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Faculty of medicine and health science

Department of laboratory medicine

Complete Blood Count And Serum Level of lipid profile In Yemeni Smokers

A graduation project submitted to Faculty to Medicine and Health Science as

a partial Fulfillment for requirement of the Bachelor Degree in

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Dedication

We have no valuable and sufficient words to express our feeling and thanks, but we would to lovingly dedication this research to our respective parents and families, to the hundreds of people in community who are in pursuit of a healthy living, to our university, doctors, friends, and all supporters who were a backbone to us.

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Abbreviations

Item	Description
ACAT	Acyl CoA: cholesterol acyltransferase
ADP	Adenosine Triphosphate
AMP	Adenosine monophosphate
AMPK	Activated protein kinase
Apo-A	Apo Lipoprotein-A
Apo-B	Apo Lipoprotein-B
ATP	Adenosine Triphosphate
BMI	Body Mass Index
CBC	Complete Blood Count
CDC	Center Of Disease Control
CETP	Cholesterol Ester Transfer Protein
CHD	Chronic Heart Disease
CHO	Cholesterol Oxidase
CO2	Carbone dioxide
Co-A	Acetyl Coenzyme A
DNA	Deoxyribonucleic acid
DPP	Dimethylallyl pyrophosphate
ER	Endoplasmic Reticulum
FPP	Farnesyl pyrophosphate
GK	Glycerol Kinase
GPO	Glycerol-3-Phosphate Oxidase
H2O	Water
Hb	Hemoglobin
HDL	High Density Lipoprotein
HDL-C	High Density Lipoprotein Cholesterol
HMG	3-hydroxy-3-methylglutaryl
IPP	Isopentenyl Pyrophosphate
IPP	Isopentenyl pyrophosphate
LCAT	Lecithin Cholesterol Acyltransferase
LDL	Low Density Lipoprotein
LDL-C	Low Density Lipoprotein Cholesterol
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
MPV	Mean Platelet Volume
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
PCV	Packed Cell Volume
PDW	Platelet Distribution Width

POD	Peroxidase
PT	Prothrombin Time
RBC	Red Blood Cell
SD	Standard Deviation
SLOS	Smith-Lemli-Opitz syndrome
SPSS	Statical Package for the Social Sciences
SR-A	Scavenger Receptor Class A
SRE	Sterol regulatory element
TGs	Triglycerides
USA	United State of America
VLDL	Very Low Density Lipoprotein
WBC	White Blood Cell

Abstract

Background: Smoking is the single largest preventable risk factor of disease and premature death and major tobacco related diseases like cardiovascular diseases and cancer, so this study aimed to identify the association between smoking and lipid profile and complete blood count parameters in Yemeni smokers.

Methods: This study was cross-sectional study carried out on 95 Yemeni adult participants (45 smokers and 50 non-smokers) aged 17 - 70 years in Sana'a city, Yemen, during 2023.

Results: There were significant increase in total cholesterol, LDL-cholesterol and mean cell volume (MCV) in Yemeni smokers compare to non-smokers (p-value = 0.00013, 0.0001, 0.048 respectively), in addition to significant correlation between smoking and total cholesterol, LDL-cholesterol and mean cell volume (p-value = 0.0001, 0.0001, 0.048 and r = -0.381, -0.387, -0.204 respectively).

Conclusion: This study concluded that serum total cholesterol, low density lipoprotein cholesterol (LDL- C) levels and mean cell volume (MCV) were found significantly higher in Yemeni smokers than non-smokers

1. Introduction

Tobacco use in any form, can be described as a behavioral process which elicits psychological and physiologic addictive mood among users. Nicotine, the active ingredient in tobacco, is highly addictive, resulting in sustained tobacco use **(Hu, et al., 2016).**

Cigarette smoking has become the choice of tobacco use among many youths and adults globally. Tobacco use is divided into combustible and noncombustible tobacco products. Combustible tobacco products include: cigarettes, cigars, cigarillos, small cigars, water pipes (hookah), and pipes. Noncombustible tobacco products include electronic cigarettes and tobacco formulations developed for chewing, dipping, or snuffing **(E Negri, *et al.* 2011).**

Cigarettes are designed to allow deep inhalation of smoke into the lungs, delivering high levels of nicotine to the brain within 10–20 s of inhalation **(Benowitz, *et al*, 2009).** This rapid rise in nicotine levels makes cigarette smoking the most reinforcing and dependence-producing form of tobacco use **(Hukkanen, *et al* , 2009).**

The epidemiologic impact and adverse health effects of cigarette smoking are significant. Reducing the prevalence of cigarette smoking and the resultant smoking-induced disease is imperative **(West, 2014).**

Cigarette (tobacco) smoking is not only common among adults, but is also common among youths. With the current trends of monetary investment into the tobacco industry, smoking poses a bigger threat to the younger population in American society **(Santhosh L., 2014).**

Cigarette addiction stems from the fact that smoking provides highly controllable doses of the drug, nicotine, rapidly to the brain in a form that is accessible, affordable and palatable **(Shahab, 2009).** Nicotine provided more slowly, for example by the nicotine transdermal patch, is much less addictive. It is possible that one or more mono-amine oxidase inhibitors in cigarette smoke add to, or synergies, the addictive properties of nicotine **(Hogg, 2016).**

Cigarette smoking has been clearly established as a risk factor for various degenerative diseases such as lung cancer and cardiovascular diseases by various scientific and epidemiological surveys **(Jha, 2014).**

Consequently, the World Health Organization (WHO) has been on the forefront to educate the public worldwide on the dangers of tobacco use, which forms the basis of its Framework Convention on Tobacco Control (FCTC) guidelines **(World Health Organization., 2013)**.

