygen radical generation may result in twofold harm to the host. For starters, ethanol may reduce the production of reactive oxygen radicals and nitric oxide in alveolar macrophages, where these mediators are important for micro bial death. Second, ethanol seems to enhance the formation of reactive oxygen radicals in the liver, which may mediate or contribute to direct tissue damage.

1.1.3. Modulation of inflammatory cytokine production by alcohol:

The pathogen's induction of inflammatory cytokines is a critical stage in the host's immunological defense. During overwhelming inflammatory reactions, additional cell types such as neutrophils, endothelial cells, lymphocytes, and activated tissue cells may also be a source of inflammatory cytokines such as TNF-, IL-1, and IL-6. Chronic alcohol consumption, especially alcoholic liver disease, has been linked to increased levels of TNF-, IL-1, and IL-6 in the blood. Increased levels of these inflammatory mediators have been linked to the majority of clinical abnormalities in alcoholic hepatitis patients (hyper-metabolism, fever, wasting, increased acute phase reactants, and reduced albumin). Patients with alcoholic hepatitis who have a high level of TNF- are said to have a poorer prognosis. The biological cause of persistent drinkers' increased inflammatory cytokine levels has yet to be determined. Monocytes from individuals with alcoholic liver disease generated more TNF- in response to lipopolysaccharide (LPS) stimulation than normal monocytes, according to one study. Alveolar macrophages from persistently ethanol-fed mice, on the other hand, produced less inflammatory cytokines, perhaps leading to lung infections.

1.1.4. Changes in bacterial pathogen response:

Because of the increased frequency and severity of infections observed in this patient group, chronic drinkers are referred to as "immuno-compromised hosts." Intracellular pathogen infection is quite common. The impact of prolonged ethanol administration on mice's susceptibility to infection by the obligatory intracellular bacterium Listeria monocytogenes has been investigated. Jerrels discovered that mice fed a Lieber DeCarli diet for 7 days before receiving a 0.5 median fatal dose of L. monocytogenes i.v. injection had bigger liver lesions

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than controls. Further research revealed that although ethanol does not impede the flow of inflammatory cells to the liver, it did decrease the host's capacity to suppress L. monocytogenes development.

Anti-Listeria defense is mainly antigen-specific, reliant on T cells, and requires the production of IFN- and IL-12. Even in mice vaccinated with L. monocytogenes, ethanol administration resulted in a 100-fold higher Listeria count in liver homogenates than controls, indicating a severe antimicrobial defense failure. Under the influence of ethanol, the cellular interactions and possible involvement of ethanol-related aberrant antigen presentation cell activity, incorrect IFN- and/or IL-12 production are yet to be investigated.

A one-week ethanol therapy before infection enhanced susceptibility to fatal pneumonia in a rat model of pneumococcal pneumonia. Ethanol feeding of rats resulted in an increase in the transmission of pneumococci from the lungs to the circulation, and once disseminated, ethanol-fed rats were unable to remove pneumococci from the bloodstream. Klebsiella pneumoniae is another infection that is difficult to eradicate in alcoholics. Experiments show that therapy with granulocyte-colony-stimulating factor (G-CSF) improves the ethanol-related poor host response to Klebsiella by activating and recruiting extrapulmonary neutrophils.

Furthermore, ethanol-exposed macrophages were shown to be more vulnerable to Legionella pneumophilia infection, a common intracellular Gram-negative bacillus. Ethanol-exposed macrophages from Legionella-susceptible A/J mice exhibited a 48-hour increase in pathogen growth, suggesting that physiological ethanol levels may compromise macrophage defense against this pathogen. Mycobacterium tuberculosis is the other main respiratory infection linked to persistent alcoholism. Alcohol's negative behavioral and social consequences, along with its biological and immuno-inhibitory properties, result in a host that is more vulnerable to Mycobacterium infection and has a reduced ability to avoid disease activation. Ethanol has been found to improve Mycobacterium tuberculosis intracellular survival in mycobacterial infectious models (Bermudez and Young, 1991). The negative effects of alcohol on the interplay between host defense and M. tuberculosis were also addressed in a recent review.

1.1.5. Viral infections:

The study of the possible link between alcohol consumption and HIV-1 infection is still ongoing. Although more data is developing on the immunological abnormalities caused by alcohol use and HIV infection, our understanding of the combined immunosuppressive consequences of alcohol use and HIV-1 infection remains restricted. The modulatory effects of alcohol on the immune system have been suggested to have a role not only in the increased risk of initial infection, but also in the fast development of HIV-1 illness. Infected peripheral blood mononuclear cells from people who had a one-dose acute alcohol infusion or binge drinking had higher HIV-1 p24 levels in vitro, according to researchers.

