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Impact of alcoholism on oral health: a narrative review

Universidade Fernando Pessoa

Faculdade de Ciências da Saúde

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(Audrey Bouskila)

RESUMO

O alcoolismo, como muitos outros vícios, é uma condição na qual uma pessoa, de um ponto de vista mental e físico, necessita de consumir álcool, apesar dos efeitos prejudiciais que causa na sua vida.

Os níveis de consumo de álcool, os padrões e o alcance das questões relacionadas com a ingestão do mesmo na comunidade são influenciados por variáveis diversas, tanto no âmbito individual, quanto social. A quantidade total de álcool ingerido e os hábitos de bebida, particularmente aqueles ligados a episódios de consumo excessivo, têm um papel significativo nas condições crónicas e agudas da saúde, nomeadamente na saúde oral.

Os efeitos do alcoolismo na saúde oral são discutidos nesta tese. São descritos quatro "tópicos" principais, nomeadamente erosão dentária, doenças periodontais, cancro oral e atendimento odontológico, os quais refletem os efeitos imediatos de tal problema na saúde oral.

Para isso, efetuou-se uma revisão de literatura, realizada através de uma pesquisa de artigos científicos publicados no PubMed e b-on, e com a qual se pretendeu analisar as etapas, causas e consequências de cada um dos "tópicos" supracitados.

Palavras-chave: "Alcoolismo"; "Saúde Oral"; "Cáries dentárias"; "Erosão dentária"; "Cancro oral".

ABSTRACT

Alcoholism, like many other addictions, is a condition in which a person, from a mental and physical point of view, needs to consume alcohol despite the detrimental effects it has on their life.

Levels of alcohol consumption, patterns and the scope of issues related to alcohol ingestion in the community are influenced by different variables, both at the individual and social levels. The overall amount of alcohol drank and drinking habits, particularly those habits linked to bouts of heavy drinking, have a significant role in how alcohol intake affects chronic and acute health conditions, namely on oral health.

The worldwide effects of alcoholism on oral health are discussed in this thesis. Four main "topics" are described, namely dental erosion, periodontal diseases, oral cancer and dental management, which reflect the immediate effects of such a problem on oral health.

For that, a literature review was carried out through a search of scientific articles published in PubMed and b-on, and with which it was intended to analyse the stages, causes and consequences for each of the aforementioned "topics".

Keywords: "Alcoholism"; "Oral health"; "Dental caries"; "Tooth erosion"; "Oral cancer".

DEDICATION

I dedicate this work to my parents, my brother Charles, my sister Laurène and my entire family for their education, love, and transmission of values that made me what I am today.

Without them, none of this would be possible. Thank you very much.

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SUMMARY

ABBREVIATIONS

ACS	American cancer society
ADH	Alcohol dehydrogenase
ADH1	Alcohol dehydrogenase 1
AH	Alcoholic hepatitis
ALD	Alcoholic liver disease
ALDH	Aldehyde dehydrogenase
ALDH2	Aldehyde dehydrogenase-2
CAL	Clinical attachment loss
CCA	Cancer council Australia
CCS	Canadian cancer society
CI	Confidence interval
Cox-2	Cyclooxygenase-2
Cr-PdG	Crotonaldehyde-derived N2-propanodeoxyguanosine
CRUK	Cancer research UK organisation
CYP2E1	Cytochrome P450 family 2 subfamily E member 1
DE	Dental erosion
dG	Deoxyguanosine
DNA	Deoxyribonucleic acid
EP	Experimental periodontitis

EtOH	Ethanol
4-HNE	4-Hydroxynonenal
iNOS	Inducible nitric oxide synthase
K_M	Michaelis constant
LDL	Low-density lipoprotein
MDA	malonaldehyde
micro-CT	Micro computed tomography
mM	milimolar concentration
N2- EtdG	N2-ethyl-2′-deoxyguanosine
N2-EtidG	N2-ethylidene-2′-deoxyguanosine
NAD^+	Nicotinamide adenine dinucleotide
NADH	Reduced nicotinamide adenine dinucleotide
$NADP^+$	Nicotinamide adenine dinucleotide phosphate
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NFκB	Nuclear factor-kappa B
OR	Odds ratio
pH	Potential of Hydrogen
PD	Probing depth
ROS	Reactive oxygen species

CHEMICAL FORMULAS

$\mathbf{Ca_5(PO_4)_3(OH)}$	Hydroxyapatite
$\mathbf{H^+}$	Hydrogen ion
$\mathbf{H_2O_2}$	Hydrogen Peroxide
$\mathbf{O_2}$	Oxygen molecule
$\mathbf{O_2^-}$	Superoxide ion
$\mathbf{OH^\bullet}$	Hydroxyl radical

I. INTRODUCTION

The World Health Organisation defines alcoholism as “a term of long use and variable meaning, generally taken to refer to chronic continuous drinking or periodic consumption of alcohol, characterised by impaired control over drinking, frequent episodes of intoxication, preoccupation with alcohol, and use of alcohol despite adverse consequences”. Physical, psychological, societal, or economic effects may be encountered (Manuel and Meenakshi, 2021).

