BACHELOR'S DEGREE FINAL PROJECT:

EFFECT OF ULTRA-PROCESSED FOOD CONSUMPTION ON THE CARDIOVASCULAR SYSTEM

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1. Abstract

Vascular diseases (CVD) are the leading cause of death in the world. There are variable risk factors that favor their appearance, one of which is diet. A balanced and healthy diet can prevent or reduce some CVD. However, in recent years the consumption of ultra-processed food (UPF) has increased. Ultra-processed foods are industrial formulations mainly based on food-derived substances that have additives to mimic their natural form. These foods are high in free sugars, fats, and sodium, and low in protein, dietary fiber, minerals, and vitamins, compared to unprocessed or minimally processed foods and products.

The main objective of this literature review is to highlight the importance of diet as a variable risk factor for CVD, reviewing the harmful effects of each additive or component on the cardiovascular system. For this purpose, databases such as PubMed or Google Scholar were consulted as a source of information, where the scientific reports used were found. Thanks to the existing literature, it is known that certain additives, such as glutamates, sweeteners, emulsifiers, or sulfites, favor the formation of atherosclerotic plaque because they increase oxidative stress and inflammation. In addition, UPF contains contaminants such as bisphenol A (BPA) that decrease certain enzymatic activities and increase oxidative stress. Finally, the high consumption of salt and fats, which cause hypertension and hypercholesterolemia, respectively, is being studied.

Based on all the scientific information reviewed and despite the limited studies that directly relate the harmful effect of UPF consumption and cardiovascular pathology, it is essential to have a healthy diet that prioritizes fresh foods and displaces other foods that have undergone processing and have had their composition altered.

Key words: cardiovascular disease, ultra-processed food, additives, hypertension, oxidative stress.

2. Abbreviations

ECV	Cardiovascular diseases
UPF	Ultra-processed food
BPA	Bisphenol A
LDL	Low-density lipoproteins
oxLDL	Oxidized low density lipoproteins
MCP-1	Monocyte chemoattractant proteins 1
VSMC	Vascular smooth muscle cells
HDL	High-density lipoproteins
MET	Basal metabolic equivalent
WHO	World Health Organization
IMC	Body mass index
DM	Diabetes mellitus
PREDIMED	Primary Prevention of Cardiovascular Disease
ENT	Chronic non-communicable diseases
JECFA	Joint FAO/WHO Expert Committee on Food Additives
FDA	U.S. Food and Drug Administration
EFSA	European Food Safety Association
GRAS	Substance generally known to be safe
IDA	Acceptable Daily Intake
MSG	Monosodium glutamate
LDH	Lactate dehydrogenase
AST	Aspartate transaminase
ALT	Alanine transaminase
TLR	Toll-like receptor
ROS	Reactive oxygen species
NFκB	Nuclear factor κB
Rel	Reticuloendotheliosis viral oncogene v-rel
IκBα	Phosphoinhibitor of κB
IL-8	Interleukin 8
SMB	Sodium metabisulfite
KATP	ATP-sensitive K+ channels
L-Ca2+	L-type calcium channels
SUR	Sulfonylurea receptor subunit

NHANES	National Health and Nutrition Examination Survey
CYP2E1	Cytochrome P450 2E1
GSH	Glutathione
GA	Glycidamide
SOD	Superoxide dismutase
GST	Glutathione-S-transferase
3-HPMA	3-hydroxypropylmercapturic acid
FRS	Framingham Risk Score
ER	Estrogen-related receptors
PPAR-γ	Peroxisome proliferator-activated receptor gamma
uBPA	Urinary BPA
CAD	Coronary artery disease
AHA	American Heart Association
NCEP	National Cholesterol Education Program

3. Introduction

Cardiovascular diseases (CVD) are currently the leading cause of death worldwide (1). While in 2012 it was estimated that 30% of global deaths were due to CVD, today at the European level 49% of deaths are due to this cause (2). In 2017, the National Institute of Statistics counted a total of 122,465 deaths in Spain due to cardiovascular diseases (3). Although these pathologies do not affect in all countries equally, since due to the standard of living and economy their incidence is higher in poorer countries, where 80% of deaths are due to this cause (1).

CVD is a group of chronic noncommunicable diseases (4) that affect the heart and circulatory system and that, in most cases, are mainly caused by atherosclerosis (2). Atherosclerosis is a multifocal, latent, immunoinflammatory disease affecting the arteries, where endothelial cells, leukocytes, and smooth muscle cells of the intima are the main cells involved in the formation of atherosclerotic plaque (5). The most susceptible areas to atherosclerotic plaque formation are those arteries with an adaptive thickening of the media and which have higher blood flow and wall tension (6).

Atherosclerotic plaque formation can remain asymptomatic for years as it progresses until it becomes complicated by thrombosis. Approximately 76% of all fatal coronary thrombi occur because of plaque rupture (5). The main cause is the high concentration of low-density lipoproteins (LDL) in the blood (7). LDL accumulates in the subendothelial space of the arterial wall and is oxidized (oxLDL), stimulating an inflammatory response in which chemotactic molecules (monocyte chemoattractant protein 1, MCP-1) and adhesion molecules such as VCAM-1, E-selectin, and P-selectin (8) are expressed and promote the transport of plasma monocytes to the arterial wall. These monocytes differentiate into macrophages and endocytose oxidized LDL, transforming into foam cells that secrete proinflammatory molecules (9). The inflammatory response also attracts circulating monocytes and T lymphocytes that stimulate the migration of vascular smooth muscle cells (VSMCs) from the tunica media into the subendothelial space, where they rapidly spread and secrete extracellular matrix proteins that contribute to atheroma formation (10).

Cholesterol homeostasis is very important for cellular functions and an imbalance of cholesterol is the basis of many cardiovascular diseases. Blood cholesterol concentration is controlled by four mechanisms: biosynthesis, absorption, export, and esterification (11). High cholesterol levels are especially dangerous when the concentration of LDL in the blood is high and that of

high-density lipoproteins (HDL) is low (12). When the amount of cholesterol exceeds the amount necessary to perform its functions in the body (production of steroids, bile acids and membranes) it leads to atherosclerosis (12, 13, 14).

Some publications cite that high HDL concentrations (above 60 mg/dL) would be protective against cardiovascular disease; and low HDL concentrations (below 35 mg/dL) would increase cardiovascular risk. However, no epidemiological study has reached consistent conclusions and, therefore, the HDL level as such says little about health (15, 16). A direct relationship between elevated blood cholesterol concentrations and increased cardiovascular risk is now proven. In a study of a group of men between 35 and 57 years of age, 46% of deaths from CVD were due to excess serum cholesterol (17). In another study involving 11,579 people, three quarters of coronary deaths were due to excess blood cholesterol (18). One study showed that at 30 years of age, for every 10 mg/dl of cholesterol, death from CVD increases by 9% (19).

As mentioned above, high concentrations of cholesterol favor the formation of atherosclerotic plaque and, therefore, CVD. However, there are other variable and invariable risk factors that facilitate atherosclerosis or contribute to the appearance of CVD. Invariable factors are those that cannot be modified, such as genetics, sex, or age. In contrast, variable factors can be modified by changing our lifestyle or taking precautions. Some variable risk factors are smoking, low physical exercise, high blood pressure, obesity, high cholesterol and triglycerides, or diabetes mellitus (2).

Smoking is an important risk factor, with a high incidence in the population. In 2016, the Ministry of Health, Consumption, and Welfare published a document stating that 23% of the Spanish population over 15 years of age smokes daily, being more common in upper-class men (20). Smoking and passive exposure to tobacco affect all stages of atherosclerosis. Studies show that it promotes inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol (21). Among the toxic substances contained in tobacco, polycyclic aromatic hydrocarbons and oxidizing gases cause adverse effects in some CVD (22). Nicotine elevates heart rate and blood pressure, as well as increases blood LDL and decreases HDL (23). Carbon monoxide inhaled due to active or passive smoking increases blood viscosity, favoring thrombus formation (24). In conclusion, many studies show that smoking causes CVD, but it also causes damage to artery walls and is associated with ischemic strokes (22).

Regarding physical activity, in the last decade the sedentary lifestyle has increased, favoring diseases such as obesity, type 2 diabetes mellitus or CVD (25). Currently in Spain, 36.7% of the adult population claims to be sedentary in their free time (20). Sedentary lifestyle includes those activities with an energy expenditure of less than 1.5 METs (MET = metabolic equivalent of task; 1 MET = ~3.5 mlO2/kg/min); such as sitting, watching television, or driving among others (26). A study has shown that an extra hour of sedentary lifestyle increases all cardiovascular risk factors (BMI, glycemia, insulin, blood lipids, etc.) (27). To promote cardiorespiratory function, improve bone health and prevent CVD, the World Health Organization (WHO) recommends at least 150 minutes of physical activity per week (28, 29).

