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Session 4: Dietary strategies to prevent and mitigate inflammatory diseases
Drinking pattern and socio-cultural aspects on immune response: an overview

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Social acceptance of drinking involves social and cultural roles and has important implications for public health. Since extensive evidence indicates that alcohol possesses immunomodulatory properties, scientists have recently debated the influence of alcohol consumption on the immune response, particularly in countries where drinking in a social setting is a part of cultural identity. Experimental and clinical data support the conclusion that alcohol is a potent immunomodulator. While high alcohol consumption suppresses a wide range of immune responses, leading to an increased incidence of a number of infectious diseases, moderate alcohol consumption may have a beneficial impact on the immune system, compared to alcohol abuse or abstinence, most likely due to the multiple components of polyphenol-rich alcoholic contributing to the protective effect seen for moderate alcohol consumption on CVD and the immune system. Despite this, the scientific literature appears to be concerned about the diseases associated with excessive drinking in some societies and cultures. Thus, the present review recognizes the importance to consider social and cultural aspects of drinking when examining the whole dimension of alcohol consumption (amount, beverage type, frequency and variability), in order to estimate global risk of consequences on host defence to better understand alcohol-related harm or benefit.

Alcohol: Immune response: Drinking pattern: Social drinking

Alcohol has been widely used for its medicinal, antiseptic and analgesic properties, throughout human history. Nowadays, alcohol is a socially accepted substance and social drinking is a part of daily life in a large number of countries and societies.

Regarding immunity, researchers have long debated the effects of alcoholic beverage consumption on immune function. Generally, while high doses of alcohol consumption can directly suppress a wide range of immune responses, increasing the incidence of a number of infectious diseases, moderate alcohol consumption may have a beneficial impact on the immune system compared to alcohol abuse or abstinence[1–5]. The relationship between alcohol exposure and either the potential health benefits or harm can eventually be considered multifactorial and depends on several factors[5].

Generally 'social drinking' refers to drinking patterns that are accepted by the society in which they occur and has often been confused with the concept of 'moderate drinking'[6]. However, social drinking may be neither moderate nor risk free; moderate drinking may be defined as drinking that does not generally cause health problems, either for the drinker or for society[6]. Even though there is no universally accepted definition of 'moderate

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consumption', according to the literature, moderate alcohol consumption is considered to be no more than one drink per day for women and no more than two drinks per day for men[7–9]. While lacking an exact definition, social drinking usually takes place with two or more participants, is satisfying to the drinker and participants, and does not impede the drinker's health, interpersonal relations, or economic functioning[10]. As we will discuss later, the role of alcohol differs widely between different countries, societies and cultures[11]. The aim of this review is to provide an overview of the immune aspects of social drinking.

Alcohol and the immune response

Alcohol abuse

Independent of social or cultural context, abusive alcohol consumption has a negative effect on organs and systems in the body, including the effects on the immune response[12–18].

Alcohol abuse seems to increase the incidence of a number of infectious diseases[19,20] inducing functional abnormalities in several immune cells such as T-cells (e.g. a reduction in CD3+, CD4+ and CD8+ cell numbers)[21] and B lymphocytes, natural killer cells and monocytes/macrophages, as well as altering cytokine production[22–24] and concentration (i.e. an increase of pro-inflammatory cytokines such as TNFα and IL-6[25–27]). Moreover, high alcohol doses and abusive alcohol consumption lead to deterioration in both non-specific and cell-mediated immunity, independent of the alcoholic beverage type[5,28–30]. The alcohol-induced specific changes on immune cell functions result in an inappropriate immune response to invading pathogens, leading to higher incidence of infections[27].

Ethanol

Although the harmful effects of alcohol abuse are well-documented, during the last decades researchers have been discussing how the consumption of alcoholic beverages may have a beneficial effect on host defence[3,5]. The main beneficial effect of moderate drinking on CVD prevention has generally been attributed to changes in the lipoprotein profile (mainly HDL-cholesterol), also reducing platelet aggregation and fibrinogen[31–36], independent of the type of alcoholic beverage consumed (liquor, beer, or wine), suggesting that this protective effect is due to ethanol itself[37].