The majority of those who drink alcohol are between the ages of 20 and 34. Excessive alcohol consumption is one of the major risk factors for human health. Regarding oral health, dental caries, gingival-periodontal disease, tongue inflammation, and oropharyngeal cancer are all common in alcoholics (Stojšin *et al.,* 2020).

People of all ages are exposed to oral acid in a variety of ways in their daily lives due to a variety of risk factors, but those who abuse alcohol have a higher chance of experiencing dental erosion (Khairnar, Wadgave and Khairnar, 2017).

Many researchers have attempted to discover and evaluate correlations between periodontitis and probable systemic illnesses such as alcoholism. Alcohol abuse can cause periodontal disease for a variety of reasons, including gingival irritation and dehydration. Moreover, poor oral hygiene habits amongst chronic alcoholics can also lead to poor immunity leading to an insufficient immune response to harmful chemicals contained in alcoholic beverages (Khairnar, Wadgave and Khairnar, 2017).

Alcohol consumption is also considered to be a risk factor for oral cancer, and combining it with tobacco consumption raises the risk due to a synergistic interaction (Khairnar, Wadgave and Khairnar, 2017).

When dealing with a substance abuser, diagnosis and treatment planning can be complicated, involving the entire area of dentistry, including dental erosion, periodontal disease progression and predisposition to cancer and even some medicine. A different/nuanced approach to treating substance abusers' health problems is required. This comes in contrast to the “traditional/normative” approach, which emphasizes morphological and technical factors as drivers of treatment necessity (Solomons and Moipolai, 2014).

This narrative review aims to address the links between alcohol and dental erosion, periodontal/gingival diseases, and oral cancer as well as the management of the alcoholic patient.

1.1. Material and methods

This is a qualitative narrative study that is appropriate to update knowledge on the following proposed theme: "Impact of alcohol on oral health". The present narrative review was carried out by listing articles from the PubMed, b-on and Google scholar databases. The indexing terms used were “Alcoholism”; “Oral health”; “Dental caries"; “Tooth erosion”; “Oral cancer".

The criteria used for inclusion were: (a) the presence of the descriptors used in the title or abstract; (b) articles published in English. Exclusion criteria were: (a) duplication of articles; (b) articles that did not correspond to the proposed theme; (c) articles whose texts are not available in their entirety. Bibliographic references from the last 10 years were used, however, publications from previous years were utilized, if they proved to be relevant. This literature review was performed based on 57 articles.

The different sources that have been studied are referenced in the bibliography available in the last section of this paper.

II. DEVELOPMENT

2.1. Ethanol metabolism

Until it is eliminated, ethanol (EtOH) is responsible for more than half of each person's energy metabolism. After intake ceases, elimination takes roughly 5 hours (7 hours total), and ethanol oxidation is the primary carbon source for energy metabolism during this period. Increased alcohol use, whether acute or chronic, lengthens the time it takes for blood alcohol levels to recover to near zero but does not affect the rate at which it is eliminated. Blood alcohol levels in EtOH-dependent people stay high throughout the day (Wilson and Matschinsky, 2020).

Alcohol dehydrogenase (ADH), catalase, and cytochrome P450 family 2 subfamily E member 1 (CYP2E1) are the three enzymes that oxidize ethanol and create acetaldehyde. The first two are of particular interest since they are responsible for the oxidation of the majority of ethanol ingested. Aldehyde dehydrogenase (ALDH) converts acetaldehyde to acetate in the following step. Acetate is discharged from the cells into the bloodstream, where it can be converted into carbon dioxide (Hoes *et al.*, 2021; Zięba, Maciejczyk, and Zalewska, 2022).

Most biological membranes are permeable to ethanol, and the concentration in all water compartments, including the brain, is similar to that in blood plasma. As a result, practically all tissues and cells throughout the body are exposed to ethanol, and its rate of metabolism is determined by local enzyme concentration. The reactions of the three ethanol oxidizing systems (Annex 1.), as well as their respective K_M (Michaelis constant) for ethanol, are as follows:

1. Alcohol dehydrogenase; ADH1, K_M = 1.4 mM:

$$\text{Ethanol} + NAD^+ \rightarrow \text{Acetaldehyde} + NADH + H^+$$

2. Catalase; K_M = 12 mM:

$$\text{Ethanol} + H_2O_2 \rightarrow \text{Acetaldehyde} + 2\ H_2O$$

3. Cytochrome P450 2E1 (CYP2E1); K_M = 8 - 10 mM:

$$\text{Ethanol} + O_2 + NADPH \rightarrow NADP^+ + \text{acetaldehyde} + \text{acetate}$$

Under all physiological conditions, reactions catalysed by catalase and CYP2E1 are irreversible. Alcohol is oxidized in practically all tissues, first to acetaldehyde, then to acetate, and lastly to citric acid via the citric acid cycle. EtOH oxidation is irreversible and uncontrolled, hence the rate is solely determined by local concentration and enzyme activity. These uncontrolled decreasing equivalents in input enhance the decrease of cytoplasmic and intramitochondrial NAD^+, as well as the cellular energy *status*.