1.1 Cholesterol

1.1.1 Structure of cholesterol

Cholesterol is a very hydrophobic compound. It consists of four fused hydrocarbon rings (A-D) called the “steroid nucleus”), and it has an eight-carbon, branched hydrocarbon chain attached to carbon 17**(Dring *et al,* 2015).** Ring A has a hydroxyl group at carbon 3, and ring B has a double bond between carbon 5 and carbon 6. **(Pei *et al,* 2013).**

1.1.2 Sterols

Steroids with eight to ten carbon atoms in the side chain at carbon 17 and a hydroxyl group at carbon 3 are classified as sterols. Cholesterol is the major sterol in animal tissues. [Note: Plant sterols, such as β-sitosterol are poorly absorbed by humans **(Ogbe, 2015).**

After entering the enterocytes, they are actively transported back into the intestinal lumen Because some cholesterol is transported as well, plant sterols appear to reduce the absorption of dietary cholesterol. This has led to clinically useful dietary treatment of hypercholesterolemia **(Wang H. H., (2013a)**

Daily ingestion of plant steroid esters (in the form of commercially available trans fatty acid–free margarine) is one of a number of dietary strategies leading to the reduction of plasma cholesterol levels **(Eckel Robert H., 2007).**

1.1.3 Cholesteryl esters

Most plasma cholesterol is in an esterified form (with a fatty acid attached at carbon 3), which makes the structure even more hydrophobic than free (esterified) cholesterol **(Ahmed, 2021).**

Cholesteryl esters are not found in membranes, and are normally present only in low levels in most cells. Because of their hydrophobicity, cholesterol and its esters must be transported in association with protein as a component of a lipoprotein particle or be solubilized by phospholipids and bile salts in the bile **(Hu, et al., 2016).**

1.2 Triglycerides

Knowledge of the way in which triglyceride is transported in the blood and of the factors that influence the transport process is essential for a proper understanding of the overall distribution of lipids in the plasma that is observed in health and disease **(Robert, 2020).**

The following account deals with triglyceride transport in normal individuals and provides a basis for comparison with states of abnormal lipid metabolism. The concentration of lipoprotein triglyceride in the plasma at any given time must represent a balance between the rate of entry into the plasma and the rate of removal. A change in concentration may therefore be the result of a change in either or both of these factors. Moreover, a primary change in one may result in a secondary change in the other. Thus, perhaps the main question to be asked, in any situation where the plasma triglyceride concentration is abnormally high, is whether this is due to a rise in the rate of entry or to a fall in the rate of removal **(Nikolaev, 2015).**

1.2.1 Entry of Triglyceride

About 30 to 40% of our calorie intake is normally in the form of fatty acids contained in the dietary triglyceride. Digestion in the intestinal lumen breaks down this triglyceride into free fatty acids and monoglycerides, and these are absorbed by the intestinal cells and re-synthesized into triglyceride which is then released into the lymphatics in lipoproteins called chylomicrons **(Dima *et al*, 2020).**

The liver is the second site of triglyceride release into the plasma. The source of the fatty acids presents in the triglyceride entering the blood from this organ depends markedly on the nutritional state. Thus, in a fasting individual, fatty acids are mobilized from the adipose tissue stores and are transported in the plasma in unesterified form bound to the plasma albumin. Most are carried directly to tissues such as muscle and are oxidized **(Ferrier, 2017).**

1.3 Low Density Lipoprotein "LDL"

1.3.1 Metabolism of LDL

LDL particles contain much less triacylglycerol than their VLDL predecessors, and have a high concentration of cholesterol and cholesteryl esters **(Boullier A L. Y., 2006).**

1.3.2 Receptor-mediated endocytosis

The primary function of LDL particles is to provide cholesterol to the peripheral tissues (or return it to the liver). They do so by binding to cell surface membrane LDL receptors that recognize apo B-100 (but not apo B-48). Because these LDL receptors can also bind apo-E, they are known as apo-B-100/apo E receptors **(Seo H, 2010).**

A summary of the uptake and degradation of LDL particles. A similar mechanism of receptor-mediated endocytosis is used for the cellular uptake and degradation of chylomicron remnants and IDLs by the liver **(Forstermann U, 2010).**

LDL receptors are negatively charged glycoproteins that are clustered in pits on cell membranes. The cytosolic side of the pit is coated with the protein clathrinid, which stabilizes the shape of the pit. After binding, the LDL-receptor complex is internalized by endocytosis. [Note: A deficiency of functional LDL receptors causes a significant elevation in plasma LDL and, therefore, of plasma cholesterol **(Van Craeyveld, 2011).**

Patients with such deficiencies have Type II hyperlipidemia (familial hypercholesterolemia, FH) and premature atherosclerosis. FH can also be caused by increased activity of a protease that degrades the receptor and by defects in apo B-100 that reduce its binding to the receptor.]. The vesicle containing LDL loses its clathrinid coat and fuses with other similar vesicles, forming larger vesicles called endosomes **(Boullier A L. Y., 2006).**

The pH of the endosome falls (due to the proton-pumping activity of endosomal ATPase), which allows separation of the LDL from its receptor. The receptors then migrate to one side of the endosome, whereas the LDLs stay free within the lumen of the vesicle. [Note: This structure is called CURL—the Compart mint for Uncoupling of Receptor and Ligand **(Van Craeyveld, 2011).**

The receptors can be recycled, whereas the lipoprotein remnants in the vesicle are transferred to lysosomes and degraded by lysosomal acid hydrolases, releasing free cholesterol, amino acids, fatty acids, and phospholipids. These compounds can be reutilized by the cell. [Note: Storage diseases caused by rare autosomal recessive deficiencies in the ability to hydrolyze lysosomal cholesteryl esters (Wolman disease), or to transport unesterified cholesterol out of the lysosome (Niemann-Pick disease, Type C) have been identified] **(Syväranta S A.-K. M., 2013).**

1.4 High Density Lipoprotein (HDL)

1.4.1 Metabolism of HDL

HDL comprise a heterogeneous family of lipoproteins with a complex metabolism that is not yet completely understood. HDL particles are formed in blood by the addition of lipid to apo A-1, an apo lipoprotein made by the liver and intestine and secreted into blood. Apo A-1 accounts for about 70% of the Apo-proteins in HDL. HDL perform a number of important functions, including the following **(Feldman *et al*, 2021).**

1.4.2 HDL is a reservoir of Apo-lipoproteins

HDL particles serve as a circulating reservoir of apo C-II (the apolipoprotein that is transferred to VLDL and chylomicrons, and is an activator of lipoprotein lipase), and apo E (the apolipoprotein required for the receptor mediated endocytosis of IDLs and chylomicron remnants) **(Yabg C-Y *et al*, 2007).**

