

The Effect Of Smoking On Liver Enzymes And Its Functions

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Abstract

Smoking has devastating and often fatal effects on human health. It has a wide range of harmful effects on the body, even on organs like the liver that don't come into direct touch with the smoke. On the liver, it causes three primary harms: toxic effects (both direct and indirect), immunological effects, and oncogenic consequences. The cytotoxic potential of the chemicals produced by smoking might contribute to liver cell damage. The purpose of this research was to provide a broad review of how smoking affects the enzymes and functions of the liver.

Keywords: Cigarette; Liver function; Smoker; Non-smoker.

1. INTRODUCTION

Smoking tobacco is the major risk factor for cancer globally, accounting for around 22% of all cancer deaths annually, and is the leading cause of avoidable mortality in affluent nations. [1] Despite the well-documented risks to human health, tobacco use is widespread. In today's society, tobacco use has become an epidemic [2]. Several types of infection, malignancies, cardiovascular ailments, and respiratory problems have pointed to it as a possible cause of their development. [3]

The nearly 4,000 chemicals found in cigarette smoke (CS) include at least 200 toxicants, 80 recognized or probable carcinogens, and high amounts of oxidants and free radicals that generate oxidative stress. Toxic and carcinogenic chemicals such as nicotine, nitrogen oxides, carbon monoxide, hydrogen cyanide, and free radicals are produced when cigarettes are smoked. In addition, carbon monoxide is produced by cigarettes and binds to hemoglobin more strongly than oxygen does, increasing the risk of several disorders including hypertension. Cancers of the lungs, kidneys, pancreas, colon, liver, and oropharynx [4] diseases such as coronary artery disease, stroke, and chronic obstructive pulmonary disease [5]. Cigarette smoking has been linked to an increased incidence of cirrhosis and may slow the progression of chronic liver illnesses and is therefore considered a risk factor for liver cancer. Additionally, cigarette smoking may amplify the liver's harmful consequences from alcohol [6]. Cigarette smoking also affects the hematological system by increasing the levels of eosinophils, basophils, monocytes, lymphocytes, platelets, and macrophages, as well as haemoglobin and RBCs [7].

There is also empirical evidence that suggests that the more cigarettes one smokes on a daily basis, the greater the rise in leucocyte count. Smoking for longer and smoking cigarettes with a higher concentration of chemicals reduces the body's leukocyte count. [8] The prognosis of patients with liver illnesses may be predicted with the use of liver function tests, which are also valuable in determining the presence and severity of any underlying conditions. Serum total protein, albumin, alkaline phosphatase (ALP), total bilirubin (TB), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) are the most typical components of a liver functions test (ALT). Albumin is well recognized as an anti-inflammatory marker and antioxidant because of its role in the negative acute phase [9]. Because of this, the current research focuses on the negative effects of smoking on hematological parameters and serum live enzyme activity in male smokers.

2. SMOKING

To smoke is to inhale the smoke produced by the combustion of a material with the purpose of gaining a sensory experience and subsequently absorbing it into the body. Tobacco leaves are the typical ingredient used to make the little, cylindrical "cigarettes" that people smoke. Most recreational drug usage involves smoking, since this allows for quick absorption of the psychoactive ingredients into the bloodstream and tissue through the lungs after burning of the dried plant leaves. Tobacco smoke contains a number of chemicals, including the pharmacologically active alkaloid nicotine,

which are vaporized into an aerosol and gas mixture upon heating. This allows the chemicals to be inhaled deeply into the lungs and subsequently absorbed into the bloodstream. [10]

Pipes, cigars, bides, hookahs, vaporizers, and bongos are a few of the many smoking accessories available. Even nonsmokers have been hypothesized to be vulnerable to smoking-related diseases. According to a study conducted in 2007, smoking kills approximately 4.9% of all people every year. Tobacco leaves are fermented and dried before being rolled into cigars, which are then lit and inhaled. The high alkalinity of the smoke from these substances causes immediate irritation to the trachea and lungs, so they are typically not inhaled. Cigar smoking rates are estimated differently depending on the population, time period, and place of the survey. Approximately 75% of global cigar sales occur in the United States and Western Europe [11]. The United States is the leading consumer country, followed by Germany and the United Kingdom. As of 2005, it was predicted that 4.3% of men and 0.3% of women would regularly smoke cigars. [12] Cigarettes, which literally translate to "small cigar" in French, are rolled or stuffed cylinders of cured and finely cut tobacco leaves and reconstituted tobacco, often combined with other additives, and smoked. To smoke a cigarette, one lights its end and draws the smoke into his or her lungs and mouth through a cellulose acetate filter. [13]

2.1 Physiology of Smoking

Tobacco's active ingredient is delivered by breathing the vaporized gas produced when the leaves are burned, which is the case with cigarettes. Absorption via the alveoli in the lung is a rapid and efficient route for delivering chemicals to the bloodstream. With a total surface area of nearly 70 m², the lungs' 300 million alveoli constitute a major organ (about the size of tennis court). Cigarette and pipe smoke are not inhaled because of their alkalinity, which is unpleasant to the trachea and lungs. This makes the procedure inefficient. Un-ionized nicotine is more easily absorbed via the mucosal membranes in the mouth due to its high alkalinity (pH =8.5) compared to cigarette smoke (pH= 5.3). [14]