Acetaldehyde is a chemically reactive molecule with substantial toxicity, and ethanol ingestion can cause unpleasant feelings of acute disease in people who have an inactive type of aldehyde dehydrogenase-2 (ALDH2) (Nishida *et al*., 2010; Wilson and Matschinsky, 2020). Acetate, the main by-product of EtOH oxidation, has a function in both energy metabolism and metabolic control.

2.2. Alcohol and dental erosion

Dental erosion (DE) is the gradual deterioration of tooth structure caused by prolonged contact with a low pH environment. It is worth nothing that it is unrelated to bacterial infection (Erpaçal, Bahşi and Sonkaya, 2018).

The principal indications of dental erosion are a loss of enamel shine, the lack of macroscopic plaque, and rounded and polished dental surfaces due to the disappearance of microarchitecture. Some characteristics can be seen after the initial dental erosion, such as smoothing out of developmental pits and grooves, dentin exposure, prominent restorations that are elevated above the surrounding tooth structure, and well-defined dentin concavities on the occlusal and incisal surfaces. Extensive mineral loss can lead to tooth shortening in more severe cases, which can cause functional and aesthetic issues. Convex tooth regions such as proximal ridges tend to become flat and even concave. When teeth are repeatedly exposed to acid, specific components of the tooth surface are selectively dissolved, resulting in tooth substance loss, hypersensitivity, functional impairment, and even tooth fracture. When excessive wear occurs, possible complications include pain, pulpal inflammation, necrosis, and periapical pathology (Stojšin *et al.*, 2020).

Exogenous or endogenous causes may be primarily responsible for DE. The location of erosive cavities is determined by the acid source and cavity depth. Low pH products (approximately at 5,5) dissolve enamel hydroxyapatite, $Ca_5(PO_4)_3(OH)$, but for lower values occurs fluorapatite dissolution (Kuchta and Szymańska, 2014; Enam *et al.*, 2017).

The erosive faculties of main alcoholic beverages and soft drinks and/or fruit juices are mixed in alcopops and cocktails. The fruit acid content in wines, of which tartaric acid is the most common, determines their ability to produce erosion. For example, the erosive potential of different wines differs due to the different combinations and amounts of acid types and other inhibitory elements present. Because of their greater concentration of titratable acids, white wines are more erosive for the teeth than red wines, although beers and ciders have a moderate erosive potential. Another element that promotes tooth wear is the astringency of alcoholic drinks, which is caused by the presence of high levels of polyphenols, primarily tannins. These compounds bind salivary proteins and mucopolysaccharides, causing their precipitation, resulting in astringency, loss of lubrication of the oral mucosa and teeth, and decreased acid protection of teeth (Peycheva and Boteva, 2016; Stojšin *et al.*, 2020).

Saliva has a critical function in maintaining a physiologically appropriate intra-oral pH. However, in the presence of excessive acidic food and beverage consumption, its protective capabilities are diminished (Loke *et al.*, 2016; Touyz, Touyz and Nassani, 2018). There is a correlation between a decreased salivary flow rate and the ability to clear acidic substances from the mouth. For instance, in individuals with low salivary flow rate, acid clearance is reduced, and less dilution of acid will be present upon attack of the tooth surface, contributing to erosion progress especially where there is a direct contact with the acid (Buzalaf, Hannas and Kato, 2012).

As previously mentioned, the acidic pH of alcoholic beverages has a direct effect on the demineralization of hard tooth tissue. The ensuing dental erosions are exacerbated by gastric hydrochloric acid, which enters the oral cavity through vomiting and regurgitation in cases of alcohol intoxication, as well as the loss of saliva's protective function owing to xerostomia, a side effect of this form of addiction. Each case of generalised erosive alterations in which no etiologic reason has been found in the process history must raise suspicion of chronic alcoholism, and this sort of defect might be considered a sign and thus employed in the diagnosis of this addiction (Khairnar, Wadgave and Khairnar, 2017).

In general, dietary choices, or the method in which these acids are eaten, also have a significant influence. The use of a straw, as well as direct ingestion techniques from bottles or cups, were all found to be strongly linked to the occurrence of DE. Dietary habits have steadily evolved during the previous decades, owing to changes in lifestyle, nutritional preferences, and the increasing availability of dietary acids (Chan *et al.*, 2020). For instance, early exposure to sour flavours boosts a child's desire for acidic foods and beverages later in life. Because of the economic boom, acidic fruits and beverages were more readily available (Gambon, Brand and Veerman, 2012).

After an erosive attack, as with alcohol one, washing with a remineralizing agent can improve enamel rehardening as a first therapeutic step. Within the constraints of the current investigation, it may be concluded that rinsing with a dental erosion prevention mouth rinse comprising fluoride and stannous ions before an erosive assault can minimise, but not completely prevent, erosion-induced weakening (Körner *et al.*, 2020).

