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Could moderate alcohol intake be recommended to improve vaccine responses?

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The impact of alcohol consumption on human health is complex and modulated by several factors such as patterns and amount of drinking, genetics, the organ system studied, as well as the sex and age of the user. There is strong evidence that chronic ethanol abuse is associated with increased morbidity and mortality, immunosuppression and increased susceptibility to both bacterial and viral infections. In contrast, moderate alcohol consumption exerts positive effects including decreased mortality, and improved cardiovascular disease and insulin sensitivity. Interestingly, accumulating evidence also supports an immune-boosting effect of moderate alcohol. In this editorial, we summarize the findings that support a positive effect of moderate alcohol on host immunity. We also discuss the limitations of the previous data and emphasize the importance of additional studies to uncover mechanisms for these immune-stimulating effects in order to extend these benefits to vulnerable segments of the population who cannot consume alcohol.

Epidemiological studies have found that regular consumption of three or more drinks (>0.1 g/kg) a day is associated with significant organ damage, increased morbidity and mortality and adverse birth outcomes. Chronic heavy drinking also increases susceptibility to both bacterial and viral infections, such as *Streptococcus pneumonia* and hepatitis C virus infections, as well as accelerates the progression of HIV infection [1]. Similarly, alcohol abuse in the form of binge drinking (defined by the National Institute of Alcohol Abuse and Alcoholism in 2004 as four or more drinks for women and five or more drinks for men in 2 h) is also strongly associated with adverse health outcomes and immune suppression, especially after trauma. This increased vulnerability is partially due to functional defects in both innate and adaptive immunity. Indeed, high doses of alcohol interfere with the ability of immune cells to migrate to sites of injury/infection and carry out effector functions such as phagocytosis, cytotoxicity and cytokine/chemokine/growth factor production [2,3]. The increased susceptibility to infection is exacerbated by increased mucosal permeability that could facilitate microbial access and entry. Specifically, chronic heavy alcohol ingestion impairs alveolar epithelial barrier function, leading to decreased alveolar liquid clearance [4]. These changes are associated with an increased risk for developing acute respiratory distress syndrome, bronchitis and pneumonia [5]. In the intestine, chronic alcohol exposure can promote the growth of gram-negative bacteria, which may result in accumulation of endotoxin as well as acetaldehyde, which increases intestinal permeability [6].

In contrast to these observations, accumulating evidence supports the health benefits of moderate alcohol consumption, defined as having up to one drink per day for women (0.25–0.5 g/kg) and up to two drinks per day (0.25–0.1 g/kg) for men [7]. Although most of the benefits of moderate alcohol consumption have been described in the

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context of cardiovascular disease [8], data from a few studies suggest additional benefits to the immune system. We recently reported that in a rhesus macaque model of voluntary ethanol self-administration, moderate ethanol consumption resulted in a more robust recall vaccine response to modified vaccinia Ankara, compared to abstinence or excessive ethanol consumption [9]. In this study, animals whose blood ethanol concentration was below 0.08 g/dl generated more robust CD8 T cells and antibody responses following modified vaccinia Ankara vaccination compared to controls. In contrast, animals whose blood ethanol concentration was consistently greater than 0.08 g/dl generated blunted T cell and antibody responses compared to controls [9]. Our studies are in line with earlier studies describing similar findings in both humans and animal models. Data from a study exploring the impact of smoking and alcohol consumption on the incidence of cold among 391 subjects intentionally exposed to five different respiratory viruses showed that moderate alcohol consumption was associated with decreased risk for clinical cold in nonsmokers [10]. A second study that analyzed the incidence of the common cold with or without alcohol consumption among 4272 subjects found that moderate consumption of wine (especially red wine) may reduce the incidence of common cold [11]. Similarly, in a rat model, low to moderate doses of ethanol resulted in a greater delayed cutaneous hypersensitivity response and improved clearance of *Mycobacterium bovis,* whereas high ethanol doses were associated with reduced delayed cutaneous hypersensitivity responses and decreased bacterial clearance [12].

While these data support an immune-enhancing effect of moderate alcohol, we must be cautious in their interpretation since they originate from only a handful of studies. Therefore, at this point, it would be extremely premature to recommend moderate alcohol consumption to boost the immune system. This could be dangerous for individuals at risk for developing an alcohol use disorder (i.e., individuals with a history of alcoholism in their family, adolescents, and people with a childhood history of trauma or abuse, among several other putative risks being studied). In addition, individuals who respond poorly to vaccination, such as infants, the elderly and the immune compromised, cannot or should not consume alcohol. Moreover, since the monkeys in the recent study [9] and humans in earlier studies [10,11] could choose to drink moderately or heavily, it remains unclear if some factor other than moderate alcohol consumption defined the moderate drinker's response to vaccine. Therefore, without a comprehensive understanding of the mechanisms underlying the immune-boosting effects of moderate alcohol consumption in these studies, we cannot yet predict who will benefit from moderate alcohol consumption. Taken together, the earlier studies in humans [10,11] and rats [12] together with our recent study in macaques [9] present a strong justification for additional studies that focus on uncovering the mechanisms underlying enhanced immune response by moderate alcohol. Future studies should also address the impact of gender, type of alcohol, and age on the ability of moderate alcohol to boost host response to a broad range of pathogens. Such comprehensive studies could identify the pathways that can be targeted via pharmacologic or genetic tools to enhance immunity in individuals who cannot consume alcohol.