Hypertension or high blood pressure, another important risk factor, is a condition in which the blood vessels have an elevated blood pressure that can damage them. Normal blood pressure in adults is 120 mm Hg when the heart beats (systolic pressure) and 80 mm Hg when the heart relaxes (diastolic pressure). Hypertension occurs when the systolic pressure is higher than 140 mm Hg and/or the diastolic pressure is higher than 90 mm Hg (30). The Framingham study was the first to relate high blood pressure to cardiovascular risk (31). Subsequently, epidemiological studies have shown its importance in atherosclerosis, heart failure, and renal failure (32). In people between 40 and 70 years of age, every 20 mm Hg increase in systolic blood pressure or 10 mm Hg increase in diastolic blood pressure doubles the risk of CVD (33). If there is no cardiovascular risk, hypertension can be treated by improving lifestyle: reducing salt and alcohol intake, quitting smoking, or engaging in regular physical activity, although in the most severe cases medication is necessary (34).

Obesity and overweight are defined as the excessive accumulation of fat that can be detrimental to health (35) Body mass index (BMI) is normally used to identify them, overweight is considered when BMI is equal to or greater than 25 and obesity when BMI is equal to or greater than 30 (35). WHO estimates that, in 2016, about 39% of adults were overweight while the 13% of adult were obese. In relation to children and adolescents overweight and obesity have increased to 18% globally (35). The accumulation of excess adipose tissue causes alterations at the metabolic level (33) but also affects the structure of the heart (36).

Another risk factor for CVD is diabetes mellitus (DM), defined as a set of metabolic disorders that result in elevated blood glucose concentration. It may be due to a failure in insulin synthesis (type 1 diabetes, DM1) or to a resistance to insulin action (type 2 diabetes, DM2) (37). In 2011, the prevalence of diabetes in the adult Spanish population was 13.8% (38). Elevated triglyceride

levels, low HDL, hypertension, or obesity are factors preceding DM2 and their combination is called metabolic syndrome (39, 40).

Many studies give important relevance to diet in order to prevent CVD. It has been shown that improving the foods we eat can prevent atherosclerosis and thus prevent some CVD (41). In 2015, 56% of deaths due to CVD in men and 48% in women were attributed to dietary factors (42). Several studies such as the Primary Prevention of Cardiovascular Disease (PREDIMED) and the Lyon Diet Heart Study have shown that following a Mediterranean diet can prevent CVD (41). The Mediterranean diet is characterized by giving preference to the consumption of vegetables, using olive oil as a source of fat, decreasing the consumption of dairy products, eating fish and poultry in moderation, limiting red meat, and eating plenty of fruit (43). A sub-study from PREDIMED showed that individuals following a Mediterranean diet had fewer monocytes, inflammatory markers, and beneficial gene changes in reference to LDL oxidation (43).

Although a clear benefit of following a Mediterranean diet has been demonstrated, in recent decades there has been an increase in the consumption of ultra-processed foods according to the NOVA classification of foods (42). The NOVA classification organizes foods according to their nature, scope, and the industrial processing to which they have been subjected. Modifications include physical, biological, and chemical processes (44). NOVA classifies foods into four groups.

Group 1: unprocessed or minimally processed foods. This group includes natural foods, parts of animals or plants that are minimally altered. Some of the modifications that these foods undergo are the elimination of inedible parts, grinding, fractioning, or cooling, among others. Within this group we would classify seeds, fruit, roots, animal muscles, eggs or milk (44).

Group 2: processed culinary ingredients. These are foods derived from group 1 that are obtained by processes such as pressing, refining, grinding and drying. They are not intended to be consumed by themselves but are intended to be used for cooking or seasoning natural foods. This group includes oil, butter, sugar, and salt (44).

Group 3: processed foods. This group includes canned vegetables and fish, fruit in syrup, cheese, and bread. They are processed by adding group 2 foods to group 1 foods. The processing they undergo is aimed at increasing their shelf life or improving their flavor. Some of the processes would be baking or, in the case of bread, non-alcoholic fermentation (44).

Group 4: Ultra-processed foods. This group of foods is characterized by not having any food from group 1 intact. Soft drinks, reconstituted meat products or preprocessed dishes would be some examples (44).

Although ultra-processed foods have a multitude of definitions (4), they all agree that they are industrial formulations made from substances derived from food or synthesized from other organic sources (44). Basically, they are foods made mostly from sugar, oils, fats, and other substances not commonly used in culinary preparations, such as hydrogenated oils, modified starches, and protein isolates (42). They undergo a series of industrial processes such as hydrogenation, hydrolyzation, extrusion, or preprocessing for frying (41), causing the synthesis of new components that affect cardiovascular health, such as acrylamide, present in thermally processed products as a result of the Maillard reaction, or acrolein synthesized after fat heating (42).

To achieve the desired taste and long shelf life, ultra-processed foods have a large number of additives that have been linked to increased cardiometabolic risk, such as glutamates, emulsifiers, sulfites, or carrageenan (42). It is also suggested that these foods may affect satiety control and glycemic responses because they have less fiber and vitamins. It has been shown that the food matrix is important in the regulation of satiety and nutrient bioavailability as processing can alter plant and animal cells in foods (4, 42).

The importance of the storage of this type of food should be emphasized since some compounds present in ultra-processed foods, such as bisphenol A, come from the packaging and have been related to an increased risk of hypertension and coronary artery disease (42).

Three surveys of the Spanish population conducted in 1990, 2000, and 2010 have made it possible to study changes in the consumption of ultra-processed foods in Spain (45). In general, few foods of this type are consumed in Spain compared with other countries, such as Canada (61.7%), the United States (57.9%), the United Kingdom (53%), France (35.9%) or Brazil (29.6%). This is largely due to the adherence to the Mediterranean diet. However, the Spanish population is moving away from this diet as it currently consumes 1.2 servings of fruit daily, far below the recommended 5 pieces of fruit (4). The ENRICA study (46) found that the most consumed ultra-processed products in Spain are meat products (17.1%), cakes and sweets (13.6%), cookies

(9.2%), yogurts and fermented milks (8.8%), jams and jellies (7.4%) and, finally, precooked dishes (7.1%) (4).

Currently, in the Spanish adult population, 19.3% of energy intake comes from ultra-processed foods (4). Consumption data at the individual level indicate that ultra-processed foods comprised 60% of energy intake in the United States, whereas in European countries the proportion ranges from 24.4% to 36% (47).

Many studies have shown that increased consumption of ultra-processed foods favored the risk of cardiovascular, coronary, and cerebrovascular diseases (42, 47, 48, 49, 50). For every 10% increase in the intake of ultra-processed foods, the risk of cardiovascular disease increased by 12% (48). Furthermore, it has been shown that the relationship between intake of ultra-processed foods and CVD risk may stem in part from the concurrent lower consumption of non-ultra-processed foods. In fact, several ultra-processed food groups were associated with an increased risk of CVD, but its natural form (42).

Currently, the biological mechanism that might link ultra-processed foods to deaths due to CVD is not known exactly. However, regular consumers of ultra-processed foods have higher concentrations of biomarkers, such as cystatin C, of renal function that have been associated with an increased risk of CVD (47). In addition, added sugars and saturated fats, which are very often present in ultra-processed products, increase the risk of coronary heart disease through insulin resistance and hyperinsulinemia. A diet rich in added sugars approximately triples the risk of mortality from cardiovascular disease (51).

Therefore, the main objective of this literature review is to discuss how the main components of ultra-processed foods affect the cardiovascular system, as well as the additives they contain.

4. The effects of various components of ultra-processed food on the cardiovascular system

Although conventional risk factors, such as genetics, diabetes mellitus, hypertension, dyslipidemia, and obesity have been identified as major contributors to increased CVD risk, almost 20% of people with CVD do not have these risks. This suggests that other factors, such as exposure to environmental pollutants, also play a role in the increase or onset of CVD because the cardiovascular system is highly vulnerable to certain toxins (52).

Focusing on diet, the increased consumption of industrialized ultra-processed foods has led to higher energy intake, increased obesity, and chronic non-communicable diseases (NCDs), including CVD (53). This type of food contains a large number of food additives that improve appearance or palatability to the consumer and are intentionally included to color, sweeten, stabilize, and preserve ultra-processed products. The use of additives in food began in the early 1800s to improve food preservation; however, their use has been increasing and, today, there are more than 2500 additives permitted and it is almost impossible to avoid them. In the European Union, they are classified into 26 classes, some of the most common additives being sweeteners, colorants, and emulsifiers. Several surveys in different populations (UK, continental Europe, USA, Canada, New Zealand, and South America) have suggested that the total intake of food additives per person in industrialized countries varies between 7 and 8 kg per year (54). In addition to these additives, certain substances, called processing contaminants, can appear during food processing and are toxic to our health (53, 55).