2.3. Alcohol and gingival/ periodontal diseases

The mouth, intestine and skin serve as interfaces between the internal human body and the external environment. It is critical for their existence that they maintain their integrity. Each barrier has its own set of needs, including maintaining commensal microbial control and reacting to

environmental shocks and pathogen invasion while performing its physiological role. In the face of these threats, the immune system is crucial for barrier integrity and is carefully tuned to barrier settings, resulting in highly-specialized immune-surveillance networks that police these locations. The oral barrier is one where proper immunological regulation commonly fails (Peycheva and Boteva, 2016).

Periodontitis, the most prevalent chronic inflammatory illness in humans, is caused by the breakdown of normal immune responses at the gingiva. This common condition weakens the periodontium, the tooth-supporting tissues, resulting in dentition impairment and tooth loss. Periodontitis has long been assumed to be caused by specific bacteria, but new evidence suggests that the condition is caused by a varied microbial community. Defects in the well-balanced inflammatory responses occurring at the oral barrier are crucial to the development of periodontitis pathology, even though they are initiated by the local microbiota. Periodontitis has been linked to the onset, aggravation, and pathogenesis of a slew of other inflammatory disorders (Konkel, O'Boyle and Krishnan, 2019). Therefore, it is critical to gain a thorough gasp of its pathophysiology.

The periodontium is affected by two prevalent disorders. The first is gingivitis, which is defined as gingival inflammation with no change in the degree of connective tissue attachment to the tooth. The illness is restricted to the gingival epithelium's soft-tissue compartment and connective tissue. The second condition is periodontitis, which is the inflammation of the teeth's supporting tissues that leads to bone loss and attachment loss. Periodontal disorders are inflammatory diseases caused by microbial etiologic factors that trigger a cascade of host responses that influence inflammatory processes. Dysregulation of inflammatory and immunological pathways cause persistent inflammation, tissue damage, and illness in those who are vulnerable (Cekici *et al.*, 2014).

Chronic inflammation of the soft tissues can be caused by excessive concentrations of organic and inorganic acids, as well as the habit of keeping the alcoholic drink in the mouth (Peycheva and Boteva, 2016).

The presence of a systemic host-mediated component in periodontitis is generally mentioned. Alcohol, acids, and sugars can briefly weaken enamel, but it quickly recovers. However, when a person consumes many alcoholic beverages in a short time, damaged enamel does not have time to heal (Manuel and Meenakshi, 2021). Chronic generalised periodontitis in alcoholics is linked

with gingival inflammation, blunting of the interdental papillae, and deep pockets, as well as bone loss (Khairnar, Wadgave and Khairnar, 2017).

According to Gay, Tran and Paquette (2018), there is a substantial link between alcohol use and periodontitis. In addition, a dose-response study revealed that increasing alcohol use by 1 gram *per* day increased the incidence of periodontitis by 0.4 percent (Çetinkaya and Romaniuk, 2020). Almeida and colleagues (2020) additionally observed that chronic alcohol consumption enhances the severity of periodontitis in a dose-dependent way, independent of the dosage drank, by raising the size of the local inflammatory response and accelerating alveolar bone resorption.

Alcohol appears to increase the risk of periodontitis and different immunological elements are thought to play a role in the development and progression of periodontal disorders. Earlier studies have suggested that alcohol ingestion could alter host defence mechanisms, which include impaired neutrophil, macrophage, and T cell functioning (Sender-Janeczek and Zietek, 2016). Another report suggested that heavy alcohol drinkers have high levels of proinflammatory cytokines, such as tumour necrosis factor-α serum levels. Based on these harmful systemic effects, it is not surprising that long-term alcohol intake was associated with increased incidence of infections. Aside from the effects of alcohol, alcoholic individuals had poor oral hygiene compared to controls in a study performed by Manicone *et al.* (2017). Consequently, in these patients, it is essential to stress the importance of good oral hygiene (Mallikarjuna and Nalawade. 2014).

The evidence for the link between alcohol use and periodontal disease has come from a variety of research contexts, including cross-sectional, longitudinal, and experimental investigations (Saini, Gupta and Prabhat, 2013). Nevertheless, several research (Amaral, Vettore and Leão, 2009; Wang *et al.*, 2016; Gay, Tran e Paquette, 2018) have found inconclusive results when it comes to the influence of alcohol on periodontal disease. Although numerous long-term studies have noticed a relationship between alcohol intake and periodontitis (Pitiphat *et al.*, 2003; Nishida *et al.*, 2008; Nishida *et al.*, 2010; Wagner *et al.*, 2017), Okamoto *et al.* (2006), for example, did not. Amaral, Vettore and Leão (2009) conducted a comprehensive review, that included five longitudinal and 11 cross-sectional investigations, and the authors established that alcohol intake may be used as a periodontitis risk indicator. Another meta-analysis, this time based on data from the association between alcohol consumption and periodontitis, was also substantiated by 18 observational studies (Wang *et al.*, 2016).