1.4.3 HDL uptake of unesterified cholesterol

Nascent HDL are disk-shaped particles containing primarily phospholipid (largely phosphatidylcholine) and Apo-lipoproteins A, C, and E. They take up cholesterol from non-hepatic (peripheral) tissues and return it to the liver as cholesteryl esters. [Note: HDL particles are excellent acceptors of unesterified cholesterol as a result of their high concentration of phospholipids, which are important solubilizers of cholesterol **(Hirayama S, 2012).**

1.5 Esterification of cholesterol

When cholesterol is taken up by HDL, it is immediately esterified by the plasma enzyme lecithin: cholesterol acyltransferase (LCAT, also known as PCAT, in which “P” stands for phosphatidylcholine). This enzyme is synthesized by the liver. LCAT binds to nascent HDL, and is activated by apo A-I. LCAT transfers the fatty acid from carbon 2 of phosphatidylcholine to cholesterol. This produces a hydrophobic cholesteryl ester, which is sequestered in the core of the HDL, and Lys phosphatidylcholine, which binds to albumin. [Note: Esterification maintains the cholesterol concentration gradient, allowing continued efflux of cholesterol to HDL] **(Itabe H, 2010).**

As the discoidal nascent HDL accumulates cholesteryl esters, it first becomes aspherical, relatively cholesteryl ester–poor HDL3 and, eventually, a cholesteryl ester–rich HDL2 particle that carries these esters to the liver. Cholesterol ester transfer protein (CETP) moves some of the cholesteryl esters from HDL to VLDL in exchange for triacylglycerol, relieving product inhibition of LCAT. Because VLDL are catabolized to LDL, the cholesteryl esters are ultimately taken up by the liver **(Catapano *et al*, 2016).**

1.6 Reverse cholesterol transport

The selective transfer of cholesterol from peripheral cells to HDL, and from HDL to the liver for bile acid synthesis or disposal via the bile, and to steroidogenic cells for hormone synthesis, is a key component of cholesterol homeostasis. This is, in part, the basis for the inverse relationship seen between plasma HDL concentration and atherosclerosis, and for HDL’s designation as the “good” cholesterol carrier **(Wang S, Smith JD)**

Reverse cholesterol transport involves efflux of cholesterol from peripheral cells to HDL, esterification of cholesterol by LCAT, binding of the cholesteryl ester–rich HDL (HDL2) to liver and steroidogenic cells, the selective transfer of the cholesteryl esters into these cells, and the release of lipid-depleted HDL (HDL3). The efflux of cholesterol from peripheral cells is mediated, at least in part, by the transport protein, ABCA1. [Note: Tangier disease is a very rare deficiency of ABCA1, and is characterized by the virtual absence of HDL particles due to degradation of lipid-poor Apo A-1.] The uptake of cholesteryl esters by the liver is mediated by a cell-surface receptor, SR-B1 (scavenger receptor class B type 1) that binds HDL. It is not yet clear as to whether the HDL particle itself is taken up, the cholesteryl esters extracted, and the lipid-poor HDL released back into the blood, or if there is selective uptake of the cholesteryl ester alone. [Note: Hepatic lipase, with its ability to degrade both TAG and phospholipids, also participates in the conversion of HDL2 to HDL3] **(Forstermann U, *et al*. 2013).**

1.7 Cholesterol and Cardiovascular diseases

Major risk factors for atherosclerosis include high plasma levels of low-density lipoprotein (LDL) cholesterol and lipoprotein(a), as well as low plasma concentrations of high-density lipoprotein (HDL) cholesterol **(Angelantonio Di E, 2009).** Because elevated LDL cholesterol levels are a major causal factor for coronary heart disease (CHD) and stroke and have been a primary target of therapy for more than thirty years, the potent HMG-CoA reductase inhibitors, statins have been developed to lower plasma LDL cholesterol levels and reduce the risk of adverse cardiovascular events **(Cholesterol Treatment, 2010).**

Moreover, reducing LDL cholesterol levels to below current guideline targets further inhibit atherogenesis and decreases adverse coronary events **(Grundy SM *et al* , 2004).** Many clinical studies have found that statins can reduce new adverse cardiovascular events and CHD mortality by ~ 35%, but even aggressive statin therapy can not completely eliminate cardiovascular risk. Approximately 65% of the patients treated with stat- ins still develop adverse cardiovascular events. Therefore, additional therapeutic interventions beyond statins are strongly needed to further reduce the risk of developing CHD and stroke **(Barter PJ, 2003).**

Cholesterol is essential for all cells in the body and it is used extensively as a major structural component of cell membranes and as a substrate for the synthesis of other steroids such as bile acids, vitamin D, and sex hormones such as estradiol, progesterone, androsterone- and testosterone, as well as adrenocortical hormones such as aldosterone and cortisone. The liver and small intestine are two crucial organs for cholesterol homeostasis. Indeed, high cholesterol biosynthesis in the liver leads to more very low-density lipoprotein (VLDL) secreted into plasma, thereby increasing plasma total and LDL cholesterol concentrations. Increased quantities of dietary cholesterol also cause plasma cholesterol concentrations to rise in most individuals **(Shen B, 2020).**

Accumulated evidence has clearly demonstrated that elevated total and LDL cholesterol levels in plasma are an important risk factor for the development of cardiovascular diseases in humans and laboratory animals **(Wang T. Y., 2013a).** Because CHD is still a leading cause of death and disability in the USA and Europe, the **(JAMA *et al*, 2001)** along with the 2012 update and the American Heart Association/ American College of Cardiology recommendations **(Greenland P, 2010)** have suggested a much lower target for plasma LDL cholesterol concentrations (i.e., < 100 mg/dL) for individuals at high risk for adverse cardiovascular events. In this way, the total number of patients requiring more aggressive cholesterol-lowering treatment increases substantially. Because the cholesterol carried in LDL particles is derived mainly from both *de novo* synthesis and absorption from the diet, a better understanding of the regulatory mechanisms of hepatic cholesterol biosynthesis and intestinal cholesterol absorption should lead to novel approaches to the treatment and the prevention of CHD and stroke. Therefore, despite major advances in the treatment of atherogenic lipoproteins, substantial residual risk in patients with CHD and stroke is under intensive investigation. Many epidemiological investigations and clinical studies have clearly demonstrated that the cholesterol contained within HDL is inversely associated with risk of CHD and is a critical component of predicting its risk **(Wang HH, 2017).**