The amount of nicotine absorbed from cigar and pipe smoke is much lower than that from cigarette smoke. Chemical processes in nerve endings are set off by the inhaled material. Naturally occurring acetylcholine is a common stimulant of the cholinergic receptors. Nicotine, which has molecular similarities with acetylcholine, may also act as a ligand and activate the receptor. [15]. Heart rate, alertness, and response times are boosted by the activation of nicotinic acetylcholine receptors, which are found in the brain and at the nerve muscular junction of skeletal muscle. Acetylcholine activation by nicotine is not physically addictive. However, dopamine is released because there are many dopamine-releasing neurons on nicotine receptors. The reward-associated dopamine release is reinforcing and has been shown to improve working memory. Similar patterns of neuronal activation are seen in response to nicotine and cocaine, lending credence to the hypothesis that both substances have shared substrates. [16]

The nicotine in tobacco is mostly destroyed by the high temperatures generated during combustion. A dosage capable of inducing moderate physical dependence and moderate to severe psychological dependence persists, nevertheless. Additionally, hormone (a MAC inhibitor) is synthesized from acetaldehyde in cigarette smoke. This seems to have a significant part in nicotine addiction, perhaps by acting as a receptor to nicotine stimuli and causing a release of dopamine in the nucleus accumbens. Rate of change research shows that chronic nicotine use reduces the reactivity of dopamine-producing nucleus accumbens cells. [17]

2.3. Effects of Smoking on General Health

Smoking is a major risk factor for heart attacks, Chronic Obstructive Pulmonary Disease (COPD), emphysema, and cancer, including lung cancer, laryngeal cancer, oral cancer, and pancreatic cancer. The first sign of a smoking-related health problem is often numbness in the hands or feet. [18]

Half of all male long-term smokers will eventually die from smoking-related illnesses. There is a clear correlation between how long and how much someone smokes and their elevated risk of illness. But if a smoker gives up the habit, their odds of suffering from these consequences and of having their body healed improve steadily. The chance of developing heart disease is halved in the year after a successful quit attempt. No two smokers face the same level of danger from cigarettes. Cigarette smokers have increased dangers in proportion to their habit [19].

2.4 Biochemical. And Physical Properties of Cigarettes

Traditionally, cigarette smoke has been thought of as having two distinct components: tar and gas. When a smoke stream is filtered using a Cambridge glass-fiber filter, which retains 99.9% of all particulate material with a size >0.1 μ m, the material retained is known as the tar or particle phase. All that makes it through the filter is the gaseous phase. Cigarette smoke includes almost ten times as many free radicals in its particulate (tar) phase as in its gas phase (>1015 free radicals/puff). Long-lived radicals are found in the tar phase (hours to months), while gas-phase radicals are more transient (7 seconds to a few minutes) (seconds) [20].

Mainstream smoke refers to the smoke exhaled by an active smoker as it enters their mouth via the tobacco. A cigarette's burning ends produce what's called "side stream" smoke. Tobacco smoke in general contains 8% tar and 92% gaseous components (Pryor .et al, 1993) [20]. The majority of secondhand smoke in the environment comes from smokers' inhaled side stream smoke (15%) and their expelled main stream smoke (85%). (Taylor .et al, 1992). In comparison to main

stream cigarette smoke, the harmful gaseous component is more concentrated in side stream smoke. Nicotine, found in the smoke's tar phase, is the chemical responsible for its addictive properties. [21]

3. TOBACCO SMOKE CONSTITUENTS

- **Carcinogens;** A carcinogen may be found in smoke or any partly burned organic materials (cancer-causing agents). Cigarette smoke contains approximately different chemicals, several of which are carcinogenic [22]. Some of the most dangerous carcinogens include:
- **Polycyclic aromatic hydrocarbons;** components of tar that are created during the pyrolysis of organic materials and released into smoke. Many of these PAHs are already harmful at normal levels, but they may become much more dangerous after being processed by the liver. When it comes to getting rid of them from the body, PAHs are a pain because of their hydrophobic nature, which makes them resistant to dissolving in water. The liver produces an enzyme called Cytochrome P450 to convert the PAH into a mutagenic epoxides that is more soluble in water but also more reactive. [23]
- **Acrolein** is a by-product of combustion that may be found in high concentrations in tobacco smoke. It is a substantial contributor to the carcinogenicity of cigarette smoke and is responsible for its offensive odor and lachromatory impact. Acrolein, like PAH metabolites, is an electrophilic alkylating agent that forms a stable hemiaminal bond with the DNA base guanine through a conjugate addition and subsequent cyclization. The acrolein-guanine adduct, like PAHs, promotes cancer by inducing mutations during DNA replication. [24]
- **Nitrosamines;** are a class of carcinogens exclusive to cigarette smoke and absent from natural tobacco. During the curing process, nitrosamines are produced on flue-cured tobacco leaves from the interaction of nicotine and other chemicals present in the uncured leaf with different oxides of nitrogen present in all combustion gases. Studies have shown that by switching to indirect fire curing, nitrosamine levels may be decreased to below 0.1 parts per million. [25]
- **Tar;** Tar is the inert, dry, particle mass of tobacco smoke that contains no nicotine. Tar's chemical components and the degree to which they contribute to tobacco's toxicity may vary greatly depending on the tobacco's origin. Tars in cigarette smoke deposit and aggregate on the respiratory tract and lung walls, blocking cilia and preventing airflow. [26]
- **Gases;** Tobacco smoke contains a large number of compounds, many of which are in the gaseous phase as well as the particulate portion (tar). There may or may not be a correlation between the concentration of these compounds and the amount of tar produced. Carbon monoxide is the most often reported gaseous chemical, ranking ninth overall (CO). Cigarette smoke releases a large quantity of carbon monoxide (thousands of parts per million). Carbon monoxide's toxicity comes from the fact that it may react chemically with hemoglobin to produce a stable compound called carboxy-haemoglobin. In doing so, oxygen-carrying hemoglobin is efficiently removed from the blood and therefore from the body's critical organs and tissues. Angina discomfort, cardiac ischaemia, and reduced blood flow to the heart have all been linked to carboxyhaemoglobin concentrations in the blood of around 2% of hemoglobin or higher in persons with cardiovascular disease. The concentrations of benzene and other compounds of interest in tobacco smoke, which are present in the gaseous phase of the smoke, are inversely proportional to the quantity of tar in the smoke. [27]
- **Nicotine** is a psychotropic drug with a significant potential for addiction. Nicotine is a stimulant and one of the key causes contributing to continuing tobacco use; however, when tobacco is smoked, most of the nicotine is pyrolyzed, leaving behind just an amount adequate to develop moderate physical reliance and mild to high psychological dependency. Many variables influence how much nicotine is taken in during smoking, including the tobacco used, whether or not the smoke is inhaled, and the use of a filter. [26]