Despite several case descriptions, it can be suggested that the occurrence of periodontitis is linked to alcohol consumption (Pulikkotil *et al.*, 2020). Therefore, detecting patients at risk for periodontal diseases may allow medical and dental providers to collaborate to develop effective primary and secondary preventive strategies, as well as control the negative effects of periodontal diseases and comorbidities, given the bidirectional relationship between these diseases (Paksoy, Ustaoğlu and Peker, 2020).

2.4. Alcohol and oral cancer

Around the world, alcohol is associated with 26.4 percent of all lip and oral cavity malignancies. Oral cancers are more common in alcoholics than in abstainers, and smoking increases the risk of cancer in alcoholics by more than twofold (Touyz, Touyz and Nassani, 2018).

EtOH's principal metabolite, acetaldehyde, is classified as a class 1 carcinogen. By disrupting DNA synthesis and repair, forming DNA adducts, and altering oncogene expression through DNA hypomethylation, these metabolites have a direct role in carcinogenesis. In addition, alcohol metabolites indirectly impact by acting as a solvent, allowing other carcinogens, such as those contained in cigarettes, to penetrate the mucosa (Tenore *et al.*, 2020).

Acetaldehyde may bind directly with DNA base pairs, forming DNA adducts (Annex 2.). N2-ethyl-2′-deoxyguanosine (N2- EtdG) is the first and most common adduct. N2-EtdG comes from N2-ethylidene-2′-deoxyguanosine (N2-EtidG), which is made by a single acetaldehyde molecule reacting directly with deoxyguanosine (dG) molecule. *In vitro* investigations revealed that N2-EtdG can inhibit replicative DNA polymerase, but not DNA polymerase, which was unaffected by this tiny adduct. This lesion may be easily circumvented by translesion DNA polymerase once a replicative polymerase is blocked. A second important adduct is α-methyl-γ-hydroxy-1, N2-propano-2′-deoxyguanosine, also referred to as crotonaldehyde-derived N2-propanodeoxyguanosine (Cr-PdG) (Hoes *et al.*, 2021).

Various mechanisms that explain the carcinogenic effects of alcohol in the development of oral cancer have been hypothesised: i) alcohol increases mucosal permeability to other toxins and carcinogens due to its dehydrating effect on cell membranes; ii) mucosal morphology changes as epithelial thickness decreases; iii) ethanol metabolism creates acetaldehyde, which breaks oral epithelial cells' DNA and induces oncogene expression in oral keratinocytes; iv) ethanol impairs salivary gland function by lowering epidermal growth factor secretion, which shields the oral

mucosa from acid-induced damage, increasing the risk of oral mucosal ulcers; and v) nutritional inadequacies caused by binge drinking can reduce the body's natural ability to utilise antioxidants to prevent cancer growth (Ravishankar, 2020).

Chronic ethanol intake can also lead to alcoholic liver disease (ALD) and cancers of the liver and other organs. The production of reactive oxygen species (ROS) is one way through which alcohol has harmful consequences. As referred (Annex 1.), ADH enzyme oxidizes ethanol with simultaneous formation of H_2O_2, while the reaction catalysed by microsomal enzymes generates hydroxyl radical ($OH^{\bullet}$), the most dangerous ROS. By activating cytochromes CYP2E1, the resulting acetaldehyde increases the ROS pool in the form of superoxide ion (O_2^-) and H_2O_2. Catalase, in this process of ethanol metabolism, does not produce ROS; on the contrary, it consumes H_2O_2 (Zięba, Maciejczyk, and Zalewska, 2022).

Both ROS and acetaldehyde activate NFκB (nuclear factor-kappa B), a key transcription factor implicated in cancer development. Inflammation-induced oxidative *stress*, which includes activated hepatic macrophages, is primarily responsible for the formation of ROS in alcoholic hepatitis (AH).

Chronic inflammation is the most significant mechanism linked to oxidative *stress* and the production of ROS, in prolonged alcohol intake. When cytokines are released, they stimulate oxidant production enzymes, such NADPH oxidase, and NFκB, which then activate oxidized LDL receptor, Cox-2, and iNOS, culminating in the synthesis of ROS. Furthermore, ROS can cause lipid peroxidation, which results in the formation of lipid peroxidation agents such as 4-hydroxynonenal (4-HNE) and malonaldehyde (MDA). Both compounds may attach to DNA and generate etheno-DNA adducts, which are extremely carcinogenic (Linhart, Bartsch and Seitz, 2014).

Cancers such as oesophageal cancer, gastric cancer, and hepatocellular carcinoma are more common in those who have the ALDH2 polymorphism. ALDH2 has also been linked to cancer prognosis since it is a cancer stem cell marker that controls cancer cell proliferation, invasion, migration, and multidrug resistance (Chang, Hsiao and Chen, 2017; Zhang and Fu, 2021).

Interestingly, it has been found that, in the first few minutes after using an alcohol-based mouthwash, salivary acetaldehyde levels rise considerably. Eight studies were included in the qualitative analysis out of 497 potentially relevant publications, totalling 43,499 subjects: two meta-analyses, a clinical trial, three case-control studies, and two cohort studies. One study

(n = 3,926) discovered a relation between alcohol mouthwash and oral cancer, two studies (n = 25,033) discovered this link when mouthwash was used frequently, three studies (n = 14,482) failed to find this connection, and two studies (n = 58) discovered a temporary increase in acetaldehyde levels in saliva after using alcohol mouthwash (Ustrell-Borràs, Traboulsi-Garet and Gay-Escoda, 2020).