All these additives enhance the flavor, color, and increase the shelf life of foods, but much research has studied their effect on health. This literature review will review how certain food additives, processing contaminants and certain components present in ultra-processed foods affect the cardiovascular system, being an important risk factor for CVD.

4.1. Glutamates

Glutamic acid and its salts, commonly called glutamates, are food additives authorized in the European Union (EU) that are added to a wide range of foods to enhance their flavor, providing an umami (salty or meaty) taste; and 10g/kg is the maximum amount allowed (58). Currently, the additives in this family are glutamic acid (E620), sodium glutamate (E621), potassium

glutamate (E622), calcium glutamate (E623), ammonium glutamate (E624) and magnesium glutamate (E625) (56).

Glutamate is found naturally in protein-rich foods, such as meat or fish, and in certain types of cheese (Roquefort and Parmesan) or vegetables (tomatoes, mushrooms, broccoli). However, it is used as an additive in certain food products, especially in bags of potato chips, sauces, pickles, and many ultra-processed foods because it increases appetite (57).

At low concentrations glutamate has several physiological functions: it is a main substrate for energy production in enterocytes, an intermediate substance in protein metabolism, a precursor of important metabolites such as glutathione (GSH, modulator of oxidative stress) or N-acetylglutamate (metabolic regulator), and also an excitatory neurotransmitter of the central nervous system (CNS). However, an increase in glutamate concentration in the CNS is mainly associated with brain damage, similar to status epilepticus, as well as with chronic neurodegeneration (57).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA), the US Food and Drug Administration (FDA) and the European Food Safety Association (EFSA) consider glutamates to be Generally Recognized as Safe (GRAS) substances. When EFSA evaluated the safety of glutamates used as food additives, it established an Acceptable Daily Intake (ADI) of 30 mg/kg body weight per day. This amount is based on the highest dose at which no adverse effects were observed in experimental animals in toxicity studies (56).

One study showed that the ADI is below doses that have been associated with monosodium glutamate (MSG) symptoms (> 42.9 mg/kg body weight per day), headache (85.8 mg/kg body weight per day), increased blood pressure (150 mg/kg body weight per day), and also increased insulin (> 143 mg/kg body weight per day) (58). However, glutamate consumption exceeds this ADI; in European industrialized countries, glutamate consumption is rated between 0.3 and 1.0 g per day (57).

Although the use of glutamates as additives is permitted, many studies have shown adverse effects on health and on the cardiovascular system. The main consequences are increased oxidative stress (5, 42, 59), biochemical changes (57, 60, 61), heart rhythm disturbances (57, 62), malignant changes in cardiac tissue (57, 61), and hypertension (58). In particular, MSG has been

associated with cardiotoxicity, low-grade inflammation, metabolic derangement, and increased oxidative stress (57).

In the NutriNet-Santé study, doses of MSG 4 mg/g body weight or more in mice increased cardiac tissue oxidative stress through lipid peroxidation (42) or, another hypothesis, through a decrease in superoxide dismutase and catalase activities in cardiac tissue (57, 59). This increased oxidative stress may be a cause for initiating atherosclerosis and other coronary heart diseases. In addition, obesogenic properties were observed, leading to a higher body mass index and a higher prevalence of metabolic syndrome (42).

Glutamate consumption can modify the concentrations of some biomarkers of heart disease, such as lactate dehydrogenase (LDH), aspartate transaminase (AST), and alanine transaminase (ALT) (60). In a study in which 4 g MSG/kg was administered subcutaneously to newborn rats, it was concluded that MSG increased the activities of these three enzymes (LDH, AST and ALT) but also increased the levels of total cholesterol, triglycerides, and decreased HDL levels (57, 60). These findings were reaffirmed in 2009, when peritoneally administering 4 g MSG/kg to rats three times a week for three weeks resulted in a significant increase in blood glucose, total lipids, triglycerides, total cholesterol, LDL cholesterol, and serum nitric oxide (57, 61).

Changes in heart rate have been observed when inoculating doses between 0.5 g MSG/kg and 1.5 g MSG/kg, as well as lethal tachyarrhythmia in rats with myocardial infarction (62). In the case of a single intravenous administration, a decrease in heart rate and bradycardia were observed when 0.5 g MSG/kg was administered (57, 62).

A very interesting study evaluated the effect of MSG present in sugar-free soft drinks (75 or 150 mg/kg body weight) after an overnight fast. Plasma glutamate level, blood pressure, heart rate, and pericranial muscle pain were evaluated for 2 hours. The glutamate level in plasma, blood pressure, heart rate, and pericranial muscle pain were assessed for 2 hours. At 30 minutes after exposure, the plasma glutamate level increased by 395% and 556% in the low- and high-dose monosodium glutamate groups, respectively. Systolic blood pressure, pericranial muscle tenderness, and stomach pain were significantly increased after high-dose monosodium glutamate. Therefore, it is considered that there is some evidence that high intake of monosodium glutamate (more than 3000 mg/day) may increase both systolic and diastolic blood pressure (58).

4.1.1. Discussion of glutamates

Although monosodium glutamate is considered a GRAS substance, its safety has been re-evaluated several times within the scientific community. Numerous negative effects have been reported in several studies, such as oxidative stress, inflammatory response, cardiac toxicity and others. However, these investigations have several shortcomings, including the lack of control groups, sample size and doses of administration, as they exceed more than those ingested through the diet. Another issue of controversy is the route of administration, as not all are of equal importance. Subcutaneous or intraperitoneal administration cannot be compared to human exposure to dietary glutamate, as they bypass the normal metabolic pathway of orally ingested monosodium glutamate.

Based on the literature found, I believe that many of the negative health effects due to glutamate have little relevance to human dietary exposure, as the doses are much lower. However, following a sedentary lifestyle, consuming large amounts of ultra-processed foods and beverages, can increase the dose of glutamate ingested and lead to serious effects on human health and, in particular, on the cardiovascular system. Therefore, the line of research into the effects of glutamate should continue to be studied. Future studies should mimic dietary glutamate consumption, i.e., adjust the route of administration as well as the dosage. In addition, added glutamate should be considered as that of natural origin in order to report meaningful data that provide real and relevant information on dietary glutamate consumption and its effects on human health.

4.2. Artificial sweeteners

Sugars can be found naturally in foods such as fruits and vegetables and do not pose a health problem. In fact, consumption of fruits and vegetables is associated with a lower risk of coronary heart disease because the sugars in these foods are found in reasonable doses and in proportions of fiber, water, and other likely beneficial components (63). The problem is refined sugars, added or artificial sugars that are used as sugar substitutes, being sweeter and without calories (64).

Six low-calorie sweeteners (stevia, acesulfame-K, aspartame, neotame, saccharin, and sucralose) are currently accepted in the USA and Europe (65) and 75% of all packaged foods and beverages in the USA contain added sugars (63). Although it has been recommended to limit the

consumption of added sugars to no more than 10% of total calories, between 2005 and 2010 their consumption has risen to almost 15% of total calories. The average daily intake of added sugars in the U.S. is 292.2 kcal, and 89.7% of these calories came from ultra-processed foods. The main sources of added sugars among ultra-processed foods are soft drinks (17.1%); juices (13.9%); milk-based beverages (4.6%); cookies and cakes (11.2%); breads (7.6%); desserts (7.3%); sweet snacks (7.1%); breakfast cereals (6.4%); and ice cream (5.9%) (71).

Marina Marinovich, Corrado L. Galli et al. studied aspartame as an artificial sweetener (66). Aspartame is an artificial dipeptide sweetener composed of the amino acids phenylalanine and aspartic acid plus a small amount of methanol. It is 200 times sweeter than sucrose. Since its approval, aspartame has been used in more than 6,000 different types of ultra-processed products, including soft drinks, desserts, ice cream, yogurt, or breakfast cereals, and is consumed by millions of people worldwide. Food advisory bodies and agencies have established an ADI for aspartame of 50 mg/kg/day in the USA and 40 mg/kg body weight in the European Union. However, the average consumption in a US dietary intake survey was 330.17 mg/day.

One line of research studied whether the consumption of artificially sweetened beverages could be a risk for coronary heart disease (72). The evidence was not sufficient to find a relationship, although there were 423 cases of coronary heart disease among daily consumers of low-calorie beverages and 301 among daily consumers of sugar-sweetened beverages. In contradiction to this study, several researchers believe that there is a relationship between the consumption of added sugars and cardiovascular pathology; there are hypotheses about some non-caloric artificial sweeteners, such as acesulfame potassium, which could accelerate the process of atherosclerosis, or sucralose, which could increase blood glucose and insulin levels (46). These hypotheses were confirmed when a study (73) showed that women who consumed an average of two or more artificially sweetened beverages per day had an increased risk of stroke, ischemic stroke, and coronary heart disease. In addition, a greater occlusion of small arteries was observed, favoring hypertension or metabolic syndrome.