4. THE LIVER

The liver is an essential organ for most creatures, including vertebrates. It may be found in humans in the upper right quadrant of the abdomen, just below the diaphragm. The liver is responsible for a broad variety of processes, such as the breakdown of harmful substances and the creation of essential biochemicals for digestion, protein synthesis, and detoxification of other metabolites. Although liver dialysis procedures may be utilized temporarily, there is yet no 10 means to permanently compensate for the loss of liver function. [28]

The liver is a gland that has several important metabolic roles in the body, such as controlling how much glucose is stored, breaking down red blood cells, making plasma proteins, producing hormones, and eliminating toxins. Bile is an alkaline chemical that assists digestion by emulsifying fats, and it is produced by this auxiliary digestive gland. High-volume metabolic events, such as the creation and breakdown of tiny and complex molecules, are regulated by the liver's highly specialized tissue, which is mostly made up of hepatocytes. [28]

There is some debate about how many tasks this organ really performs, although most textbooks agree that there are at least 500 [29]. In contrast to other organs, the liver has the remarkable ability to regenerate cells that have been damaged by a very transient injury or illness. However, long-term, repetitive liver injury may cause lasting alterations that compromise the liver's ability to perform its vital functions. The liver is supplied with blood through the hepatic portal vein and the hepatic arteries. The hepatic portal vein delivers venous blood drained from the spleen, gastrointestinal system, and other organs to the liver, where it supplies roughly 75% of the liver's blood supply. The liver receives all of

its blood supply from arterial blood, which is carried to it via the hepatic arteries. Both the hepatic portal vein and hepatic arteries contribute to the liver's oxygen supply. [30]

Bile ducts are formed when bile canaliculi in the liver join together. These tubes are referred to as intra-hepatic bile ducts while they are located within the liver, and as extra-hepatic bile ducts after they have left the liver (outside the liver). Ultimately, the intrahepatic ducts empty into the right and left hepatic ducts, which join to create the common hepatic duct. The common bile duct is formed when the cystic duct from the gallbladder merges with the common hepatic duct. The common bile duct carries bile straight to the duodenum, whereas the cystic duct connects the gallbladder to the digestive system for temporary bile storage. [31]

4.1. Liver Physiology

Hepatocytes are the liver cells responsible for performing the liver's many tasks. There isn't yet a machine or artificial organ that can fully replace the liver. Liver dialysis is an experimental therapy for liver failure that attempts to mimic the liver's normal function. Up to 500 distinct tasks have been attributed to the liver, most of which are performed in tandem with other bodily structures. [30]

Gluconeogenesis (the synthesis of glucose from certain amino acids, lactate, or glycerol), glycogenolysis (the breakdown of glycogen into glucose), and glycogenesis (the creation of glycogen from glucose) are all functions of the liver in carbohydrate metabolism (muscle tissues can also do this).

Protein synthesis and breakdown are two of the most important aspects of metabolism, and they both primarily occur in the liver. Cholesterol synthesis, lipogenesis, and triglyceride generation are all lipid metabolic processes that the liver is responsible for (fats), the liver is responsible for producing most lipoproteins. Factors I (fibrinogen), II (pro-thrombin), V, VII, VIII, IX, and XI, as well as protein C, protein S, and anti-thrombin, are all produced by the liver. The liver is the primary organ responsible for producing RBCs in the first trimester fetus. The bone marrow takes over nearly entirely by the 32nd week of pregnancy. The liver is responsible for producing and excreting bile (a yellowish liquid) that is necessary for emulsifying fats and aiding in the absorption of vitamin K from food. While part of the bile is kept in the gallbladder, the rest is sent straight to the duodenum. Polypeptide protein hormone IGF-1 is produced in the liver, and it has anabolic effects both throughout childhood and later in life. Another important source of thrombopoietin is the liver. In the bone marrow, platelets are produced in response to a hormone called thrombopoietin, a glycoprotein. [31]

Insulin and other hormones are metabolized, and bilirubin is glucuronidated for easier elimination through bile. Most drugs and harmful compounds (via methylation, for example) go through a process termed drug metabolism in the liver. When the metabolite is more harmful than the original substance, toxication might occur. Toxins are more easily eliminated by bile or urine when they are conjugated. Ammonia is processed into urea in the liver (urea cycle). [31]