Although the presence of alcohol in the formulation of gluconate chlorhexidine mouthwashes does not appear to affect their antimicrobial potential or taste perception (Cantarelli *et al.*, 2017), the alcohol-free version of another widely used commercial mouthwash composed of essential oils (eucalyptol, menthol, thymol, methyl salicylate - Listerine® Zero) still deserves attention due to the lack of scientific evidence (Vlachojannis *et al.*, 2016). According to an update on the efficacy and safety (in relation to cancer) of Listerine® products, the evidence of effectiveness for Listerine® with alcohol is high, but only modest for Listerine® Zero, based on the majority of three confirmatory trials and several exploratory investigations carried out so far (Vlachojannis *et al.*, 2016).

Data from Denmark and Norway verified the trend changes in male and female oral cancer. Overall, relative survival for these malignancies has increased, but it differed for one cluster of oral cancers, oropharyngeal and nasopharyngeal cancers, which had 60 - 70 percent 5-year survival, and hypopharyngeal cancer, which had a 25% male survival rate. Old individuals had a poor prognosis in all of these malignancies (Koskinen *et al.*, 2022).

Alcohol intake is responsible for around 4% of cancer cases worldwide, equal to more than 740,000 cancer cases in 2020. Despite this, public understanding of the causal relationship between alcohol and cancer is poor, and alcohol consumption is on the rise in various parts of the world (Rumgay *et al.*, 2021).

2.5. Alcoholism in dental management

Dentists play a critical role in the early detection of alcoholism-related disorders (Mallikarjuna and Nalawade, 2014). In fact, dentists must include in their diagnostic skills the ability to identify the patient with a high consumption of alcohol. Dental *status* can often reflect the patient's perception of health and disease. The improvement of a suitable treatment plan for these patients needs to take into account their generally untrustworthy nature.

The case management of a substance abuser is likely to differ from that of a non-addicted patient. Individuals who consume excessive amounts of alcohol may have difficulty accepting, obtaining, and completing dental treatment. Oral health care can resume once the addiction has been treated and any associated medical difficulties have been addressed.

It may be necessary to recommend the patient to a physician for the treatment of linked possible or imminent medical concerns. The health questionnaire and following verbal interview should raise the relevant questions during the dental session. Patients should be educated about their problems and made participants in deciding the best course of action. A functional treatment plan should be thought of as dynamic rather than static. It should change in response to changes in the patient's oral or overall health. The order in which treatments should be performed may vary, but some general recommendations can be used to schedule procedures at first (Solomons and Moipolai, 2014).

Advanced dental erosion frequently necessitates expensive and invasive functional and cosmetic repair. It is critical that health practitioners understand the erosive potential of nutrition and diet-related behaviours, as well as the increased impact they may have on vulnerable populations (Chan *et al.*, 2020). As a result, investigating the association between alcohol and periodontal disease is critical, as alcohol usage may pose a risk for this disorder (Saini, Gupta and Prabhat, 2013).

III. DISCUSSION

Because of the substantial differences in quantities of fat and water in their bodies, and the low lipid: water partition coefficient of ethanol, the same dosage of alcohol *per* unit of body weight can yield highly varied blood alcohol concentrations in different individuals. Because of their larger amount of body fat, women have a lesser volume of distribution for alcohol than males. When given the same quantity of alcohol as g *per* kg body weight, women will have greater peak blood alcohol levels than males, but there will be no differences when given the same dose per litter of body water. The stomach's first-pass metabolism of alcohol, which may be faster in men, may also contribute to women's higher blood alcohol levels (Cederbaum, 2012).

Evidences suggest that oral microbiota dysbiosis is connected to local oral diseases, such as dental caries and periodontitis and potentially to systemic illnesses, including cancer. Excessive alcohol ingestion has a deleterious impact on the oral microbiome, or oral microbial habitats. In fact, several researches refer that alcohol intake may affect the oral microbiota in several ways: i) by

direct cytotoxic effects on bacteria; ii) by disturbing saliva-bacterium interactions, and iii) by offering ethanol as a substrate for bacterial metabolism (Touyz, Touyz and Nassani, 2018).

Animal studies revealed that diet containing 20% of ethanol increases colonization by *Streptococcus mutans*, a caries-linked bacterium, and considerably reduces the number of detectable bacterial species in the oral biofilms of rats. Large population-based studies have consistently demonstrated that alcohol consumption is associated with increased risk of periodontal disease in a dose-dependent fashion. Evidence also shows that the oral microbiome is closely tied to oral health *status* (Sheth *et al.*, 2016).

Despite scientific studies, the effects of alcohol on salivation are not well identified and understood (Peycheva and Boteva, 2016). Nevertheless, it is well referenced that alcoholics had significantly fewer teeth and more active caries lesions, as well as a tendency to have more endodontically treated teeth than non-drinking controls. So far, no significant variations in the number of periapical lesions in endodontically treated teeth have been discovered (Peycheva and Boteva, 2016).