In recent years, the consumption of an ultra-processed product with a large number of added sugars, energy drinks, with an average of 11.35 g of sugar/100 g, has increased among the young population. At the beginning of the 21st century, the first doubts arose about their toxicity to the cardiovascular system, and it has now been demonstrated that the consumption of a can of energy drink (355 ml) increased blood pressure and heart rate (68).

As an added sugar, added fructose, usually found in the form of sucrose or high fructose corn syrup (HFCS), increases oxidized low-density lipoprotein (oxLDL), promotes foam cell formation, abnormal blood flow, inflammation, increased expression of cell adhesion molecules, pro-coagulation, and increased intracellular oxidative stress. All this promotes the formation of atherosclerotic plaque (63).

4.2.1. Discussion of artificial sweeteners

Sugars found naturally in foods such as fruits and vegetables do not pose a problem for coronary heart disease. In fact, fruits and vegetables are associated with a lower risk of coronary heart disease and cardiovascular mortality. The sugars in these foods are found in reasonable doses and in the context of fiber, water, and other likely beneficial components. The problem is refined sugars and ultra-processed products are of greater concern and a linear relationship has already been found between the dietary contribution of ultra-processed foods and the dietary content of added sugars.

The study on energy drinks (68), which contain large amounts of artificial sugars, showed that consumption of energy drinks can lead to an adverse hemodynamic profile with increased cardiac load and decreased cerebral blood flow velocity. This is probably due to an interaction between caffeine and sugars in the cardiovascular system. Although these effects have only been studied in healthy young people, they are likely to be more severe in people with a history of cardiovascular pathology.

After conducting this literature review I can say that limiting the consumption of ultra-processed foods can be a very effective way to reduce added sugars and the harmful effects on the cardiovascular system.

4.3. Emulsifiers

While the consumption of some food additives, such as artificial sweeteners, can be limited through food choices, avoiding the intake of emulsifiers is much more difficult as they are commonly added to a wide variety of foods in the modern Western diet (54).

Within the food industry, emulsifiers were introduced in the 1930s. They were initially incorporated into margarines and were later widely used in the baking industry as preservatives

to prevent aging and improve the firmness and bulk of bakery products. Synthetic emulsifiers are often incorporated in doses of 0.2% to 0.5% by weight of the flour (54). Emulsifiers such as lecithin (E322) make it possible to form or maintain a homogeneous mixture of two or more immiscible phases, while emulsifying salts convert the proteins contained in cheese into a dispersed form and thus achieve a homogeneous distribution of fat and other components (sodium lactate, E325) (54).

Some of the emulsifiers often found in ultra-processed foods, carboxymethylcellulose and polysorbate-80, have shown a potential role in the induction of low-grade inflammation and obesity or metabolic syndrome in mice (42).

In recent years, the use of carrageenan as a food additive (E407) has increased as it has a multitude of functionalities, such as thickener, emulsifier, stabilizer, or gelling agent (69). Because of its broad functionality, carrageenan is found in a multitude of processed products, from milk shakes to sausages and hams. JECFA has recommended that carrageenan be excluded from infant formula and that a re-evaluation of carrageenan content in the diet be carried out (70). However, this compound is currently a food additive classified by the FDA as a GRAS substance, and EFSA declares carrageenan as a permitted food additive (69).

Currently, the ADI for carrageenan is not specified and intake levels in the Western diet have not been evaluated. However, the evolution of carrageenan consumption in the United States has been monitored, where in 1972, the daily intake of carrageenan was 45 mg per day, while in 1977, a daily intake of 100 mg was estimated. In 2003, the amount of carrageenan ingested in the South Florida population was reported to be 7.7 g per day (69).

Since the 1970s, extensive studies have been conducted on the adverse effects of carrageenan on human health. A multitude of in vivo and in vitro studies have shown that carrageenan causes an increase in colon tumors, an increase in small intestinal tumors, increased cell proliferation in the crypts of the colon, ulcerations of the cecum and large intestine, and loss of epithelial cells (69). In addition, a recent study (70) reported that carrageenan could cause glucose intolerance, insulin resistance, and inhibition of insulin signaling in cell and animal models (42). Carrageenan also induces inflammation through an innate immune pathway mediated by toll-like receptor (TLR) 4 (Figure 1) and a pathway mediated by reactive oxygen species (ROS). These cascades lead to nuclear factor κB (NFκB) activation via canonical and noncanonical cascades involving the v-rel reticuloendotheliosis viral oncogene homolog A (RelA) and v-rel reticuloendotheliosis

viral oncogene B (RelB). Carrageenan activates an innate immune-mediated inflammatory pathway via TLR4 and B cells, leading to an increase in phosphoinositide κB inhibitor (IκBα), which enables nuclear translocation of NFκB and subsequent transcriptional events necessary for inflammation, including increased interleukin-8 (IL-8) production (70).

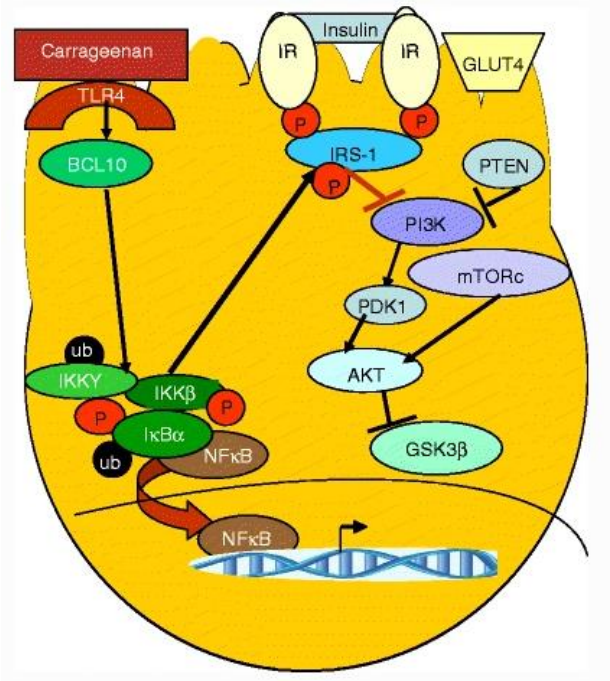

Figure 1 (70). Schematic representation of the interrelationship between carrageenan-induced inflammation and inhibition of insulin signaling. IR, insulin receptor; ub, ubiquitin; PTEN, phosphatase and tensin homolog; GSK, glycogen synthase kinase.

All these results show how carrageenan can cause glucose intolerance, insulin resistance and inhibition of insulin signaling, becoming a risk factor for CVD.

4.3.1. Discussion of emulsifiers

Based on the literature reviewed in this work, it appears that inadequate characterization and understanding of the macromolecular features of carrageenan are part of the existing gaps on the effects it can cause. Therefore, I believe that structure-function studies of carrageenan would be necessary.

In general, when reviewing the information studied on carrageenan, I deduce that it can now be considered an alarming factor for human health and its intake should be controlled. Furthermore, if it has been recommended that carrageenan be excluded from infant formulae, its use in other foods should be controlled and the population should be informed of its presence.

Nowadays, choosing whether or not to ingest emulsifiers is very complicated as they are present in many foods. It is believed that emulsifiers can have cumulative effects that can lead to chronic inflammation, diabetes and metabolic syndrome. Therefore, future research should focus on studying the harmful effects of these additives in the long term.

4.4. Sulphites

Humans are exposed to sulfites both exogenously and endogenously. Endogenous sulfites are generated as a result of the metabolism of sulfur-containing amino acids. Exogenous sulfites exist in various foods and beverages, either naturally or as a product of fermentation (71). The sulfites authorized by the EU according to Annexes I and II of Regulation (EC) No 1333/2008 are sulfuric acid (E513) and its sodium (E514), potassium (E515), calcium (E516), and ammonium (E517) salts (75).

Due to their antioxidant and antimicrobial properties, sulfites are found mainly in foods such as wine (they prevent the proliferation of bacteria or yeasts), crustaceans (they prevent browning of the product), in prepared meat products (they maintain their pink color) and other products such as mashed potatoes or ready-to-eat sauces (59, 72, 71).

According to one study (72), among the young population, young children are considered to be the group most exposed to sulfites in the diet. The mean exposure ranged from 0.4 mg sulfite/kg body weight per day in infants, 35 mg sulfite/kg body weight per day in toddlers, and from 3 mg sulfite/kg body weight per day in adolescents.

It has been shown that sulfites consumed in high oral doses, found in some ready-to-eat sauces, caused cardiac damage in rats (4). However, among the sulfites accepted as food additives, it is known that sodium metabisulfite (SMB) can react with acids and water releasing toxic SO_2 gas and is more prone to react with acids and water (71). Currently, SMB is used as a preservative in the production of ultra-processed foods because of its ability to inhibit the growth of microorganisms and its antioxidant properties. One study (71) shows how the SMB metabolite, SO_2, can affect the cardiovascular system by increasing the expression of ATP-regulated K^+ channels and decreasing the expression of L-Ca^{2+} channels in the heart. Because of this, this literature review will pay special attention to the effect of SMB on the cardiovascular system.