The HDL particles were first found in the 1960s after isolation by ultracentrifugation. After a method to precipitate Apo-B containing lipoproteins was established, it could determine the cholesterol content of HDL in individual healthy subjects and patients with CHD. As a result, large scale epidemiological studies on the relationship between the plasma concentrations of HDL cholesterol and the prevalence of CHD were extensively performed **(Soran H, 2011).** The Framingham Heart Study showed the first compelling evidence of the strong inverse association between HDL cholesterol concentrations and CHD. Based on these epidemiological findings, a widely acknowledged concept was proposed that HDL might have properties that protect against CHD, leading to the idea that HDL is the “good” cholesterol, as opposed to LDL “bad” cholesterol. As a result, a new concept was addressed that therapeutic intervention to raise plasma HDL cholesterol concentrations would reduce risk of CHD, which was supported by a series of animal studies in the 1980s and 1990s **(Autran D, 2001).**

Subsequently, many advances were made in understanding the molecular and genetic regulation of plasma HDL metabolism. Animal studies have found that the infusion of HDL into rabbits reduces a risk of developing diet-induced atherosclerosis.13 In addition, atherosclerosis is protected in mice overexpressing apolipoprotein A-I (Apo-A-I), the major HDL protein, even a high-cholesterol and high-fat diet is fed. A further study that is performed in mice with pre-existing atherosclerosis finds that overexpression of Apo-A-I leads to regression of pre-existing atherosclerotic disease. Taken together, these animal studies and preclinical results match the epidemiological investigations and clinical studies, as well as strongly support the hypothesis that HDL is a key target for a novel therapeutic approach to reducing risks of developing atherosclerosis. However, human genetic analysis and some failed clinical trials have created skepticism about the importance of HDL on the prevention and the treatment of CHD. Despite the properties of HDL consistent with atheroprotection **(Wang HH, 2017).**

1.8 Health Impact of Smoking

Tobacco smoking increases the risk of contracting a wide range of diseases, many of which are fatal. Stopping smoking at any age is beneficial compared with continuing to smoke. For some diseases, the risk can be reversed while for others the risk is approximately frozen at the point when smoking stopped. Tobacco smoking is estimated to lead to the premature death of approximately 6 million people worldwide and 96,000 in the UK each year **(Action on Smoking and Health, 2016b) (World Health Organization,2013)**.

A 'premature death from smoking' is defined as a death from a smoking-related disease in an individual who would otherwise have died later from another cause. On average, these premature deaths involve 10 years of life years lost **(US Department of Health and Human Services, 2004)**.

Many of these deaths occur in people who have stopped smoking but whose health has already been harmed by smoking. It also happens to be the case that smokers who do not stop smoking lose an average of 10 years of life expectancy compared with never-smokers and they start to suffer diseases of old age around 10 years earlier than non-smokers **(Jha & Peto, 2014)**.

Most smoking-related deaths arise from cancers (mainly lung cancer), respiratory disease (mainly chronic obstructive pulmonary disease – COPD), and cardiovascular disease (mainly coronary heart disease) **(Action on Smoking and Health, 2016b)**. Smoking is an important risk factor for stroke, blindness, deafness, back pain, osteoporosis, and peripheral vascular disease (leading to amputation). After the age of 40, smokers on average have higher levels of pain and disability than non-smokers **(US Department of Health and Human Services,2004)**.

Smoking in both women and men reduces fertility Smoking in pregnancy causes underdevelopment of the fetus and increases the risk of miscarriage, neonatal death, respiratory disease in the offspring, and is probably cause of mental health problems in the offspring **(Action on Smoking and Health, 2013)**.

People used to think that smoking was protective against Alzheimer's disease but we now know that the opposite is the case: it is a major risk factor for both Alzheimer's and vascular dementia **(Ferri *et al*., 2011;) (US Department of Health and Human Services, 2004)**.

There is a positive association between average daily cigarette consumption and risk of smoking-related disease, but in the case of cardiovascular disease the association is non-linear, so that low levels of cigarette consumption carry a higher risk than would be expected from a simple linear relationship **(US Department of Health and Human Services, 2004)**.

Tobacco smoke contains biologically significant concentrations of known carcinogens as well as many other toxic chemicals. Some of these, including a number of tobacco-specific nitrosamines (particularly NNK and NNN) are constituents of tobacco, largely as a result of the way it is processed, while others such as benzopyrene result from combustion of tobacco **(Action on Smoking and Health, 2014b)**.

These chemicals form part of the particulate matter in smoke. Tobacco smoke also contains the gas, carbon monoxide (CO). CO is a potent toxin, displacing oxygen from hemoglobin molecules. However, acutely the amount of CO in tobacco smoke is too small to lead to hypoxia and the body produces increased numbers of red blood cells to compensate. The nicotine in tobacco smoke may cause a small part of the increase in cardiovascular disease but none or almost none of the increase in risk of respiratory disease or cancer **(Benowitz, 1997, 1998)**.

It is the other components of cigarette smoke that do almost all the damage. It has been proposed on the basis of studies with other species that nicotine damages the adolescent brain but there is no evidence for clinically significant deficits in cognition or emotion in adults who smoked during adolescence and then stopped **(US Department of Health and Human Services, 2004)**.

Exposure to second-hand smoke carries a significant risk for both children and adults. Thus, non-smokers who are exposed to a smoky environment have an increased risk of cancer, heart disease and respiratory disease **(Action on Smoking and Health, 2014a).**

Smokers who stop before their mid-30s have approximately the same life expectancy as never smokers **(Doll, Peto, Boreham, *et al*, 2004) (Pirie, Peto, Reeves, Green, *et al*, 2013)**. After the age of 35 years or so, stopping smoking recovers 2–3 months of healthy life expectancy for every year of smoking avoided, or 4–6 h for every day **(Jha & Peto, 2014)**.