Some studies have evaluated the effects of drinking on the clinical periodontal condition (Hornecker *et al.*, 2003; Pitiphat *et al.*, 2003; Pulikkotil *et al.*, 2020). Authors have reported relationships between alcohol consumption and probing depth (PD) and clinical attachment loss (CAL) (Tezal *et al.*, 2001; Sender-Janeczek and Zietek, 2016). Overall, the findings suggest that light to moderate alcohol use has no influence on the onset of pocket development, which is an important feature in the pathogenesis of periodontitis (Sankaranarayanan, 2019).

In a paper published by Frazão *et al.* (2020), thirty-two Wistar rats were randomly allocated into four groups: control (C), ethanol (3g/kg/ day; 3 days On-4 days Off protocol by gavage for 28 days, EtOH), experimental periodontitis (EP) and experimental periodontitis plus ethanol administration (EP + EtOH). On day 14^{th}, periodontitis was induced by ligatures that were placed around the lower first molars. On day 28^{th}, the animals were euthanized and mandibles were submitted to stereomicroscopy for exposed root area analysis and micro-computed tomography (micro-CT) for the evaluation of alveolar bone loss and microstructural parameters. The outcomes demonstrated that excessive and episodic ethanol use leads to a decline in alveolar bone quality compared to controls (1.06 ± 0.10 *vs* 0.77 ± 0.04; p-value < 0.0001). Periodontitis was worsened, both qualitatively and quantitatively, by excessive exposure to alcohol. As a result, the authors have concluded that alcohol consumption may be linked to the modification of periodontitis development and the intensification of bone tissue destruction.

Periodontal examination included assessing the CAL for the entire tooth structure of the oral cavity. A William's probe was employed in assessing the pocket depths and attachment loss of each individual subject grouped into alcoholic and non-alcoholic patients, in a work carried out by Manuel and Meenakshi (2021). In this study, the unadjusted relationship between alcohol consumption and CAL seems to have a directly proportional relationship with each other.

Preventive approaches, such as early detection of at-risk patients, can help to avoid erosion. Dental erosion can be influenced by oral hygiene. The use of toothbrushes shortly after eating acidic meals is not advised by doctors. Furthermore, recent research has concluded that brushing is ineffective as a preventative approach. Brushing teeth right after eating acidic foods promotes increased enamel loss, yet it has been proposed that this theory be reconsidered. Active compounds in toothpastes, like fluoride, have been shown to slow the advancement of dental erosion by preventing their mechanical harmful effects. Actually, rinsing with a dental erosion prevention mouth rinse comprising fluoride and stannous ions before an erosive assault can minimise, but not completely prevent, erosion-induced weakening of enamel (Körner *et al.*, 2020).

Various dental care solutions are available to help prevent dental erosion, however there is no perfect material (Erpaçal, Bahşi and Sonkaya, 2018). It is critical that health practitioners understand the erosive potential of nutrition and diet-related behaviours, as well as the increased impact they may have on vulnerable populations (Chan *et al.*, 2020).

The function of alcohol in the development of cancer is debatable. Although it is impossible to designate alcohol as a "complete" carcinogen, many researchers believe it is a promoter/co-carcinogen and an independent risk factor for mouth cancer (Webber *et al.*, 2016). Actually, Çetinkaya and Romaniuk (2020) consider that increased alcohol use, both in terms of quantity and duration, is associated to a higher risk of oral cancer.

On their separate websites, the American Cancer Society (ACS) and the Canadian Cancer Society (CCS) neglected to accept that there is no safe level of alcohol use when it comes to cancer risk. The Cancer Research UK organisation (CRUK) and the Cancer Council Australia (CCA), on the other hand, adopted the following statements: "expert reports have established that there is no safe lower limit of alcohol consumption where cancer risk is not raised" and "cancer risk, however, increases from the first alcoholic drink" consumed. The ACS and CCS are unable to fully warn the public about the complete range of risks associated with alcohol consumption due to a lack of such declarations (Amin, Siegel and Naimi, 2018).

Muwonge *et al.* (2008) used a nested case-control design using data from a randomised control study performed in Trivandrum, India, between 1996 and 2004 to assess the impact of drinking on the risk of oral cancer. They observed a statistically significant increase in the risk of oral cancer in males who reported consuming alcohol. Both former and present male drinkers were found to have a non-significant increased risk of mouth cancer (Odd ratio (OR) = 1.4, 95% Confidence Interval (CI) = 0.9 - 2.0).

More recently, Di Credico *et al.* (2020) demonstrated that the risk of cancer increased sharply as the number of drinks *per* day raised, with no discernible threshold impact at lower levels. The incidence of oral cavity, hypopharyngeal, and laryngeal malignancies did not differ by years of drinking for any intensity level, suggesting that there was no influence of duration. The risk of oropharyngeal cancer rose with time spent up to 28 years, then levelled off. The risk was highest at greater levels of intensity and duration (OR = 7.95 for the oral cavity, 12.86 for the oropharynx, 24.96 for the hypopharynx, and 6.60 for the larynx).