Glucose (in the form of glycogen), vitamin A (1-2 years' supply), vitamin D (1-4 months' supply), vitamin B12 (1-3 years' supply), vitamin K, iron, and copper are only few of the many chemicals stored by the liver. 13 Effects on immunity are processed in the liver. Antigens entering the liver via the portal system are 'sieved' by the liver's immunologically active reticuloendothelial system. Albumin, the primary osmolar component of blood serum, is produced in the liver. The kidneys produce the enzyme renin in response to a drop in blood pressure, and angiotensinogen, a hormone that increases blood pressure. [31]

4.2 Liver Disorders

Liver illness comes in over a hundred different forms. Hepatitis, or inflammation of the liver, may be both acute and chronic. It is most often caused by viruses (viral hepatitis), although other factors, such as liver toxins (e.g., alcoholic hepatitis) or autoimmunity (autoimmune hepatitis), or even genetics, can play a role. Liver cells may die from viral hepatitis, excessive alcohol intake, and other kinds of liver toxicity, leading to cirrhosis, which is the creation of fibrous tissue (fibrosis) in their place. If you have cirrhosis, your liver will collapse slowly but surely over time. There are two types of liver tumors: primary liver cancer (hepatocellular carcinoma or hepatoma) and metastatic liver tumors that spread from other malignant tissues, most often the lungs, the pancreas, the digestive system, or the ovaries. Hemochromatosis is a liver-damaging inherited disorder. Gilbert's syndrome is a hereditary disease of bilirubin metabolism that affects around 5 percent of the population and may induce moderate jaundice in those who have it. Deficit in UDP glucuronyltransferase (Crigler-Najjar illness), this is a symptom of Dubin-Johnson syndrome, in which the liver cells are unable to properly excrete bilirubin. Hepatocyte damage, such as in cirrhosis, or bile duct injury, such as in rotor syndrome, may both lead to intrahepatic cholestasis. In addition, there are a number of liver disorders that only affect children, such as biliary atresia, alpha-1 antitrypsin deficiency, and progressive familial intrahepatic cholestasis. [32]

4.2 The Effects of Tobacco on The Liver

A number of organs, including the liver, are harmed by smoking despite having no connection to the activity. The liver is an important organ since it is responsible for the biotransformation of noxious compounds including medications, opioids, alcohol, and more [41]. Nonalcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma are only two of the many chronic liver disorders that smoking cigarettes may bring on (HCC). Epidemiological studies have shown that

smoking raises the incidence of primary biliary cirrhosis (PBC), and may raise the risk of liver fibrosis in individuals with chronic hepatitis B virus or hepatitis C virus infection, and may reduce the effectiveness of antiviral therapy. [33]

4.2.1. Liver Cancer and Tobacco Smoking:

From Risky Habits to Cancer Development. Smoke contains compounds with carcinogenic potential, such as tar, vinyl chloride, nitrosamines, and hydrocarbons. [34] Cigarette smoke is a primary source of 4-aminobiphenyl, a liver carcinogen linked to HCC. HCC risk is increased in persons with viral hepatitis who also smoke. Heavy smokers have an increased risk of developing HCC due to an accumulation of iron in the fibrosis-inducing hepatocytes. Combined with smoking, HBV and HCV cause hepatocarcinogenesis (Figure 3). Tobacco smoke contains 4-aminobiphenyl, a liver carcinogen, which increases the likelihood of developing HCC. Cigarette smoking is associated with an increased risk of HCC in people with viral hepatitis. [35]

New evidence from Taiwan and China [36] shows that smoking is associated with liver cancer patients regardless of HBV status. Smoking is linked to a decrease in the "genome guardian" tumor suppressor gene p53. T-cell responses for tumor cell analysis are dampened by the presence of tar and nicotine [37].

Heavy smokers have elevated iron levels in their hepatocytes, which promotes fibrosis and HCC growth. In addition to HCV and HBV, smoking is a major contributor to the development of hepatic cancer. Depressed mood is also frequent among heavy smokers, which raises their risk of acquiring cancer. [37] Tobacco smoke's carcinogens wreak havoc on cells by causing DNA damage and mutations in genes. These genetic aberrations promote unchecked cell division and inhibit the body's own mechanisms that would otherwise restrict the expansion of abnormal cells, ultimately leading to cancer [38]. Here are some possible mechanisms:

Tobacco use has been linked to a variety of health problems, including

(1) **Direct toxic effects:** on organs including the liver that are unrelated to smoking. Cigarette smoking increases the production of the inflammatory cytokines TNF-, IL-6, and IL-1, all of which contribute to liver cell damage [35]. (See Image 1) It generates cytotoxic compounds; these chemicals activate stellate cells and set off the fibrosis process via direct oxidative stress due to lipid peroxidation. Hepatic lesions and necro-inflammation are both brought about by the poisons produced by smoking. It also has a role in the progression of cirrhosis caused by hepatitis B virus (HBV). Fibrogenesis in the liver is a potential outcome of iron accumulation, which may be triggered by smoking. [35]

(2) **Indirect toxic effects:** Tissue hypoxia is caused by increased levels of carboxyhemoglobin and decreased RBC oxygen delivery due to smoking. The production of erythropoietin is prompted by hypoxia, and this hormone guides bone marrow hyperplasia. Causes oxidative stress in hepatocytes and subsequent secondary polycythemia and increased red cell mass [35]. (Figure 1).