Several Japanese authors (71) studied the effect of SMB on rat hearts administered SMB (control group, 130 mg SMB/kg, 260 mg MDB/kg, and 520 mg SMB/kg). This study suggests that, through inotropic effects, SO_2 can activate the expression of ATP-sensitive K^+ channels (KATP) by increasing the mRNA and protein levels of Kir6.2 and SUR2A, whereas it inhibits the expression of L-type calcium channels (L-Ca^{2+}) by decreasing the mRNA and protein levels of $Ca_v1.2$ and $Ca_v1.3$ in rat hearts.

KATP channels are hetero-octameric protein complexes consisting of two subunits: a pore-forming subunit Kir6 and a sulfonylurea receptor subunit (SUR). In cardiac KATP channels, Kir6.2 is the major site of ATP-induced inhibition and SUR2A predominantly regulates K+ efflux through adenine nucleotide binding and catalysis. KATP channels can increase myocardial oxygen delivery and decrease oxygen consumption, thereby improving cardiac function and myocardial energy metabolism, preserving normal cell structure, regulating vascular tension, and changing ion distribution between both sides of cardiac myocytes. It is assumed that defects in the channel-forming proteins, disruption in metabolism or miscommunication between the different channels could cause heart disease. On the other hand, L-Ca^{2+} channels are mediators of Ca^{2+} influx, essential for the function of ventricular cardiac myocytes. L-Ca^{2+} channels are multimeric complexes consisting of a pore-forming α1 subunit and auxiliary subunits. The α1 subunit is classified as $Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$, $Ca_v1.4$. Ca^{2+} influx through L-Ca^{2+} channels are important for cardiac function because it triggers excitation-contraction (EC) coupling, modulates the shape of the action potential, and causes cardiac arrhythmias (71).

SMB modifies the mRNA and protein levels of KATP channel subunits in rat hearts. The mRNA level of Kir6.2 was significantly increased in rat hearts treated with 260 and 520 mg/kg SMB compared with the control group (Fig. 2A). When SUR2A mRNA levels were evaluated in rat hearts exposed to SMB (Fig. 2C), an increased presence of SUR2A was observed in rats exposed 260 and 520 mg SMB/kg. Furthermore, SUR2A protein levels were significantly increased in hearts treated with the highest concentration of SMB (520 mg/kg) relative to the control group (Fig. 2D) (71).

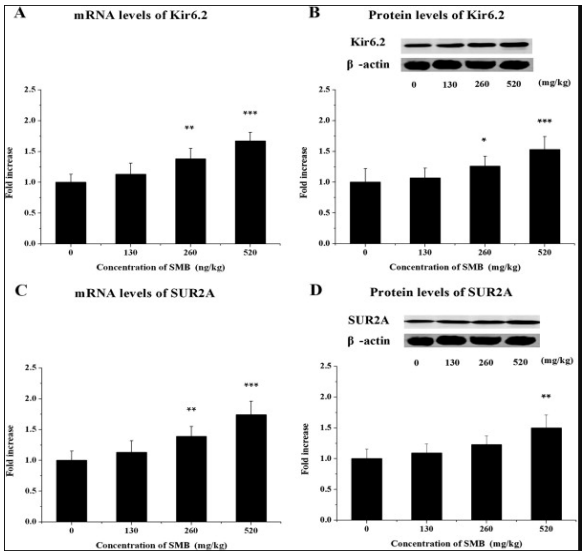

Figure 2. SMB effects on mRNA and protein expressions of Kir6.2 (A and B) and SURA (C and D) in rat cardiac tissues (71).

Figure 3 shows the effect of MSB on the mRNA and protein levels of the L-Ca^{2+} channel subunits in rat hearts. Both mRNA and protein expression of both subunits ($Ca_v1.2$ and $Ca_v1.3$) is decreased with MSB treatment at the highest concentration (520 mg/kg) (71).

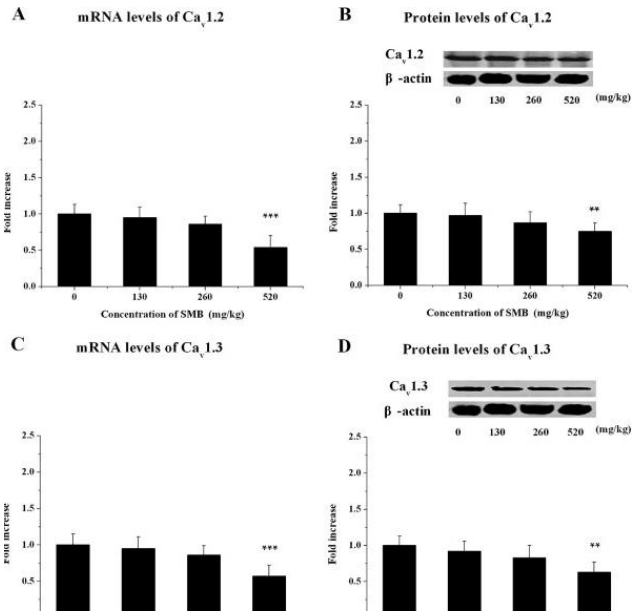

Figure 3. Effects of MSB on $Ca_v1.2$ (A and B) and $Ca_v1.3$ (C and D) expression (71).

Histopathology of the heart was studied by performing hematoxylin and eosin (HE) staining of cardiac tissue. Upon observations, the groups of rats that had been given 130 and 260 mg SMB/kg (Fig. 4 B and C) had normal myocardial fibers and muscle bundles with normal architecture as the control group (Fig. 4A). However, some lesions were observed in the 520 mg/kg SMB group (Fig. 1D), such as inflammatory cell infiltration in the myocardium. Cardiac myofibrils in this group were found to have a disordered pattern compared with the control

group. In addition, myocardial gap expansion was observed in rat hearts compared with those in the control group (71).

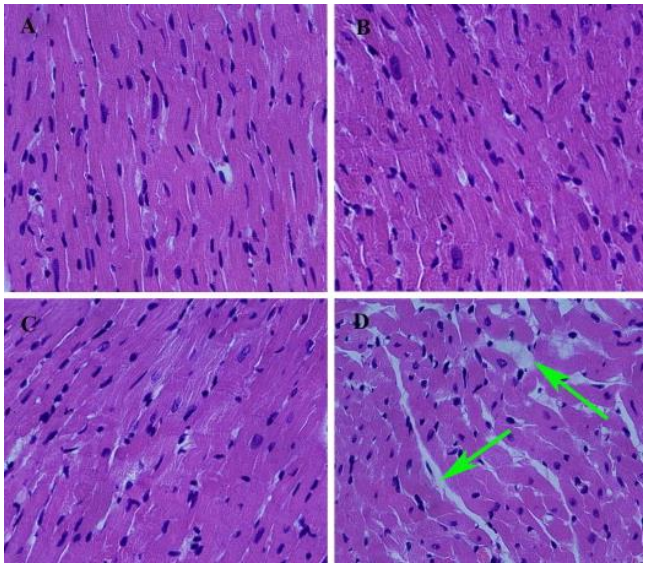

Figure 4. Hematoxylin and eosin staining in cardiac tissues of rats exposed to SMB. A: Control group. B: 130 mg / kg SMB group. C: 260 mg/kg SMB group, (D) 520 mg/kg SMB group. Arrows indicate the sites of abnormal histological changes in rat cardiac tissues (71).

These results suggest that SMB at the concentration of 520 mg/kg could have potential damage to rat hearts.

4.4.1. Discussion of sulphites

It is now known that the metabolic product of sodium metabisulfite (SMB), SO_2, is associated with cardiovascular disease, neurotoxicity, genotoxicity, and mortality of many brain disorders (71).

In the work by Quanxi Zhang, Yunlong Bai et al. (71), the results suggest that SMB and SO_2 derivatives increased K^+ currents in the cardiovascular system due to an increase in the expression of K^+ channel subunits. They also proved that SO_2 derivatives could cause cardiac myocyte injury by changing extracellular Ca^{2+} concentration through voltage-gated Ca^{2+} channels. In addition, histopathological damage was observed in rat heart by supplying 520 mg SMB per kg body weight. From all these results, I believe that there is a need for improved education regarding the potential side effects of SMB to eliminate unnecessary morbidity and mortality.

4.5. Acrylamide

Recently, acrylamide has been discovered in foods (73). It is naturally created in starch-containing food products during everyday cooking processes at high temperatures and low humidity (74). Therefore, acrylamide is considered a contaminant of the heat-induced process, where the main chemical reaction taking place is the Maillard reaction (53). The Maillard reaction results in foods with a color and aroma that are organoleptically palatable, but has negative effects such as decreased nutritional value, altered protein digestion, and the production of toxic products (74, 75).