The hazards of using mouthwashes and mouth rinses that include alcohol are enlarging (Peycheva and Boteva, 2016). Nonetheless, there is little evidence to believe that the use of alcohol-based mouthwashes can impact the development of oral cancer (Argemí *et al.*, 2020).

Ustrell-Borràs, Traboulsi-Garet and Gay-Escoda (2020) consider that it is impossible to say whether mouthwash usage is a separate risk factor for the development of head and neck cancer. When it happens in combination with other carcinogenic risk factors, however, the risk rises. According to the authors, in the first few minutes after using an alcohol-based mouthwash, salivary acetaldehyde levels rise considerably. Nevertheless, there is no indication that a high frequency of mouthwash usage increases long-term salivary acetaldehyde levels. There is not enough data to declare if using alcohol-based mouthwash is a risk factor for oral or oropharyngeal cancer. Still, when it happens in conjunction with other risk factors such as smoking or drinking, it raises the risk (Ustrell-Borràs, Traboulsi-Garet and Gay-Escoda, 2020).

A total of 14 papers, 11 case-control studies and 3 clinical trials, were collected. Three case-control studies revealed no statistically significant evidence of a link between mouthwash usage and oral cancer, whereas the other eight found statistically significant evidence. Because of the genotoxicity and mutagenic capability of alcohol in continuous contact with oral tissues and mucous membranes, the three clinical studies found a relation between the use of mouthwashes containing alcohol and the risk of developing cancer. The meta-analysis found an OR = 1.480 and a *p*-value = 0.161 (95 percent CI: 0.855; *p*-value = 2.561) for studies of cancer risk and mouthwash

consumption in the presence of alcohol, and an OR = 1.057 and *p*-value = 0.364 (95 percent CI: 0.951; *p* -value = 1.174) for studies of cancer risk and mouthwash use in the absence of alcohol (Argemi *et al.*,2020).

In a paper published by Kim and Nam (2022), mouthwash containing *Sambucus williamsii* var. coreana extract was found to have effective antibacterial activity against oral microorganisms. By using mouthwash containing *Sambucus williamsii* var. coreana extract, *S. mutans* was drastically decreased from the moment after "treatment" to 5 days after application. Authors concluded that the bacterium's inhibition and death were visible shortly after gargling. *S. mutans* is frequently seen in the early stages of dental plaque. This bacterium is hazardous because it promotes other oral disorders by producing an acidic environment through sugar metabolism and aiding the attachment of different bacteria.

IV. CONCLUSION

Evidence supporting the harmful effects of alcohol use disorder on dental health has so far been presented. Due to alcohol intake, the process of ethanol oxidation is prolonged, which contributes to tooth erosion.

Alcohol influences periodontitis as well. This chronic inflammatory illness impairs the normal immune reaction of the gingiva, compromising the periodontium and the tissues supporting the teeth, ending in dental decay and impairment.

Carcinogens form as a result of a disturbance in DNA synthesis and repair: since alcohol acts as a solvent, the carcinogens infiltrate the mucosa more easily. The drying membranes enhance mucosal permeability, which can lead to morphological alterations in epithelial thickness.

Finally, dentists are crucial in detecting alcoholism-related diseases early on. They must have the capacity to detect patients with high consumption of alcohol as part of their diagnostic abilities. The development of an appropriate treatment strategy for these individuals must take into consideration their general lack of trustworthiness.

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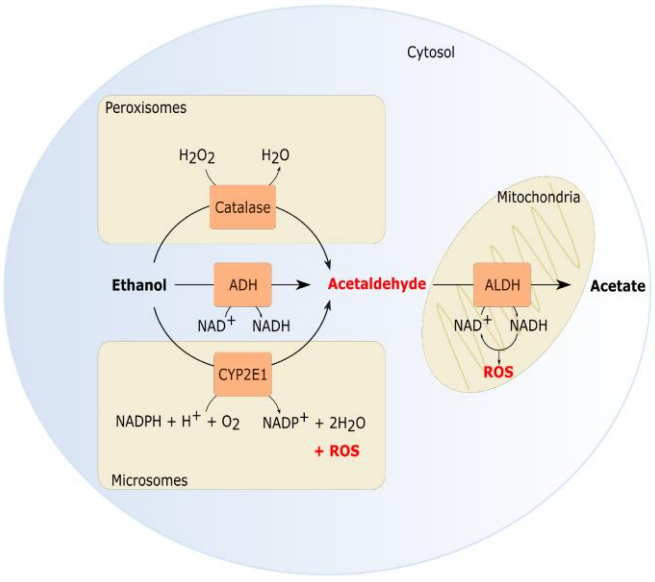
VI. ANNEXES

Annex 1. Oxidative ethanol metabolism (Hoes *et al.*, 2021).



Annex 2. Reaction of acetaldehyde with dG to form a variety of adducts (Hoes *et al.*, 2021).