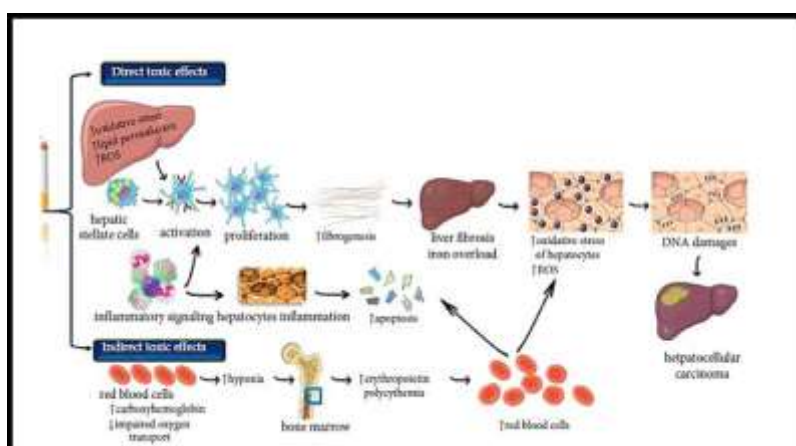


Figure 1: Tobacco smoke may cause molecular changes that result in liver cancer, as seen in this hypothetical diagram. ROS (reactive oxidative specie) ↑ (increase), ↓ (decrease). [35]

4.2.2. Inflammation, Tobacco, Hepatocellular Carcinoma, and Oxidative Stress:

Making Connections. Smoking tobacco is a significant risk factor for the development of hepatocellular carcinoma [39] due to the inflammation and chronic liver damage it generates. HSCs are the central player in the development of liver disease (Figure 2).

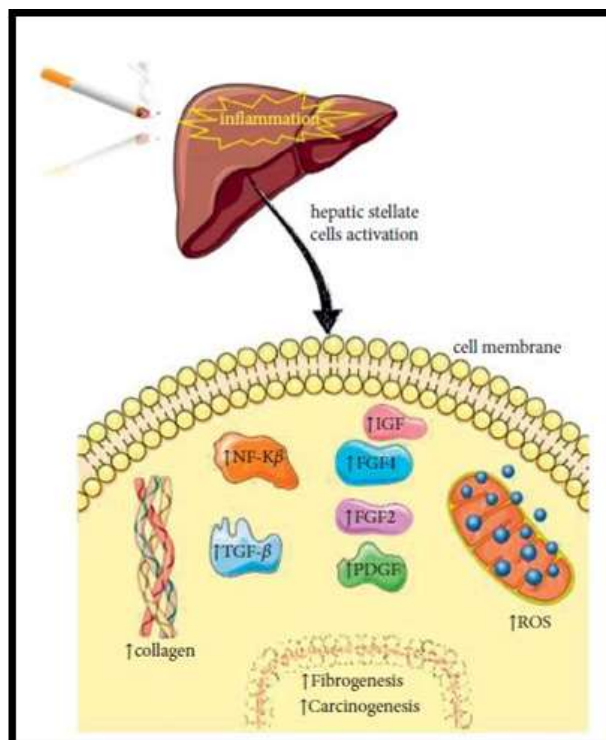


Figure 2: Important molecular pathways, include the connection between inflammation, reactive oxygen species, and liver cancer. Abbreviations and symbols—↑: increase; ↓: decrease: FGF: fibroblastic growth factors;; IGF: insulin-like growth factor, ROS: reactive oxygen species; PDGF: platelet-derived growth factor< TGF-β: transforming growth factor-β;. [39]

4.3. Liver Function Tests

1-Markers for hepato cellular necrosis (ALT; most specific for hepatocyte injury, AST; less specific than ALT significant presence in other tissues, LD least specific and significant presence in other tissues.)

2- Tests to assess liver disorders (Total bilirubin, direct bilirubin (conjugated), indirect bilirubin (UN conjugated), Albumin, Ammonia, Alph fetoprotein). -

3- Marker that reflect cholestasis (Alkaline phosphatase, Gammaglutamyl transferase.) [40]

5. LIVER ENZYMES

I. Aspartate Transaminase

Code of enzymes (EC 2.6.1.1) one kind of transferase enzyme is aspartate transaminase (AST), also known as aspartate aminotransferase (AAT), aspartate sulfhydryl aminotransferase (ASAT), and serum glutamic oxaloacetic transaminase (SGOT). The term "transaminase" describes what it does best. Aspartate aminotransferase (AST) is a crucial enzyme in amino acid metabolism because it catalyzes the reversible transfer of a -amino group from aspartate to glutamate. Coenzyme pyridoxal phosphate (PLP). 15 Although AST is present in all human tissues, it is most abundant in the heart, liver, and skeletal muscle, with lesser amounts in the kidneys and red blood cells. [41]

In general, two isoenzymes are found in eukaryotic organisms. GOT1/cAST, the cytosolic isoenzyme, is mostly found in erythrocytes and cardiomyocytes, whereas GOT2/mAST, the mitochondrial isoenzyme, is primarily found in liver. These isoenzymes have a sequence homology of about 45%, lending credence to the theory that they descended from a single ancestral AST by gene duplication. AST is mostly used in the clinic for assessing hepatic dysfunction and skeletal muscle involvement. Within 6-8 hours after a myocardial infarction, AST levels begin to increase, peak at 24 hours, and return to normal within 5 days. Some disorders that affect other body systems, such as pulmonary embolism, may also cause an increase in AST levels. Acute hepatocellular abnormalities are associated with elevated AST levels. Viral hepatitis may cause levels to rise to 100 times the ULN. Cirrhosis causes a fourfold increase in URL. Quantitative values between 5 and 30 U/L are used as a reference (37C). Fetoprotein lph [41].