Unfortunately, this area remains poorly understood due to a paucity of studies on the consequences of moderate alcohol consumption on the immune system. Several of these studies have reported decreased production and/or circulating levels of inflammatory mediators. Specifically, TNF-α and IL-1β production by human monocytes, isolated 18 h after moderate vodka consumption, in response to lipopolysaccharide or staphylococcal enterotoxin B stimulation is reduced [13]. Moderate consumption of wine or gin for 28 days also leads to reduced plasma levels of inflammation markers fibrinogen, IL-1α and soluble C-reactive protein, as well as decreased expression of endothelial adhesion molecules such as very late antigen-4 and lymphocyte function associated antigen-1 on the monocytes [14]. Moderate consumption of vodka for 28 days led to an increase in plasma adiponectin levels and a decrease in pro-inflammatory IL-1 receptor antagonist, IL-18, and acute-phase proteins ferritin and α1-antitrypsin [15]. Reduced inflammation following moderate alcohol consumption can be largely attributed to the inhibition of NF-κB translocation into the nucleus [13,16]. Alcohol consumption also modulates in a dose-dependent manner the expression of toll-like receptors which initiate inflammatory responses via intracellular signal transduction cascades that include activation of NF-κB [17]. Taken together, these studies suggest that moderate alcohol consumption decreases the levels of mediators of 'pathological inflammation'. On the other hand, moderate alcohol consumption increases the factors that play a critical role in resolution of infection, notably the number of peripheral white blood cells; levels of circulating immunoglobulins; plasma levels of IL-2, IL-15 IL-4, IL-10, RANTES (CCL5) and *Monokine induced by IFN-γ* (CXCL9); production of the cytokine IFN-γ; and monocyte oxidative burst [9,18]. These changes in mediator production are reflected at the level of gene expression. Indeed, moderate alcohol consumption significantly alters the expression profiles of genes involved in 'immune response', such as antigen-presentation pathways, and B- and T-cell receptor signaling and IL-15 signaling pathways in human leukocytes [15]. Specifically, moderate alcohol consumption increases the expression of HLA-F, IL-15B, IL-2Rb, IL-1R and K-ras, while decreasing the expression of NF-κB, Stat5A, tissue inhibitor of metalloproteinases-2 and Tapasin [15]. Finally, moderate alcohol consumption increases plasma antioxidant levels, while alcohol abuse increases plasma pro-oxidant activity [19].

Another mechanism by which moderate alcohol consumption might increase resistance to respiratory infections is by modulating ciliary movement. Constant beating of cilia of the mucociliary apparatus plays an essential role in clearing bacteria and impurities from the airways. An early study showed that ethanol exerts concentration-dependent biphasic effect on the ciliary movement wherein low concentrations of ethanol increase and higher concentrations decrease the beating frequency of cilia [20]. Therefore, the exposure to moderate levels

of ethanol may augment mucociliary clearance, thereby enhancing bacterial clearance from the respiratory tract.

In summary, although our first study in macaques, together with the earlier studies in rats and humans are clearly suggestive of an immune-boosting effect of moderate alcohol consumption, they are too preliminary to be used as a basis for public policy recommendations. More importantly, the segments of the population that generate poor responses to vaccination are infants, the elderly and immune-compromised individuals for whom alcohol consumption cannot be recommended. Rather, we believe that these data signal an urgent need for additional studies that focus on understanding the molecular basis of dose-dependent modulation of immunity by ethanol. Special emphasis should be given to the areas of epigenetics and gene regulation since the metabolites of ethanol significantly affect the immune system by modulating gene expression by binding transcription factors and/or modifying chromatin structure [1]. These studies should be performed in a clinical setting or using animal models that faithfully mirror the metabolic and behavioral complexity of humans. This is especially important given that the production of several neurotransmitters including corticosteroids, catecholamines and neuropeptides, which have been shown to modulate immune activity, is influenced by ethanol. Therefore, it is unlikely that the mechanisms underlying a beneficial effect of moderate alcohol drinking can be fully understood by simply studying the immune cells *in vitro* in the presence or absence of ethanol because immune cells carry out their functions in a multicellular environment in which alcohol has widespread effects. Understanding these pathways will have a far-reaching impact on our understanding of the immune-enhancing mechanisms of moderate alcohol, thereby revealing the molecules or pathways that can be pharmacologically or genetically manipulated to improve the immune response to vaccination and infection in vulnerable populations who cannot consume alcohol.

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