Some authors have highlighted the importance of the type of alcoholic beverage consumed and the amount of alcohol *per se* while evaluating the immune response, but this is still a matter of debate. Two decades ago, some researchers already indicated that alcohol *per se* has a significant negative effect on the non-specific cells of the immune system (basically a reduction of natural killer cell activity) in mice[38]. Other animal studies have shown that the consumption of alcohol itself, even in moderate amounts, leads to lower levels of leucocytes[39], suggesting that alcohol can impair host defence to subsequent bacterial and viral challenges[23]. On the contrary, some authors have suggested that low ethanol intakes by the consumption of low amounts of distilled spirits, also show a stimulatory effect on cellular immune responses[1]. In addition, results from an epidemiological study have suggested that ethanol itself might be largely responsible for the potential anti-inflammatory effects of moderate alcohol consumption, basically by a reduction of immune-related systemic inflammatory markers[40]. Therefore, further research seems to be necessary to clarify the effects of alcohol itself on immunity.

Polyphenol-rich alcoholic beverages

Natural polyphenol compounds have been shown to possess different biological properties, such as anti-bacterial, anti-carcinogenic, anti-inflammatory, anti-viral, anti-allergic and immunostimulatory[41]. Polyphenols are present in plants such as fruit, legumes, cereals, teas, herbs and spices[42]. Specific fermented alcoholic beverages also contain numerous polyphenolic substances. For example, red wines contain many bioactive flavonoids and antioxidants[43] and beer contains phenolic compounds derived from hops and malts[44]. Several studies have stressed the importance of different active components contained in fermented alcoholic beverages such as wine or beer on immunity and inflammation, which may exert protective effects[5,25,35,39].

Although alcohol *per se* reliably increases HDL-cholesterol levels, other effects on oxidation, endothelial function and the immune response seem to be due to the substances prevalent in polyphenol-rich alcoholic beverages other than ethanol itself[5,31,35,45].

It is well established that alcohol consumption and its subsequent metabolism by the liver generates reactive oxygen species interfering with several immune cell functions[39]. Some authors have suggested that phenolic antioxidants present in fermented alcoholic beverages such as red wine, may scavenge reactive oxygen species, preventing the impairment of immune cell functions, due to alcohol consumption[39,46]. Moreover, alcohol seems to enhance the bioavailability of these antioxidant components[8,47].

It is important to keep in mind that those polyphenol-rich alcoholic beverages also contain significant amounts of other components such as vitamins and minerals that could be contributing to the preventing effect. To sum up, it is reasonable to suggest that the components of polyphenol-rich alcoholic beverages could contribute to the protective effect of moderate alcohol consumption on CVD and infection risk, representing a key to understanding the synergistic effect of both ethanol and these components.

Alcohol and inflammation

Inflammation plays a crucial role in both the initiation and progression of atherosclerosis and several types of immune cells including monocytes, macrophages, T lymphocytes and cytokines are involved[48]. Evidence is growing that the protective CVD effects associated with moderate alcohol consumption are largely due to an anti-inflammatory effect[35,49–53].

Increased pro-inflammatory cytokines such as TNFα and IL-6 concentrations have frequently been found in alcoholic pathology[25,26]. On the other hand, while a decrease in IL-10, IL-2 and interferon-γ levels have frequently been found in alcoholic pathology[25,26], moderate wine and beer consumption in human subjects has been shown to increase the production of anti-inflammatory IL-10 cytokine, also reducing some of the inflammatory mechanisms involved in atheromatous plaque formation[4,37].

Reviewing the literature, the relationship between the alcoholic beverage type and inflammation remains unresolved and requires further research. Moderate distilled alcohol consumption (2 ml vodka/kg body weight) has been suggested to show dual anti-inflammatory effects that involve IL-10 increase and a decrease of monocyte pro-inflammatory response that together support an anti-inflammatory mechanism for moderate alcohol intake in CVD prevention[54]. Although some authors have suggested that the anti-inflammatory effect is attributed to alcohol itself[55], polyphenol-rich alcoholic beverages have shown a more pronounced anti-inflammatory effect than distilled spirits[35,37,47,56,57]. In this direction, previous animal studies showed the strong anti-inflammatory activity of some compounds presented in fermented alcoholic beverages, such as resveratrol in red wine[58]. In conclusion, different types of alcoholic beverages all seem to have the same inhibitory effect on inflammatory response[5,35,54,59], but further investigation into the specific effects of alcohol on inflammation functions should help to define the potential inflammatory effects of social drinking[27].