Stopping smoking has different effects on different smoking-related diseases. Excess risk of heart attack caused by smoking reduces by 50% within 12 months of stopping smoking. Stopping smoking returns the rate of decline in lung function to the normal age-related decline, but does not reverse this; it reduces the frequency of ‘exacerbations’ (acute attacks of breathing difficulty resulting in death or hospitalization) in COPD patients. Stopping smoking 'freezes' the risk of smoking related cancers at the level experienced when stopping occurs but does not decrease it in absolute terms **(US Surgeon General, 1990)**. Smokers who stop show reduced levels of stress and mood disorder than those who continue **(Royal College of Physicians and Royal College of Psychiatrists, 2013)**. They also report higher levels of happiness and life satisfaction than those who continue **(Shahab & West, 2009, 2012)**. This suggests that smoking may harm mental health, though other explanations cannot be ruled out on the current evidence.

1.9 Diseases Caused by Smoking

Cancer

Smoking is currently the largest preventable cause of cancer-related deaths, accounting for approximately 30% of cancer related deaths **(Benowitz, N.L, 2010)**. Carcinogens in cigarette smoke bind to human DNA, resulting in DNA damage and gene mutations. These genetic changes lead to uncontrolled cell growth and inhibit normal mechanisms that restrain cell growth and spread, resulting in cancer. A causal relationship has been established between cigarette (tobacco) smoking and lung cancer, the leading cause of cancer-related deaths. There is also a causal relationship between cigarette smoking and cancers of the head, neck, liver, bladder, cervix, esophagus, colon, and rectum **(Soghoian, S. Nicotine. 2015)**. The evidence is insufficient to conclude that there is a causal relationship between smoking and cancers of the breast and prostate, however there is an increased risk of dying from cancer in smokers with breast, prostate, and other cancers **(U.S. Department of Health and Human Services.2014)**.

Cardiovascular Diseases

There is a causal relationship between cigarette smoking and cardiovascular events. Major mechanisms underlying smoking-induced cardiovascular disease include endothelial dysfunction, prothrombotic effects, inflammation, altered lipid metabolism, increased demand for

myocardial oxygen and blood, decreased supply of myocardial blood and oxygen, and insulin resistance **(U.S. Department of Health and Human Services. 2014)**. Cigarette smoking and exposure to second hand smoke are major causes of coronary heart disease, stroke, aortic aneurysm, and peripheral arterial disease **(Fiore, M.C.; *et al* 2011).**

Cigarette smoking and secondhand smoking are also a major cause of death due to CVD. Annually, 194,000 deaths from cardiovascular disease in the U.S. are smoking-related **(Harris, K.K.; *et al* 2016)**.

Respiratory Diseases

Cigarette (tobacco) smoking is also associated with the development of chronic pulmonary diseases. In fact, cigarette smoking is the primary cause of COPD in the U.S **(Rakel, R.E.; *et al 2011*) (GOLD, 2017)**.

Some of the mechanisms involved are loss of cilia in the lungs, mucus gland hyperplasia, and overall inflammation resulting in the abnormal functioning of the lungs as well as injury. Cigarette smoking may exacerbate asthma in adults. Underlying mechanisms may include chronic airway inflammation, impaired mucociliary clearance, increased bronchial hyperresponsiveness, increased development of T helper cell 2 (Th2) **(J. Environ. Res, 2017)**

pathways relative to Th1 pathways, increased production of IgE, and greater allergic sensitization **(Twyman, L, *et al 2014*).** Smoking also increases the risk of developing tuberculosis and dying from tuberculosis **(U.S. Department of Health and Human Services, 2014).**

Reproductive Effects

Maternal cigarette (tobacco) smoking causes several reproductive abnormalities. Carbon monoxide in cigarette smoke binds to hemoglobin, depriving the fetus of oxygen, ultimately resulting in low birth weight **(Fiore, M.C.; *et al* 2008)**. Other toxins in tobacco smoke including nicotine, cadmium, lead, mercury, and polycyclic aromatic hydrocarbons, have been found to cause sudden infant death syndrome, premature births, and decreased fertility in women **(Benowitz, N.L.; *et al* 2010)**.

More recent evidence indicates a causal relationship between maternal cigarette smoking and orofacial clefts and ectopic pregnancies. A causal relationship between smoking and erectile dysfunction in men has also been established **(O’Brien, C.P. 2017)**.

Additional Effects

Smoking impairs immune function, resulting in an increased risk of pulmonary infections and rheumatoid arthritis **(Rakel, R.E.; *et al* 2011)**. It also affects the gastrointestinal tract, increasing the risk of peptic ulcer disease. There is also increased risk of hip fractures and low bone mineral density in postmenopausal women who smoke. Additionally, smokers with diabetes have a higher risk of developing complications, including nephropathy, blindness, peripheral neuropathy, and amputations **(O’Brien, C.P. 2017)**. Recent evidence indicates that the risk of developing type 2 diabetes is 30–40% higher in smokers that nonsmokers. Passive (second-hand) smoking has also been linked with negative health consequences such as low-birth rate in offspring of mothers exposed to second-hand smoke, sudden infant death syndrome, and type 2 diabetes mellitus **(U.S. Department of Health and Human Services, 2014)**.

Literature review

Many studies had conducted to determine the association between smoking and lipid profile and complete blood count: In Iraq, a study conducted by *Al-Jaf* and colleagues **(*Al-Jaf* etal.,2020),** the study Targets different groups that consist of 46 smoker group and 20 non-smokers as control group,this study concludes that the mostly altered lipid parameters in the smokers is TG Whereas the less one is total cholesterol that could be worsened by increasing in some obesity indexes. In Bangladesh a study conducted by Nath and colleagues **(Nath etal.,2022),** a total of 160 healthy male subjects aged above 30 years were selected; among them 80 were smokers and 80 were age matched apparently healthy non smokers for comparison, study showed that: The smokers had significantly increased levels of total cholesterol, triglyceride, LDL-C and decreased HDL- C level in comparison to non-smokers (P-value <0.05). It was observed that total cholesterol, serum triglycerides and LDL- C levels were highest in heavy smokers, less in moderate smokers and least in mild smokers, but HDL- C levels were highest in mild smokers less in moderate smokers and least in heavy smokers.

2. Aims of the study

2.1 General aim

The general aim of this study is to evaluate the association between smoking and complete blood count and serum level of lipid profile in Yemeni smokers and nonsmokers.