EFSA has identified acrylamide content in food as a public health concern (53). The European Commission developed the Acrylamide Regulation 2017/2158, which obliges food processors and food business operators in Europe to reduce the presence of acrylamide according to the principle of as low as reasonably achievable (53). However, the average adult dietary intake of acrylamide was estimated to be 0.4 g/kg (73).

Tareke et al. demonstrated the presence of relatively high levels of acrylamide in commercial heat-processed foods and in foods cooked at high temperatures, especially in carbohydrate-rich foods. These findings stimulated worldwide studies on the determination of acrylamide levels in foods (76). The biomarkers used in these studies are the adducts formed as a result of the reaction between the α-NH_2 group of the N-terminal valine of hemoblobin with both acrylamide [N-(2- (2-carbamoyl)-l-valine] and its metabolite glycidamide [N-(2-(2-carbamoyl-2-hydroxyethyl)-RS-valine)] (52, 76). Tareke et al. found that rats treated with a fried food diet had significantly higher levels of the hemoglobin (Hb) adduct of acrylamide than those fed a control diet (76).

In 2002, an international health alarm was raised about acrylamide because it was found in many ultra-processed foods, such as potato chips or crackers (52). It was then that acrylamide and its harmful effects on human health began to be studied. In the NHANES (National Health and Nutrition Examination Survey) study, acrylamide was associated with increased odds of CVD (42). One study reported that consumption of French fries with a high acrylamide content modified markers of oxidative stress and inflammation (52) and it has been postulated that the toxicological effect of acrylamide may be associated with failures in its metabolism (Figure 5), specifically due to an imbalance between the CYP2E1 toxicological pathway and the glutathione detoxification (GSH) pathway (77).

Acrylamide, once absorbed, can undergo epoxidation at cytochrome P450 (CYP2E1) leading to glycidamide (GA) or be conjugated with glutathione GSH by glutathione-S-transferase and subsequently excreted in the urine as mercapturic acid (54). GA is a reactive epoxide metabolite that is suspected to be responsible for the genotoxic effects of acrylamide. Although both compounds are known to have other deleterious effects, such as pro-oxidation (73).

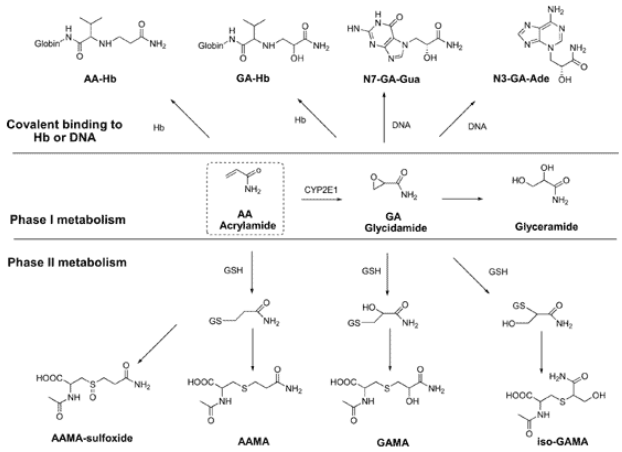

Figure 5. Acrylamide metabolism (77)

In one study, antioxidants, superoxide production and certain enzyme activities were measured on zebrafish groups that had been treated with acrylamide and other control groups. The results showed that the level of reactive oxygen species (ROS) increased significantly, and superoxide dismutase (SOD) activity decreased significantly in the groups treated with 2.0 mM acrylamide. GSH content and glutathione-S-transferase (GST) activity were also significantly decreased in the 2.0 mM acrylamide-treated groups. All these lead to an increase in oxidative stress. In addition, this study showed that acrylamide caused altered lipid metabolism, modified cardiac morphology and function, reduced cardiomyocyte proliferation, and altered atrioventricular canal differentiation and valve development (78).

All these results imply that acrylamide can activate the antioxidant system, but continuous long-term exposure to acrylamide at high doses may induce oxidative stress, cause chronic inflammation, and contribute to the progression of early atherosclerosis as well as to the increased risk of coronary artery disease (52).

A major source of acrylamide is tobacco smoke. Separate analyses were performed according to five common types of CVD in the group exposed to environmental tobacco smoke. 3.4%, 4.2%, 3.4%, 4.4%, 4.4%, and 3.8% of participants reported having congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke, respectively (52). It was also shown that

AA present in tobacco smoke could affect erythrocyte deformability and thus increase blood viscosity in rats, indicating an increased risk of CVD (52).

4.5.1. Discussion of acrylamide

Although the Spanish Agency for Food Safety and Nutrition believes that the overall contribution to dietary acrylamide exposure is limited if a normal varied diet is followed (78), EFSA has identified acrylamide content in food as a public health concern (53).

After carrying out this literature review on acrylamide, I believe it is a toxic compound for human health and an ADI should be established to limit exposure or even prohibit its presence in food. Future lines of research could focus on clinical studies, with people of all age groups and study the long-term effect of acrylamide and its possible accumulation in the body. I believe that this research would be useful since we are exposed to this compound from a very early age, consuming cereals, and cookies since childhood.

Exposure to acrylamide cannot be known exactly as it does not appear in the composition or ingredients shown on the packaging of processed foods, but we can reduce its consumption by avoiding ultra-processed foods as acrylamide originates after thermal processing.

4.6. Acrolein

Acrolein is a reactive α, β-unsaturated aldehyde found primarily in tobacco smoke, wood smoke, or gasoline and diesel exhaust. However, acrolein is also present in beverages and foods, such as coffee, alcohol, cheese, and doughnuts; and heating and cooking of fats, oils, and sugars has been shown to increase acrolein content (55). The phenomenon by which acrolein is formed is called hydrolytic rancidity, where glycerol from diglycerides is dehydrated at high temperatures. Therefore, acrolein can be found in ultra-processed foods, such as fried foods, and is more abundant if overheated, old, spoiled, or poor-quality oils are used (79).

Although it is not known exactly how much acrolein we ingest through the diet, animal studies have shown that exposure to acrolein causes extensive cardiovascular injury. Among these, acrolein affects the mesenteric bed and aortic reactivity, produces left ventricular dilatation and dysfunction, and dilated cardiomyopathy. Acute acrolein consumption has also been shown to induce lipoprotein modification and systemic dyslipidemia, leading to increased plasma levels of

low-density lipoproteins and triglycerides. While chronic exposures increase platelet activation and reduce bleeding time. In addition, it has recently been reported that acrolein may affect vascular repair capacity as this compound suppresses circulating levels of $Flk^+/Sca\text{-}1^+$ cells (55). This same study (55) demonstrated that acrolein-modified proteins exist in oxidized low-density lipoprotein and in human atherosclerotic lesions. Acrolein-modified low-density lipoprotein by SR-A1 receptors was found to be involved in foam cell formation and atherosclerotic lesions. Adduction of apoA-1 by acrolein has been shown to prevent reverse cholesterol transport.

The largest study on acrolein exposure was evaluated in 211 participants of the Louisville Healthy Heart Study at risk for cardiovascular disease by measuring urinary levels of the major acrolein metabolite, 3-hydroxypropylmercapturic acid (3-HPMA) (55). Acrolein exposure was associated with suppression of circulating angiogenic cell levels, platelet activation, as well as increased risks of CVD (42). After adjusting for several variables, 3-HPMA levels were positively associated with circulating levels of platelet-leukocyte aggregates, linking acrolein exposure with platelet activation in humans (55).

On the other hand, platelet activation has been shown to induce IL-1β, IL-8, and MCP-1 in monocytes, and to promote monocyte recruitment into atherosclerotic arteries and accelerate atherosclerotic lesion formation in apoE-depleted mice. Taken together, these findings indicate that, in addition to serving as a biomarker of platelet activation, these aggregates may contribute significantly to the initiation and progression of atherothrombosis (55).

To determine whether acrolein exposure is associated with CVD risk, the cohort was divided into low (FRS <20) or high (FRS ≥ 20 or experienced a cardiovascular event) CVD risk groups. As shown in Figure 6A, individuals at low risk had significantly lower 3 - HPMA levels than those in the high-risk category while in the non-smoking population, the concentration of 3-HPMA was significantly lower in individuals in the low-risk category (Figure 6B). These findings indicate that nonsmokers with lower levels of 3-HPMA were at lower risk of CVD. Furthermore, after excluding individuals with preexisting CVD, 3 - HPMA levels were found to be significantly lower in individuals with low FRS (Figure 6C) (55).