Drinking pattern

Epidemiological studies have demonstrated that there is a J-shaped relationship between alcohol intake and total mortality, but there may be differences in the strength of this relationship across the main categories of alcoholic beverages: beer, wine and distilled spirits[60]. While wine is commonly believed to confer the most protection against total mortality, distilled spirits are believed to confer the weakest protection[61]. There is emerging evidence that the pattern of drinking (i.e. drinking with meals, abstention, followed by binge drinking) and the alcoholic beverage type influence the impact of the overall alcohol consumption on immunity, morbidity and mortality[5,61].

According to WHO, countries have been classified into four score categories (1 to 4) reflecting the mortality and morbidity risk associated with different amounts of alcohol intake. For example, category 1, characterized by the least-risky drinking pattern (light to moderate alcohol consumption with meals and without heavy drinking bouts) is associated with a lower burden of mortality and morbidity. On the contrary, category 4 is the most-risky drinking pattern characterized by the highest level of irregular drinking and is associated with a high burden of morbidity and mortality[62]. The least-risky categories (1 and 2) were associated with the consumption of fermented beverages such as wine and beer, whereas the most-risky categories (3 and 4) were associated with the consumption of distilled spirits.

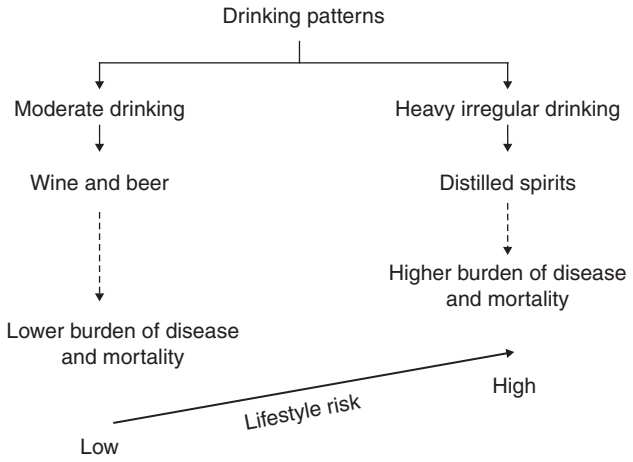

Fig. 1. Drinking pattern and lifestyle risk.

Therefore, according to Fig. 1, an emerging approach to the study of social drinking on mortality and disease burden in populations is to consider both the volume and pattern[61]. On the other hand, there are also several lifestyle factors such as cultural, socio-economic status, diet and physical activity habits that must be taken into account to elucidate the global effects of alcoholic beverages on health and immunity[5,60].

Social and cultural aspects of drinking

From the earliest times to the present, alcohol has played an important role in society. It is important to remember that alcohol has significant social consequences in most societies by way of celebration, stress reduction, appetite improvement, social interaction enhancement and feelings of well-being[63].

There is, however, a lack of an exact definition of 'social drinking'; while in some societies alcohol consumption is associated with some related problems such as violence or anti-social behaviour, in others (such as the Mediterranean), drinking is accepted and even associated with health-related benefits. These differences are primarily determined by social and cultural factors, rather than the different levels of consumption or genetic differences[64]. For example, the traditional Mediterranean diet has long been praised for its health benefits, which are characterized by high consumption of vegetables, fruits, nuts, legumes, cereals, seafood and olive oil, along with a moderate amount of red wine or beer[65]. Moreover, even total abstention from alcohol may be associated with health risks[66].

Some decades ago, cultural and socio-demographic differences were reported in the association between moderate alcohol consumption and CVD protection[67]. Since the protective effect of alcohol consumption has been found to be greater for populations studied in the Mediterranean countries than in other countries[68], it is reasonable to suggest that social, as well as cultural aspects influence the effects (positive or negative) derived from alcohol consumption. Moreover, since there has been an increased interest in how genes regulate alcohol drinking and

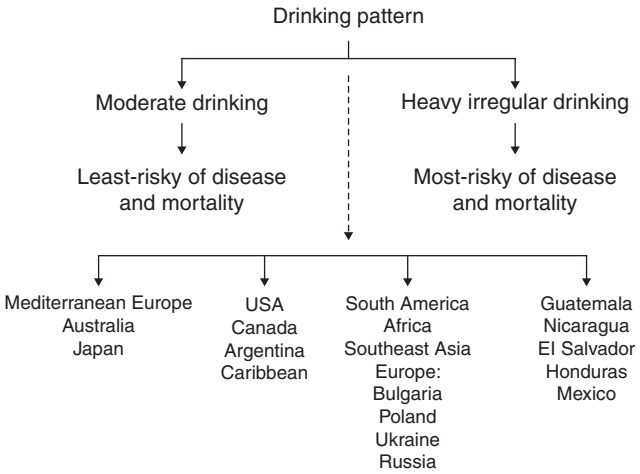

Fig. 2. Drinking pattern and worldwide distribution (from Rehm *et al.*[62,70]).