2.2 Specific aims

1- To compare Complete Blood Count (CBC) and lipid profile in Yemeni smokers and nonsmokers.

2- To identify the correlation between smoking where Hemoglobin (Hb), Red Blood Cells (RBC) and lipid profile.

3. Materials, Methods, and Subjects

3.1 Materials

Complete blood counts reagents (Roche, Germany)

Table 1 Reagents of whole blood diluent for hematological analycer

	Name Of Reagent	Amount
1	Sodium Chloride	< 0.9 % (g/dl)
2	Potassium chloride	< 0.01 % (g/dl)
3	Buffer	< 0.03 % (g/dl)
4	Stabilizer	< 0.01 % (g/dl)

Table 2 Reagents of whole blood lysing for hematological analyzer

	Reagent Name	Amount
1	Sodium Chloride	< 0.58 % (g/dl)
2	Organic acid	< 0.25 % (g/dl)
3	Quaternary Ammonium salt	< 4.2 % (g/dl)

3.1.1 Triglyceride kit

Table 3 Triglyceride kit (Biosystem, EU) consist of

	Reagent Number	Reagent Name	Amount
1	R1	Pipes buffer (PH 7.5)	50 mmol/l
		4-chlorophenol	5.0mmol/l
		Magnesium ions	4.7 mmol/l
		ATP	1.0 mmol/l
		Lipase	1.0 u/ml
		Peroxidase	0.5 u/ml
		Glycerol kinase	0.4 u/ml
		Sodium azide	0.05%
2	R2	4-aminoantipyrine	0.4 mmol/l
		Glycerol-3-phosphate oxidase	1.5 U/l
		Sodium azide	0.095 %
3	R3	Triglyceride standard	2.28 mmol/l

3.1.1.1 Triglycerides assay

Principle

Triglycerides are determined after enzymatic hydrolysis with lipase, the indicator is quinonimine formed from hydrogen peroxide,4-aminoantipyrine and 4-chlorophenol under the catalytic influence of peroxidase. The color intensity formed is measured at 500 nm.

$$\text{Triglycerides} \xrightarrow{\text{lipase}} \text{glycerol} + \text{fatty acids}$$

$$\text{Glycerol} + \text{ATP} \xleftrightarrow{\text{GK}} \text{glycerol} - 3 - \text{phosphate} + \text{ADP}$$

$$\text{glycerol} - 3 - \text{Phosphate} + \text{O2} \xleftrightarrow{\text{GPO}} \text{dihydroxyacetone phosphate} + \text{H2O2}$$

$$\text{2H2O2} + 4 - \text{aminophenazone} + 4 - \text{chlorophenol} \xrightarrow{\text{POD}} \text{quinoneimine} + \text{4H2O}$$

Where GK is: Glycerol kinase.

GPO: Glycerol-3-phosphate oxidase.

POD: Peroxidase.

Procedure

To three tubes labeled sample, standard and blank, 1 ml of working reagent were pipetted, followed by 10 µl of serum sample, standard solution and water respectively, then mixed and incubated at 37 C° for 5 minutes. The absorbance was measured spectrophotometrically within 60 minutes of the test and standard against reagent blank at 500 nm.

Calculation

The concentration of triglycerides was calculated according to the following equation: Triglycerides concentration (mmol/l) =Absorbance of sample X concentration of standard /Absorbance of standard.

3.1.2 Cholesterol kit

Table 4 Cholesterol kit (Biosystem, EU) consist of

	Reagent Number	Reagent Name	Amount
1	R1	Phosphate buffer (PH 6.5)	100 mmol/l
		4-Aminophenazone	0.25 mmol/l
		Phenol	5.0 mmol/l
		Peroxidase	> 5.0 KU /l
		Cholesterol esterase	> 150 U/l
		Cholesterol oxidase	> 100 U/l
		Sodium azide	0.05 %
2	R2	Cholesterol standard	5.17 mmol/l
		4-Aminophenazone	0.25 mmol/l
		Phenol	5.0 mmol/l
		Peroxidase	> 5.0 KU /l
		Cholesterol esterase	> 150 U/l
		Cholesterol oxidase	> 100 U/l
		Sodium azide	0.05 %
2	R2	Cholesterol standard	5.17 mmol/l

3.1.2.1 Total cholesterol assay

Principle

Cholesterol is determined after enzymatic hydrolysis and oxidation. The indicator quinonimine is formed from hydrogen peroxide and 4-aminoantipyrine in the presence of phenol and peroxidase. The color intensity formed is measured at 500 nm.

$$\text{Cholesterol ester} + \text{H2O} \xrightarrow{\text{CHE}} \text{Cholesterol} + \text{fatty acids}$$

$$\text{Cholesterol} + \text{O2} \xrightarrow{\text{CHO}} \text{Cholestene} - 3 - \text{one} + \text{H2O2}$$

$$2\text{H2O2} + \text{Phenol} + 4 - \text{aminoantipyrine} \xrightarrow{\text{POD}} \text{quinoneimine} + \text{H2O}$$

Where CHE is: Cholesterol Esterase.

CHO: Cholesterol Oxidase.

Procedure

To three tubes labeled sample, standard and blank, 1 ml of working reagent were pipetted, followed by 10 µl of serum sample, standard solution and distilled water were added respectively, then mixed and incubated at 37 C° for 5 minutes. The absorbance of sample and standard was measured within 60 minutes, spectrophotometrically at 500 nm against the reagent blank.

Calculation

The concentration of total cholesterol was calculated according to the following equation: Concentration of cholesterol in the sample (mmol/l) = Absorbance of sample X concentration of standard /Absorbance of standard.

3.1.3 HDL cholesterol kit

Table 5 HDL cholesterol kit consists of

	Reagent Name	Amount
1	Phosphotungstate	14 mmol/L
2	Magnesium chloride	1 mmol/L
3	Preservative	1 × 4 ml
4	HD L cholesterol standard	50 mg/dL
5	HDL cholesterol concentration	23 mg/dl

3.1.4 LDL-Cholesterol kit

1. 1 x 10 ml Precipitant solution.
2. Dropper for 100 tests.
3. Ready-to-use.