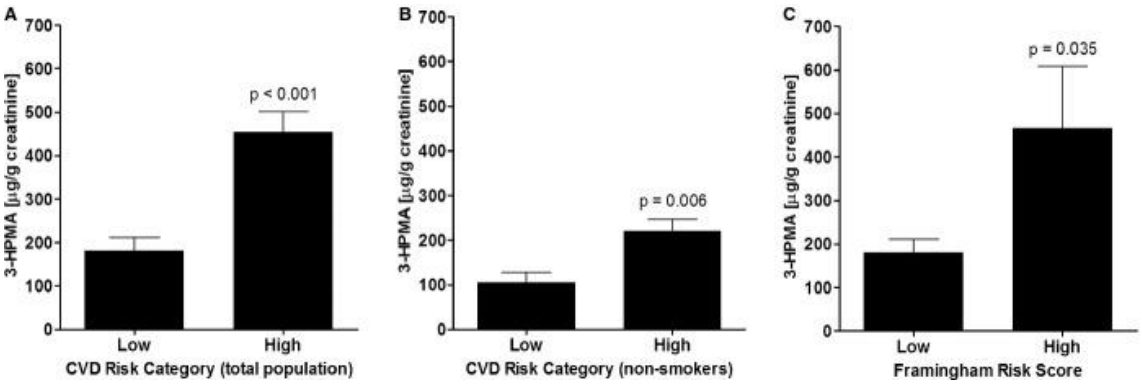

Figure 6. Association between CVD risk and 3 - hydroxypropylmercapturic acid (3 - HPMA) (57).

4.5.1. Discussion of acrolein

Like acrylamide, acrolein is a processing contaminant, but this compound appears after heating and cooking of fats, oils, and sugars (55). Therefore, acrolein can be found in ultra-processed foods, such as fried foods.

The results found are based on exposure to acrolein present in tobacco smoke. Therefore, the exposure is by inhalation and not by the oral route as it would be in the case of ultra-processed foods. The exact amount of acrolein present in foods is not currently known; therefore, we could not assume that all these harmful effects on the cardiovascular system could appear when eating a diet with a high consumption of ultra-processed foods. Future research should study the presence of acrolein in food and establish what effects it would cause if administered orally.

4.6. Bisphenol A

Ultra-processed foods may be contaminated by contact materials including bisphenol A (BPA), judged to be "a substance of very high concern" by the European Chemicals Agency and found in a recent meta-analysis to be associated with an increased risk of cardiometabolic outcomes, in particular, hypertension and coronary artery disease (46).

BPA is a synthetic monomer used in the manufacture of polycarbonate plastics and epoxy resins, with worldwide production estimated at 3.8 million tons in 2006. BPA has been shown to be very common in our environment as more than 90% of people have detectable levels of BPA present in urine, which is the primary route of excretion in humans (91).

The data on BPA exposure are confusing. Several studies suggest that the amount of BPA that would enter the human body daily would be slightly less than 1 microgram per kilogram. On the other hand, a scientific committee of the European Commission estimated that it would be up to 1.6 microgram/kg body weight per day via the dietary route, and a study in New Zealand spoke of about 4.8 micrograms per day through the diet alone (81).

The main source of human exposure to BPA is through ingestion of food that has been stored or reheated in BPA-lined containers, since this compound is not chemically bound and can be transferred to food (80, 81). It is known that certain factors such as packaging time, temperature or the nature of the food contained can increase the release of the substance. A study conducted at the Japanese Universities of Nagasaki and Kumamoto showed how heat increased the migration of BPA into food by up to 51.7% (82). In addition, a study showed how avoiding canned foods, putting plastic in the microwave, or not using plastic bottles for three days reduced BPA levels by up to 75% (83).

It has been observed that BPA is an endocrine disrupting chemical because of its ability to interfere with both the synthesis and the effect of certain hormones in the blood, inducing obesogenic or diabetogenic effects. The mechanism by which it acts is not known exactly, but as structurally similar to 17β-estradiol, it is believed to occur through estrogen-related receptors (ER), the G protein-coupled estrogen receptor GPR30 and peroxisome proliferator-activated receptor gamma (PPAR-γ). Binding of BPA to these receptors has been shown to induce insulin resistance, adipogenesis, pancreatic beta-cell dysfunction, inflammation, and oxidative stress (80).

The relationship between BPA exposure and the risk of cardiometabolic disorders is reviewed below. Urinary BPA (uBPA) concentration was measured in the studies used. Four cross-sectional studies reported a positive linear association between uBPA and CVD. In the NHANES investigation between 2003 and 2004, an increased risk of CVD (myocardial infarction, angina pectoris, or coronary heart disease) was associated with higher uBPA concentration, but there was no increased risk of stroke. The only prospective study, conducted within the EPIC-Norfolk cohort, reported a positive association between uBPA concentrations and coronary artery disease (CAD) incidence up to 10 years after BPA measurement, with a significantly increased risk of CAD (84). In addition, uBPA has been linked to hypertension, a risk factor for CVD. Both Shankar and Teppala (using data from NHANES 2003-04) and Shiue et al. (NHANES 2009-10) showed a positive association between uBPA and hypertension (80).

4.6.1. Discussion of bisphenol A

It is known that certain factors such as packaging time, temperature or the nature of the food contained can increase the release of the substance (82). This is important because many ultra-processed foods require rapid preparation before consumption, such as heating the food together with the container in the microwave for a certain time. These preparations would increase the concentrations of BPA and other possible contact contaminants and, therefore, the amount to which we are exposed.

The European Chemicals Agency has defined BPA as "a substance of very high concern" because it is associated with an increased risk of cardiometabolic pathologies, in particular hypertension and coronary artery disease (42). After reviewing the bibliographic information, I believe that the existing studies are sufficient to accept BPA as a hazardous substance for human health and to take measures to control its presence in food. One possible measure would be to prohibit containers that could release BPA into food or not to preheat certain containers before consumption.

Future lines of research should focus on the mechanism of action of BPA, studying it more precisely to find out how it affects the cardiovascular system. If the mechanism is known, medicines can be sought to reduce its effect, although the best medicine might be to stop consuming as many ultra-processed foods as possible.

4.7. High salt content

Most ultra-processed foods are high in salt (sodium chloride), sodium used as a synonym. The main foods with a high salt content are condiments such as sauces, broths, powdered soups, and processed meats (84). In a study where 520 products were analyzed, 37% had excessive sodium content, of which 90% corresponded to sausages and "miscellaneous products", including dressings (88%) and prepared mixes and flours (81%) (85). Coinciding with these results, two studies carried out in the United Kingdom and Australia (86, 87) reported that processed meat, packaged bread, dairy products and sauces and dressings are the products with the highest salt content.

For most of our evolution, humans consumed less than 0.25 g of salt per day (88). Currently, the estimated dietary intake of salt is between 9 and 12 g per day in most countries of the world,

whereas the WHO recommended daily salt intake is 5 g (89). In 2005, only 9.6% of adults met the recommended guidelines for sodium intake (88).

Excessive dietary salt intake is associated with an increased risk of hypertension, which in turn is a particularly important risk factor for cardiovascular pathologies. However, a reduction in dietary salt intake leads to a considerable reduction in blood pressure in both hypertensive and normotensive patients (89). One study (88) concluded that a reduction of only 3 g/day predicts a decrease in blood pressure of 3.6 to 1.9 mm Hg in hypertensive subjects and 1.8 to 0.8 mm Hg in normotensive subjects. It should be noted that not all people react in the same way to changes in dietary salt intake, dividing people into salt-sensitive and salt-insensitive groups. It is estimated that about 50-60% of hypertensives are salt sensitive. In addition, salt hypersensitivity varies according to genetic polymorphisms, increases with aging, in black people, and in people with metabolic syndrome or obesity (89).

Several mechanisms have been proposed for salt-dependent hypertension, including blood volume, altered renal functions and sodium balance disorders, impaired renin-angiotensin-aldosterone system reaction and associated receptors, central stimulation of sympathetic nervous system activity, and possibly also inflammatory processes (89). One mechanism by which high salt intake and hypertension are related is exchangeable sodium. Elevated sodium and low potassium inhibit the sodium pump, increase intracellular sodium, and drive calcium into cells, ultimately inducing vascular smooth muscle contraction and increased peripheral vascular resistance. A new mechanism of action identified is excess sodium stored in the subcutaneous lymphatic system, where it becomes osmotically inactive, as it may act as a fluid buffering system to attenuate the increase in blood pressure during excessive salt intake. Another hypothesis posits that hypertension is a genetic disorder, which is expressed when salt intake is excessive. In the Framingham Offspring cohort, heterozygous carriers of rare genetic variants (Bartter and Gitelman syndromes), identified in 1.2% of the study cohort, had systolic blood pressure 6 to 9 mm Hg higher than that of noncarriers (88).

Data reveal that hypertension causes between 4 and 9 million deaths annually worldwide and is responsible for at least 45% of deaths from heart disease and 51% of deaths from stroke (80).