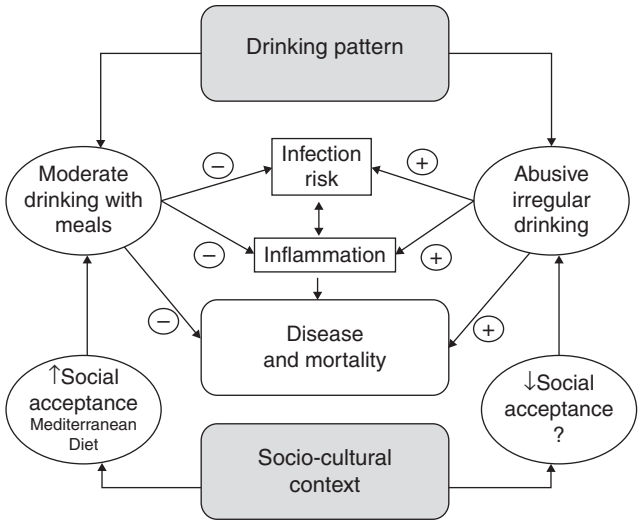

Fig. 3. Relationships between drinking pattern and socio-cultural context on disease, mortality and host defence global risk.

contribute to alcoholism, we cannot forget the genomic or epigenetic basis and influence of these effects of alcohol consumption on highly regulated cellular pathways[69].

Regarding drinking pattern and worldwide distribution (Fig. 2), curiously the drinking pattern classified as least-risky (described earlier as light to moderate; category 1) has been found only in Europe, Australia and Japan[62,70]. On the contrary, the most-risky drinking pattern associated with a high burden of morbidity and mortality was found in Central America (for example, Guatemala and Nicaragua)[62,70].

Even among the countries with least risk of morbidity and mortality, the social context seems to be a determining factor while examining the effects of alcohol consumption on health. A recent prospective study conducted in Japan (19 356 men, 40–69 years of age) examined the effects of social support on the relationship between drinking and CVD, finding that the health benefits of light-to-moderate drinking (less risk of mortality and CVD) are more pronounced in men with greater social support[71]. The authors found that those subjects with low social support had more unhealthy lifestyles and mental stress which activates neuro-endocrine components including the hypothalamic–pituitary–adrenal-axis and the autonomic nervous system, which lead to an increased risk of CVD.

It has been also suggested that the prevalence of alcohol-related problems is not directly related to average *per capita* consumption. While countries with low average consumption (such as Ireland and Iceland) often register relatively high rates of alcohol-related social and psychiatric problems, others countries with much higher levels of consumption (such as France and Italy) score low on most indices of problem drinking[64].

Since social behaviours including drinking may have their origins in adolescence, special attention focused on this risk population is necessary[72]. The relevance of parental supervision has been underscored for increased educational achievement, and has been associated with a reduced risk of alcohol-related problems in adolescents[73].

Summary

Although research evidence supports the benefits of moderate alcohol consumption on health, the scientific literature also appears to be concerned about the diseases associated with excessive drinking in some societies and cultures[74].

This review recognizes the importance to consider social aspects of drinking while examining the whole dimension of alcohol consumption (amount, beverage type, frequency and variability), in order to estimate the global risk of consequences on the host defence to better understand alcohol-related harm or benefit[70,74,75] (Fig. 3).

A more flexible approach to alcohol policy development which emphasizes patterns of drinking and educational measures within their appropriate cultural context is still necessary[66]. Lastly, though light-to-moderate alcohol consumption can be part of a healthy lifestyle for those who choose to consume alcohol, consumers must keep in mind that alcohol abuse is still considered as a major public health and social problem, the consequences of which extend beyond the subjects directly involved[76]. A specific prevention for adolescents should play the most important role in a comprehensive plan to reduce alcohol-attributable burden[62]. Educational approaches may be used in order to reduce alcohol-related harm, including education of children and adolescents in school, the development of drinking guidelines, labelling of alcoholic beverage products with warnings; school-based activities carried out as part of school plus family initiatives and as part of community action projects.

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