The concentrations in the reagent solution are:

1. Polyvinyl sulphate 0.7 g/L
2. EDTA Na 2 5.0 mM
3. Polyethylene glycol monomethyl ether 170 g/L

3.1.5 Instruments

- Hematology analyzed KX21 (Roche, Japan)
- PhotometerBTS350 (UV/VIS), (Biosystem, E.U)
- Centrifuge 6000 rpm (Hitch, Germany)
- Water bath

3.2 Methods

3.1 Study design:

A comparative cross sectional study**.**

3.2 Study Area:

Sana'a city, Yemen**.**

3.3 Sample size and sampling:

Sample size was 95 participants , which calculated according to Nath et al, 2022 by using Open Epi program using 95% confident level and mean ±SD of total cholesterol in smokers is 205 ± 51 and mean ±SD of total cholesterol in non-smokers is 172 ± 29 and the ratio of case to control 1:1, and power of study 80%,and divided into two groups:

Group I : 45 Smokers (cases).

Group II :50 non-smokers (controls)

3.4 Inclusion criteria:

Smokers and nonsmokers male and female individuals .

3.5 Exclusion criteria

Subjects with diabetes mellitus, heart diseases , chronic renal disease, and other diseases, and non-Khat chewing.

3.6 Data collection:

A questionnaire for each male and female will be filled with the participants information (This includes the age, gender, smoking time, weight, heights).

3.7 Sample collection

A- Four ml of venous whole blood will be collected from donor to EDTA and plan tube serum for CBC , lipid profiles, after 12 – 14 hours fasting.

3.8 Statistical analysis

Data were analyzed by the SPSS Version 20 (Social Package of Statistical Science) computer program by LEAD Technologies; Inc. USA. Data were checked for normally distribution and the results were expressed as Mean ± SD for normally distributed variables and as median (interquartile range) for non-normally distributed . Differences in variables that were normally distributed were tested using independent sample T test and for non-normally distributed we used ManWhitney test . The significant differences were indicated if P-value was < 0.05.

3.9-Ethics Statement:

All participants in this study a consent Form was given, and information about the experimental procedures before giving their written consent.

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4. Results

In this study there were 95 participants (45 participants were smokers (33 males and 12 females) and 50 participants were non-smokers 33 males and 17 females)) aged 17-70 years.

From table 6, there were significant increase in total cholesterol and LDL-cholesterol in Yemeni smokers compare to non-smokers (p-value = **0.00013**, **0.0001** respectively) by 18.4 % and 26 % respectively, but other biochemical variables show non-significant differences in this study.

Table 6 Comparison of Anthropometric and biochemical variables in Yemeni smokers and non-smokers

Variables	Non-Smokers	Smokers	P. value
Age (years)	24.2 ± 6.5	27.8 ± 9.9	0.044
BMI (kg/m^2)	21.9 ± 3.8	23.4 ± 4.2	0.07
Cholesterol (mmol/l)	3.8 ± 0.64	4.5 ± 0.88	**0.00013**
Triglycerides (mmol/l)	0.88 (0.49)	1.0 (0.91)	0.46
LDL–C (mmol/l)	2.3 ± 0.56	2.9 ± 0.78	**0.0001**
HDL–C (mmol/l)	1.0 ± 0.22	1.0 ± 020	0.83

Data were presented as mean ±SD for all parameters except triglycerides presented as median (interquartile range).

P-value ≤ 0.05 is considered statistically significant.

Table 7 Comparison of complete blood count variables in Yemeni smokers and non-smokers

Variables	Non-Smokers	Smokers	p. value
Hemoglobin (g/dl)	15.8 ± 1.7	15.9 ± 1.6	0.9
Hct (%)	45.4 ± 3.7	44.8 ± 4.2	0.46
MCV (fl)	82.7 ± 4.6	84.8 ± 5.5	**0.048**
MCH (pg)	29.2 ± 2.4	30 ± 2.6	0.15
MCHC (g/dl)	353 ± 14.7	353 ± 11.7	0.93
RBC (X 10^{12}/L)	5.5 ± 0.44	5.3 ± 0.63	0.083
WBC (X 10^{9})/L	5.4 ± 1.6	5.6 ± 1.5	0.55
Platelets (X 10^{9})/L	262 ± 60	273 ± 66.5	0.43

Data were presented as mean ±SD for all parameters

P-value ≤ 0.05 is considered statistically significant.

From table above, there was significant increase in mean cell volume (MCV) in Yemeni smokers compare to non-smokers (p-value = **0.048**), but other variables show non-significant differences.

Table 8 shows significant correlation between Smoking and total cholesterol and LDL-cholesterol (p-value = 0.0001).

Table 8 Correlation between Smoking and lipid profile, and BMI

		Total cholesterol (mmol/l)	**Triglycerides (mmol/l)**	**LDL-cholesterol (mmol/l)**	**HDL-cholesterol (mmol/l)**	BMI (Kg/m^2)
Smoking	r	-0.381	-0.088	-0.387	-0.021	-.188
	p-value	**0.0001**	0.39	**0.0001**	0.83	0.068

r =Correlation Coefficient

The table 9 shows significant correlation between Smoking and Mean cell volume (p-value = 0.048).

Table 9 Correlation between Smoking and hematological variables

		Hemoglobin (g/dl)	**Hct (%)**	**MCV (fl)**	**MCH (pg)**	**RBC ($X10^{12}$/L)**
Smoking	R	-0.013	0.077	-0.204	-0.147	0.179
	p-value	0.90	0.45	**0.048**	0.15	0.83

r =Correlation Coefficient

5. Discussion

Cigarette smoking is a global escalating public health problem that estimated to kill 6 million people and causes over hundred billion dollars of economic damage worldwide each year **(Parchwani DN, 2013).** In this study, we investigated the relationship between tobacco smoking and lipid profile and complete blood count variables.