4.7.1. Discussion of high salt content

Considering the data on salt intake, excessive salt intake is associated with an increased risk of hypertension, which in turn is an important risk factor for cardiovascular pathologies. Several mechanisms have been proposed for salt-dependent hypertension, including blood volume, altered renal functions and sodium balance disorders, impaired renin-angiotensin-aldosterone system reaction and associated receptors, central stimulation of sympathetic nervous system activity, and possibly also inflammatory processes (89).

As has been demonstrated in some studies, the reduction of salt intake in the diet leads to a considerable decrease in blood pressure, both in hypertensive and normotensive patients (89). In my opinion, there should be nutritional education that informs about the negative effects that excess salt can cause, as well as substitutes for salt, such as spices or homemade condiments.

4.8. Saturated and trans fats

As a biochemical term, fats designate various types of lipids consisting of one, two or three fatty acids bound to a glycerol molecule. Fats must be included in the diet because they perform vital functions for our organism, such as the energetic function, since they provide 9 kcal per gram. In addition, cholesterol forms cell membranes and is a precursor of important molecules (91).

According to their chemical structure, fats are divided into saturated, monounsaturated, polyunsaturated and trans fats. Saturated fats, which generally come from animal origin, are naturally solid at room temperature and have no double bonds in their chain. Monounsaturated fatty acids are usually liquid at room temperature and have one double bond in their chain, while polyunsaturated fatty acids have one or two double bonds in their structure. Polyunsaturated fatty acids include omega-6 and omega-3. Finally, trans fats are fatty acids with double bonds in the trans position (91, 92). They come naturally from milk fat and ruminant meat; however, they can be formed from a chemical process by partially hydrogenating vegetable oils. The process involves adding hydrogen under pressure in the presence of nickel, a metal that is used as a catalyst for the reaction. Baked foods such as cookies, industrial baked goods, convenience foods, snack foods, ice cream, shakes, and fried foods such as potato chips, corn, and other snacks are the foods that contain the highest amounts of trans fats (93, 94).

Colloquially, we speak of "good" and "bad" fats. Good" fats include polyunsaturated and monounsaturated fats. They are so called because their consumption can lower blood cholesterol levels and thus protect against coronary heart disease. However, these fats have a high caloric value and increase triglyceride levels in the blood. On the other hand, "bad" fats increase cholesterol production, cause blood vessel clots and atherosclerosis. Saturated and trans fats belong to this group and their consumption should be limited (92).

Currently, it is recommended to consume less than 10% of calories from saturated fat but the average intake of saturated fat in U.S. adults is 11% and only 5% of adults consume <7%, and 30% to 40% consume <10% (95). As for trans fats, they are estimated to be between 3% and 7% of the fats consumed (93). These latter data are surprising because since 1961, the American Heart Association (AHA) has recommended the reduction of saturated fats in the diet to reduce the risk of CVD (95). More than 30 years of research led the National Cholesterol Education Program (NCEP) to conclude that saturated fatty acids were the dietary component that most promoted the increase in plasma cholesterol. Reducing consumption of saturated fatty acids should be practiced prudently by reducing consumption of foods rich in this type of fat, not by eliminating classes of foods. Some changes can be made in food formulations or preparation practices (type of frying fat). These modifications may decrease the palatability of the food, which is a challenge for the food industry (99). The main sources of saturated fats to be decreased are butter, lard, beef tallow, palm oil, and coconut oil (95).

The scientific rationale for reducing saturated fats in the diet has been and continues to be based on the well-established effects of saturated fats in increasing low-density lipoprotein (LDL) cholesterol, a major cause of atherosclerosis. In addition, reducing saturated fats and replacing them with polyunsaturated fats has reduced the incidence of CVD. Populations with a very low intake of saturated fats, such as those in East Asian and Mediterranean countries, have very low rates of CVD (95).

When we consume trans fatty acids, they are absorbed by the digestive tract and pass into the blood. They are incorporated into the cell membrane where they replace phospholipids, which are normally the fats that make up cell membranes and these lose or decrease their flexibility and fluidity, so that other molecules, such as cholesterol, cannot attach to the membrane and remain free, increasing blood cholesterol levels. In addition, they increase the formation of cholesterol esters that are responsible for the development of the atherogenesis process. As esterified cholesterol increases, the exchange of cholesterol from HDL to LDL proteins, which

have the capacity to be deposited in the arterial wall, increases. This causes calcium deposits, and the so-called atheroma plaque is formed (91). Therefore, the first effect of trans fatty acids is to increase total cholesterol levels, especially LDL cholesterol ("bad cholesterol"), while decreasing HDL cholesterol ("good" cholesterol) (91).

An intake of more than 1 gram per day of trans fat produces an increase in carotid artery stiffness. Interestingly, this same effect is observed with saturated fat consumption, but in amounts greater than 10 grams per day. In other words, trans fat has the same effect on the arterial wall as saturated fat, but at much lower amounts of consumption (91).

On the other hand, trans fatty acids increase blood triglyceride levels and hypertriglyceridemia is associated with the risk of cardiovascular disease. In addition, trans fatty acids have been shown to increase inflammation at the level of endothelial cells since, by incorporating into the membranes of cells, both endothelial and white blood cells and adipose tissue cells, they affect the pathway that initiates the mechanisms of inflammation. Inflammatory factors play an important role in the development of diabetes, atherosclerosis, plaque rupture and sudden cardiac death (91).

Fat has also been linked to hypertension. One study (96) compared a diet with 27% total fat where 16% was saturated versus another with only 6% saturated fat of the 27% total fat. The results showed similar sodium levels, but systolic and diastolic pressures were 5.5 and 3.5 mmHg lower with the reduced fat diet (84).

Ultra-processed foods are characterized by a high saturated fat content. In addition, the cooking methods of these foods can change their composition and effects on the body. Frying creates desirable products because of their characteristic brown color, crispness, and flavor. In addition, they also contain trans fatty acids generated during processing (90).

4.8.1. Discussion of saturated and trans fats

It has been shown that trans fats are incorporated into the membrane of cells, replacing phospholipids, and causing a loss of flexibility and fluidity in these cells. As a consequence, molecules such as cholesterol cannot attach to the membrane and remain free, increasing blood cholesterol levels. In addition, trans fats increase the formation of cholesterol esters, favoring the passage of this molecule towards LDL proteins with the capacity to be deposited in the

arterial wall, favoring calcium deposits, and promoting atherogenesis, an important risk factor for CVD. Trans fats are also proinflammatory compounds, increasing blood triglycerides and blood pressure (91).

Because of all these detrimental effects, the consumption of both types of fats, trans fats and saturated fats, should be reduced. In agreement with many studies, I believe that following a balanced diet where polyunsaturated fats predominate over other fats leads to improved health and even weight loss. It was in 1950 when this avenue of research began, and it was reported that replacing saturated fat from animal products with polyunsaturated fat from vegetable oils substantially reduced serum cholesterol levels (95).

In today's society, I believe that the word "fat" gives respect. Much of the blame I associate with the food industry and beauty standards. Supermarkets are full of foods with the word "light" and the phrase "low fat" to make it seem healthier. However, just because a food contains fat does not mean it is unhealthy. The fat present in natural foods such as nuts or salmon is necessary for our organism; and, in addition, it provides flavor. In this type of food where fat is eliminated or reduced, an attempt is made to compensate the taste by adding compounds such as sugar and salt, to make them more attractive and better tasting. Therefore, this type of ultra-processed food is not better for having less fat.

I believe that a good dietary education is necessary. It is important to know how to choose the fats we consume, but never to eliminate them from our diet. The population should be made aware of the important functions that fats have in the body.

6. Conclusions

After reviewing the literature on how the consumption of ultra-processed foods affects the cardiovascular system, I can affirm that the additives contained in these prepared foods or certain characteristics, such as the high salt and fat content, favor the appearance of CVD. Specifically, they contribute to the manifestation of certain risk factors, such as hypertension or oxidative stress, which promote this type of disease.

During the search process, I have realized that there is very little research directly linking the consumption of ultra-processed foods and CVD. There are studies on the harmful effect of certain components on human health, but not in proportions or routes of administration comparable to exposure to these toxicants in food. Therefore, future lines of research should focus on this relationship between food and the cardiovascular system and investigate the overall effect of all the additives and components of ultra-processed food. They should be based on today's real situation, both quantities consumed and frequency of consumption in all population groups, from the very young to the elderly.

I believe that my research has highlighted the importance of food. In recent years, the consumption of ultra-processed food has increased exponentially, and this affects health, albeit silently for years. It is necessary that prepared foods contain all the nutritional information and their exact composition to avoid consuming certain additives or toxins. In addition, with this literature review I would like to promote "Realfooding" which consists of eating only natural food or trying to avoid processed and ultra-processed food as much as possible. I believe it is a healthy lifestyle that as many people as possible should know about in order to avoid that the consumption of ultra-processed foods can be very harmful over the years.

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