II. Alanine Transaminase

Alanine transaminase (ALT) is a transaminase enzyme (EC 2.6.1.2) that breaks down alanine. Formerly known as serum glutamate-pyruvate transaminase (SGPT) or serum glutamic pyruvic transaminase (SGPT), it is now more often known as alanine aminotransferase (ALAT) (SGPT). In a reversible transamination process, ALT transfers an amino group from L-alanine to -ketoglutarate, yielding pyruvate and L-glutamate as byproducts. Coenzyme pyridoxal phosphate (PLP). ALT is widely distributed throughout the body but is especially abundant in the liver. One of the transferases, it is the one most closely associated with the liver. [41]

ALT is routinely tested in the clinic as part of a diagnostic examination of hepatocellular damage. Hepatocellular dysfunction is associated with much greater increases than either extra- or intra-hepatic obstructive condition. The presence of liver damage may be determined by measuring ALT with an increased AST. Muscular dystrophy is not accompanied by a discernible elevation in ALT levels, and neither are pulmonary embolisms nor severe pancreatitis. ALT 6–37 U/L is the reference range (37C) [41]

III. Gamma-Glutamyl Transferase (EC 2.3.2.2)

One such enzyme is gamma-glutamyl transferase (also known as gamma-glutamyl trans peptidase, gamma-GT, GGT, GGTP, and gamma-GT). It acts as a catalyst for the transfer of glutathione's gamma-glutamyl moiety to an acceptor, such as an amino acid, peptide, or water, resulting in glutamate (Bishop et al, 2010). GGT is essential for the gamma-glutamyl cycle, which is responsible for the production and breakdown of glutathione as well as the elimination of toxic byproducts such as drugs and xenobiotics. [42]

Evidence suggests that GGT may also have a prooxidant function, with regulatory effects on several levels of cellular signal transduction and cellular pathology.[43] Kidney, brain, prostate, pancreas, and liver tissue are rich in GGT activity. However, the majority of assay's clinical uses are limited to the diagnosis of liver and biliary system problems. [41]

The Importance of GGT in Clinical Practice All forms of hepatobiliary illness are associated with an increase in level, with values reaching 2–5 times the UL (example viral hepatitis, alcoholic cirrhosis) a very sensitive measure of this syndrome Rises before to and persists higher than ALP, AST, and ALT; increases by 5-3 times the URL in cases of intra- and post-hepatic biliary tract blockage. Drugs like phenobarbital and phenytoin, as well as alcohol, might increase GGT activity. In contrast to alkaline phosphatase, which would be raised in the presence of bone disease or during pregnancy, GGT levels would be normal. At 37 degrees Celsius, the reference range for male GGT is 55 U/L, whereas for females it is 38 U/L [40].

IV. Alkaline Phosphatase (EC 3.1.3.1)

The hydrolase enzyme alkaline phosphatase (also known as ALP, ALKP, ALPase, Alk Phos) removes phosphate groups from a wide variety of substrates, including nucleotides, proteins, and alkaloids. The process of eliminating the phosphate group is termed dephosphorylation. According to their namesake, alkaline phosphatases perform best in a basic medium. Basic phosphatase is another name for this enzyme. [43]

Humans have alkaline phosphatase in all of their tissues, although it is found in the highest concentrations in the liver, bile ducts, kidneys, bones, intestinal mucosa, and placenta. Common to humans and other animals are many different isozymes of the alkaline phosphatase enzyme: ALPI (intestinal; 150 kDa molecular weight), ALPL (tissue-nonspecific; liver, bone, and kidney), and ALPP (placental) (Regan isozyme) [40]

An increase in ALP a serum activity is associated with hepatobiliary illness and bone diseases (with osteoblastic involvement), both of which have important clinical implications. Increased levels in hepatobiliary illnesses are caused by obstructive disease, and the ALP rises more sharply than the ALT and AST do. Cholestasis induces ALP production in biliary tract obstruction, leading to serum ALP levels 3–10 times higher than the upper reference range. Extrahepatic obstruction typically results in a greater increase in ALP than intrahepatic obstruction does; hepatitis and cirrhosis are hepatocellular conditions associated with an increase in ALP of up to three times the upper reference limit; the highest elevation of ALP is observed in Paget's disease; and ALP levels increase with healing bone fracture. When compared to adults, ALP levels are typically greater in youngsters because of ongoing bone development. Hypophosphatasia is characterized by low levels of serum ALP due to a deficiency of the ALP bone isoenzyme. This condition refers to a lack of bone calcification. The placenta is a source of alanine aminotransferase (ALP), hence ALP levels are naturally elevated during pregnancy. Serum gamma-glutamyl-transferase levels may be used to determine the cause of increased ALP levels (GGT). Elevations in both ALP and GGT together are suggestive of hepatobiliary illness. [40]