In the present study, there were significant increase in total cholesterol and LDL-cholesterol in Yemeni smokers compare to non-smokers (p-value = **0.00013**, **0.0001** respectively) same results were reported by **(Devaranavadgi BB, 2012).** The possible mechanisms for increasing total cholesterol and LDL-cholesterol are: Nicotine stimulates the release of adrenaline from the adrenal cortex leading to stimulate lipolysis that increases serum concentration of free fatty acids (FFA) which further stimulates hepatic synthesis and secretion of cholesterol **(Sondermeijer et al, 2013).**

On the other hand, there is no difference in HDL-cholesterol level between smokers and non-smokers in this study that was also reported in the previous studies **(Guedes, 2007), (Arslan, 2008).** The result of this study disagrees with previous study **(Prabha V., 2015).** The probable explanation could be due to factors such as age, diet, physical activity, body weight, duration of smoking or intensity of smoking in study group. Triglycerides in this study shows non-significant increase in Yemeni smokers compare to non-smokers, this study disagrees with previous study **(Mohammed, 2016),** the possible explanation is: in previous study, the sample size was large (143 participants), and intensity of smoking was different.

From the study it was observed that Mean Cell Volume (MCV) was significantly higher (p-value=0.048) in Yemeni smokers as compared to non-smokers, this finding agrees with pervious study **(Pedersen KM, 2019).** The mean corpuscular volume could be increased due to alterations in lipid and protein composition in erythrocyte cell membranes arisen from oxidative stress or free radicals but also due to the toxic effects in the bone marrow of acetaldehyde from cigarette smoke **(Padmavathi P, 2010) (Buckley *et al*., 2015).**

On the other hand, there were non-significant differences in hemoglobin, hematocrit, mean cell hemoglobin (MCH), mean cell hemoglobin concentration

(MCHC), red blood cells count, white blood cells count and platelets count in Yemeni smokers compare to non-smokers. On the contrary, a study by **(Pedersen KM, 2019).** reported that there were significant differences in complete blood count variables among smokers as compared to non-smokers. The differences of the current study and the previous study **(Pedersen KM, 2019).** may be due to ethnic's variation in study population, sample size in previous study was larger (104607 participants), age factor (20-100 years), study design (cohort study).

Pearson correlation was used to investigate the relationship of smoking with lipid profile, BMI, and complete blood count variables. A significant correlation was found between smoking and total cholesterol, LDL-cholesterol and mean cell volume (p-value = 0.0001, 0.0001, 0.048 respectively).

6. Conclusion

This study concluded that serum total cholesterol, Low Density Lipoprotein Cholesterol (LDL- C) levels and Mean Cell Volume (MCV) were found significantly higher in Yemeni smokers than non-smokers. As per the existing literature, these changes in lipid profile may lead to future fatal cardiovascular diseases among the smokers.

7. Recommendation

We recommended the following:

1-Further work up involving study the effect of heavy smoking for long period.

2- Further work up involving large number of Yemeni smokers.

3-The health policy-makers in Yemen should take an active role in planning strategies to increase the awareness of the health risk of smoking.

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الملخص العربي

الخلفية: التدخين هو أكبر عامل خطر يمكن الوقاية منه للإصابة بالأمراض والوفاة المبكرة والأمراض المتعلقة بالتبغ مثل أمراض القلب والأوعية الدموية والسرطان ، لذلك هدفت هذه الدراسة إلى تحديد العلاقة بين التدخين ومستوى الدهون و تعداد الدم الكامل لدى المدخنين اليمنيين.

المنهجية: هذه الدراسة عبارة عن دراسة مقطعية أجريت على ٩٥ مشاركًا يمنيًا بالغًا (٤٥ مدخنًا و ٥٠ غير مدخن) تتراوح أعمارهم بين ١٧ - ٧٠ عامًا في مدينة صنعاء ، اليمن ، خلال عام ٢٠٢٣م

النتائج: كانت هناك زيادة معنوية في الكوليسترول الكلي والكوليسترول الضار ومتوسط حجم الخلايا لدى المدخنين اليمنيين مقارنة بغير المدخنين (القيمة الاحتمالية = ٠.٠٠٠١٣ ، ٠.٠٠٠١ ، ٠.٠٤٨ على التوالي) ، بالإضافة إلى ارتباط معنوي بين التدخين والكوليسترول الكلي. كوليسترول LDL ومتوسط حجم الخلية (القيمة الاحتمالية = ٠.٠٠٠١ ، ٠.٠٠٠١ ، ٠.٠٤٨ و r = -0.381،

-0.387، -0.204 على التوالي).

الاستنتاج: كانت هناك زيادة معنوية في الكوليسترول الكلي والكوليسترول الضار ومتوسط حجم الخلايا لدى المدخنين اليمنيين مقارنة بغير المدخنين (القيمة الاحتمالية = ٠.٠٠٠١٣ ، ٠.٠٠٠١ ، ٠.٠٤٨ على التوالي) ، بالإضافة إلى ارتباط معنوي بين التدخين والكوليسترول الكلي. والكوليسترول الضار ومتوسط حجم الخلية (القيمة الاحتمالية = ٠.٠٠٠١ ، ٠.٠٠٠١ ، ٠.٠٤٨ و r = -0.381

، -0.387، -0.204 على التوالي)..

Questionnaire

Name: **Age:**

Gender:

Weight: **BMI:**

Hight:

Do you smoke cigarettes?

Yes ☐

No ☐

On average, how many cigarettes/cigars per day do you smoke?

1- 1-3 per day ☐ 2- 2-5 per day ☐

3- Can per day ☐

4- More (How many?) ☐

If you use a form of tobacco other than cigarettes, how many times per day do you use it?

Never ☐ not every day ☐ 1-10 ☐ 11-20 ☐

الجمهورية اليمنية
وزارة التعليم العالي والبحث العلمي
الجامعة الإماراتية الدولية
كلبة الطب والعلوم الصحية

قسم الطب المخبري

العد الدموي الشامل ومستوى الدهون في المدخنين اليمنيين

مشروع تخرج مقدم لكلية الطب والعلوم الصحية كمتطلب للحصول على درجة البكالوريوس في الطب المخبري

مقدم من:

١- احمد السمومي
٢- فاطمة المنج
٣- حمزة متاش
٤- هبه الدبعي
٥- جابر الوجيه
٦- مرام العنسي
٧- محمد ظافر
٨- رائد نجار
٩- رحاب بناء

تحت إشراف

الأستاذ الدكتور. وليد أحمد الدبعي

أستاذ الكيمياء الحيوية في كلية الطب والعلوم الصحية

١٤٤٥ هـ

٢٠٢٣م