A prospective research of 199 HIV-1-positive, drug-using individuals found that ethanol use (no alcohol, fewer than 21 drinks per week, or more than 21 drinks per week) had no effect on the proportion of CD4-positive cells. However, between 2 and 5 years after seroconversion, the proportion of CD8-positive T cells rose substantially among the heaviest drinkers. While the clinical relevance of this finding has to be investigated further, this research indicates that HIV-1 positive individuals who also drink alcohol may have more immunological alterations. According to a case report of an HIV-1 infected person who drank heavily, his HIV-1 infection progressed quickly and he developed AIDS. Mice fed a liquid chronic alcohol diet and infected with the murine model of AIDS (MAIDS) virus exhibited no increase in MAIDS infectivity and only a modest delay in the development of MAIDS-

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related immunological alterations, in contrast to human findings. Other MAIDS research in Watson's group suggests that ethanol may hasten the onset of AIDS by altering cytokine synthesis. Taken together, our present understanding indicates that alcohol consumption (both acute and chronic) increases host vulnerability to HIV-1 infection and contributes to the disease's rapid development. However, further study is required to understand the cellular and intracellular processes through which ethanol intake may affect HIV-1 infection biology and clinical outcomes.

Hepatitis C infection is another viral illness where alcohol use has been proven to have a negative impact on the disease's natural course. Alcohol intake seems to increase clinical progression and liver damage in individuals with chronic hepatitis C infection, according to recent studies. Although the immunological processes that lead to chronic hepatitis C infection are yet unknown, aberrant levels of monocyte-derived mediators, especially IL-12 and inflammatory cytokines, have been proposed to play a role in the development of the hepatitis C virus and consequent liver damage.

2. DISCUSSION

Immune regulatory proteins generated by lymphoid cells, cytokines, have the ability to influence lymphoid and non-immune cell activities (neurons, endocrine organs, etc.). The study of cytokines, such as interferons and interleukins, is a fast expanding field of immunology as scientists gain a better knowledge of the biological origins and interactions of the different members of the cytokine superfamily. As a result, the impact of chronic or acute alcohol consumption on cytokine generation and function is only partly known. IL-2 is one of the most essential cytokines for T cell survival, proliferation, and growth. Alcohol has no impact on T cells' capacity to generate IL-2, according to in vitro studies. Ethanol is thought to influence T cell IL-2 usage, although the intracellular processes remain unknown. Alcohol consumption was linked to lower serum IFN-, IFN-, and IL-2 levels in people. Reduced IFN- levels in chronic drinkers may play a role in several of the immunological changes. IFN-, in combination with IL-12 produced by macrophages, is believed to be essential for the activation of a Th1-type cellular immune response. A new study on IL-12 supports reduced Th1-type immune response following chronic alcohol consumption, in addition to decreased IFN- levels in chronic alcoholics. Exogenous IL-12 treatment improved the delayed-type hypersensitivity response in mice that had been continuously fed alcohol. Th2-type cytokines such as IL-4, IL-10, and IL-13, on the other hand, stimulate Th2-type immune responses and humoral immunity. In addition, Th2 cytokines suppress the production of Th1 and inflammatory cytokines. The impact of acute or chronic alcohol consumption on the synthesis and activity of these key cytokines is currently unknown. However, in the absence of adequate IFN-stimulation, like in chronic alcoholics with low IFN-levels, a preferred Th2 induction may ensue.

3. CONCLUSION

Recent study by a growing number of experts interested in the immunomodulatory effects of alcohol has shown that both acute and chronic alcohol consumption have significant immune system modulatory effects. Alcohol may weaken host defense against future bacterial and viral assaults, according to animal and human models of acute, moderate alcohol consumption in vivo. The findings also indicate that the consequences of acute alcohol intake are very temporary. Further research into the clinical consequences of such a transitory immunological decline after acute, moderate alcohol use is needed. In some kinds of infections, failure to mount an adequate first immunological response to pathogens is likely to have a significant and possibly long-term impact on the immune system. The immune system's response to acute alcohol use is of special relevance because of the possibility of

increased vulnerability to HIV, mycobacterial infections, and other diseases. We are also learning more about the complicated picture of immunosuppression in chronic drinkers. In the advanced chronic alcoholic population, further research is required to distinguish the immunomodulation caused by chronic alcohol use from that caused by other immunomodulatory diseases such as malnutrition, vitamin shortages, and liver disease. Understanding the details of immunological changes induced by chronic alcohol use will be required for developing more targeted treatment methods to alleviate chronic drinkers' immunosuppression.

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