6. THE EFFECT OF SMOKING ON LIVER ENZYMES

Both present and previous cigarette smokers have reduced levels of serum albumin, globulin, and all other protein fractions compared to nonsmokers (Al-Khayat et al., 2001). The albumin levels of chronic hepatitis patients who were current smokers were significantly lower than those of nonsmokers. However, research into the molecular processes by which coffee consumption and cigarette smoking lower blood protein and albumin levels is still in its infancy. Our findings provide credence to the latter group of studies, which found that cigarette smoking had no effect on either AST or ALT, contrary to the claims of some earlier researchers who found that smoking raised ALT. Our multivariate analysis revealed higher ALP levels in current smokers compared to never- and ex-smokers, but this trend was not supported by data on average daily or lifetime cigarette use. Several osteoporosis investigations have shown that current smokers had elevated blood ALP levels, a sign of bone breakdown. [45]

Since we could not find a consistent link between smoking and ALP level after adjusting for a number of confounding variables, it is possible that the effects of smoking on ALP level are confounded by several extra hepatic processes. In order to assess its prognostic implications and possible value in the monitoring of treatment, several epidemiological studies have revealed that elevated plasma uric acid is a risk factor for cardiovascular illnesses. [46]

It is unclear if an elevated plasma uric acid level is a direct or indirect result of the underlying causes of cardiovascular disease. Although plasma uric acid may have a role in platelet adhesiveness, aggregation, or inflammation and may be involved in the genesis of hypertension, its precise involvement in this constellation is still unclear. [47]

Higher plasma uric acid levels are found in patients with cardiovascular diseases, suggesting that any protective antioxidant effect of uric acid is hidden by other negative effects in these pathogenesises. However, there is also some evidence that an increase in plasma uric acid is protective against the cardiovascular diseases, as uric acid acts as an endogenous antioxidant [47].

For both sexes, smokers in this research had considerably lower plasma uric acid levels compared to nonsmokers. This might prove that cigarette smoking increases uric acid levels in both sexes. We also found a negative link between these variables and a person's smoking habits, both in terms of how many cigarettes they smoked daily and how long they had been smokers. We also found that the uric acid levels drop after 5 years of smoking. This result is consistent with previous research demonstrating that oxidative stress rises with each cigarette smoked and that plasma uric acid levels are lower in habitual smokers. [48]

Even in the absence of dietary changes, other investigations have shown that nonsmokers who are exposed to cigarette smoke had a considerably lower plasma antioxidant status compared to unexposed nonsmokers. Other research has shown that uric acid treatment boosts systemic antioxidant defenses and facilitates the return of endothelium-dependent vasodilation. The inhibition of xanthine oxidase by cyanide, which is removed as thiocyanate, may account for the reduced levels of uric acid seen in smokers. [49]

Thus, in situations characterized by an increase in cardiovascular risk and oxidative stress, such as smoking and a reduction in its level, which increases susceptibility to oxidative damage and accounts for the excessive free radical production, high plasma uric acid concentrations may be protective. With this in mind, it has been acknowledged that uric acid's antioxidant qualities may provide some degree of protection against the progression of atherosclerosis. [49]

There was a considerable difference in the plasma creatinine levels of smokers and nonsmokers, although the results were not clinically significant. Since creatinine determination has been reported to be useful in evaluating the renal handling of uric acid and since creatinine concentrations are highly dependent on endogenous production as well as on renal excretion, this can confirm that all of the subjects studied are without any renal failure. [50]

Smokers have lower plasma uric acid levels because their bodies produce less of the acid naturally. This result is consistent with previous research showing that cigarette smoke, a major cause of oxidative stress, and a lack of dietary antioxidants contribute to a decrease in antioxidants, particularly uric acid, among smokers. [51]

The associations between smoke and urea or uric acid are modest but substantial. In order to determine if the cause of these associations is the same, one must first postulate a hypothetical renal mechanism. Uric acid derives from the oxidation of purines, whereas urea is a byproduct of the breakdown of proteins and amino acids. While both molecules are in the bloodstream, they do not interact with one another in any way. The kidneys are responsible for excreting both, and they tend to fluctuate similarly throughout disease processes; for example, an increase in blood uric acid is a well-known early indicator of renal failure. Tobacco's known activity on the metabolism of catecholamines and the effect of these chemicals on renal function lends credence to the idea that uric acid and urea are excreted at a higher rate while one is under the influence of the drug. [52]

Also many researches indicate the cigarettes vapor undergo metabolic activity by cytochrome enzymes p450 of reactive electrophiles which cause nitrosative stress which lead to cytotoxicity, mutation, cancer [52]. Also the cigarette vapor contain large number of toxic chemical materials which cause hepato cellular toxicity as nicotine. Oxidative stress resulted from smoking lead to stimulation of NADPH oxidase which lead suppression of anti-oxidase and increase fat oxidation. [53]

These effects will lead increase damage of liver cells and activation of hepatic satellite cells and liver fibrocytes. While other liver fibrosis cells as mesangial cells which stimulated by smoking vapour results as nicotine resulted in increase extracellular matrix proteins. Other cause of liver fibrosis is iron deposition. [54]

All these results are corresponding with the researcher [47], who proved that the increased activity of liver enzymes resulted from hyper nitrosative stress [55] indicate in his research which include (139) smokers to study the changes in the biochemical parameter of liver enzymes in smokers that the smoking lead to increasing in the activity of liver enzymes AST, ALT, ALP due to its content of nicotine tar, free radicals which lead to increase its concentration in blood.

Abdrabo et al. (2013) [56] in a study about the effect of smoking on the Biochemistry of serum between people of Sudan which include (105) smoker and (105) nonsmoker at the ages rated 25-63 years old and approved that the smoking lead to increase the level of transported liver enzyme because of oxidative stress.

Abdalsalam and Alsalhen (2014) [57] explained in their study about the effect of smoking on some of liver functions in smoker males that the smoking vapor has many effect on the liver functions because its contain free radicals, which lead to oxidative stress and increase fat oxidation and all studies explain that the increasing of ALP in the serum of smoker as compared with non-smoker, Al-Khayat et al. (2001) [54], Ahmed and Weisberg (2001) [46]. Explain that the alkaline phosphatase has specific relationship with cigarette vapor also with smoking period.

Kahnamoei and Javid (2014) [58] explained that the smoking lead to cardiovascular system diseases, Respiratory system disease, lung and mouth cancer, cancer don't related with nicotine, but related with carcinogenic agents in cigarettes vapor and other studies indicate that the smoking has greater effect on the serum ALP which consider as good marker to wounds or damage in bile ducts, added to that , the increasing the activity of AST and ALT in the serum indicate to the damage in hepatocytes (Bishop et al. (2005) [41].

7. STRATEGIES ON SMOKING CESSATION

It can be divided into three main approaches: therapeutic, methods for public health and alternative approaches.

7.1. Nonpharmacological Interventions for Smoking Cessation:

Telephone counseling, self-help programs, cognitive-behavioral treatments including client and group counselling, service provider interventions, and fitness programs are all examples of effective therapeutic ways to preventing smoking. Acupuncture, aversion therapy, and hypnosis are just some of the alternative therapies that are out there. Health promotion strategies include educational campaigns, policy reforms, and media campaigns [60].

The most widely used tobacco products are cigarettes, cigars, cigarillos, and pipes. In several parts of the world, people also regularly use "smokeless tobacco." Preparations for nasal inhalation, chewing, or inserting as a wad in between the gums and cheeks are the norm. Similar to cigarette smoking, smokeless tobacco uses tobacco that has been dried and crushed into fine particles, Attempts to quit smoking often begin with the decision to abstain from smoking cigarettes as of a certain date, and continue with the deliberate fight against the urge to smoke that this decision entails. A "lapse" occurs when a person returns to smoking after an extended period of abstinence, even if it's only a few cigarettes. Relapse occurs when a person returns to daily smoking after quitting. Short-term abstinence is considered to be a period of 4 weeks, whereas long-term abstinence is considered to be a period of 6 months to a year. Since there is no universally accepted definition of "quit date," it's crucial to get accurate information regarding how long someone has been smoke-free before applying this label to them [61].

7.2. Current Pharmacological Treatment of Cigarette Smoking.

Drug therapy should be included of any smoking cessation program, in addition to behavioral and environmental approaches. Nicotine replacement therapy, bupropion sustained release (SR), varenicline, nicotine gum, nicotine lozenge, transdermal nicotine patch, and nicotine inhaler are the seven smoking cessation medications authorized by the Food and Drug Administration. These medications are considered "first-line" under the United States Public Health Service [62] criteria.

8. OVERALL CONCLUSIONS AND PERSPECTIVES

Cigarette smoking is still the most common way that people use tobacco. Because smoking has so many negative consequences on health, it's important to keep working to reduce the number of people who start up the habit. The present tobacco epidemic highlights the need for smoke-free environments and anti-smoking initiatives aimed at young people. Public health campaigns aimed at discouraging people from smoking will help lessen the impact of secondhand smoke on those who choose not to light up. In order to effectively treat nicotine addiction, it is necessary to employ both behavioral and pharmaceutical methods.

Both the risks and rewards of quitting smoking are plain to see. The adverse effects on oral and systemic health slowly fade with time. When you finally quit the habit of smoking, you immediately lower your chances of developing heart issues or dying before your time. Regular decreases in heart rate and blood pressure occur. Cancers of the throat, esophagus, kidneys, bladder, and pancreas are on the decline. Breathing problems should improve temporarily. [63]

If a smoker gives up the habit before the age of 35, he or she may expect to live as long as a nonsmoker. It barely adds another 2–3 months to its life expectancy beyond age 35, which translates to just 4–6 hours every day. When weighed against the risks of continuing to smoke, quitting at any age is preferable. The risk of developing certain diseases actually decreases after quitting smoking, while the risk of developing others essentially stops growing at the time of quitting. In conclusion, there is no clear cut relationship between cigarette use and the processes that initiate and drive the development of hepatocellular carcinoma. Contributing factors include effects on the liver both directly and indirectly, the function of inflammation, and ROS production. To the development and activation of fibrogenesis and carcinogenesis pathways. This article's clinical implications stem from our improved knowledge of the pathophysiological processes through which activated HSCs play a role in carcinogenesis, and the subsequent identification of novel treatment targets aimed at their suppression.

Many studies results revealed that:

1. Serum AST, ALT, and GGT activities are a significant positive correlation with age, and were no correlation between ALP and age.
2. The mean of serum AST, ALT, ALP and GGT are significantly increased in smoker when compared to nonsmokers.
3. Serum AST, ALT, ALP activities showed significantly positive correlation with number of cigarettes and there was no correlation between GGT activities and number of cigarettes smoked per day.
4. Serum AST, ALT, ALP and GGT activities are a significant positive correlation with duration of smoking.

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