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Study of Prevalence, risk factors and role of oxidative stress in diagnostic and pathophysiology of coronary artery disease relate to metabolic syndrome in Algerian population

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إهداء

قال عز من قائل: {يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ} (سورة المجادلة ; الآية 11)، {وينصرك الله نصرا عزيزا} (سورة الفتح ; الآية 03).

الحمدالله الذي منّ علينا بأن رفع درجاتنا في الدنيا وآتانا من عنده رحمه وعلّمنا من لدنه علما، لنلتحق بمركب البحث عن كنوز الأرض وأسرار السماء.

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HAMMADI MAROUA

ABSTRACT

This work was aimed to investigate the prevalence of coronary artery disease and its associated risk factors and to evaluate the biochemical, hematological and oxidative stress markers in order to predict the coronary artery disease in patients suffering from metabolic syndrome (MetS) in El Oued population.

About epidemiological study of cardiovascular disease, 23422 patients were conducted. The 300 patient's participants, who came from various El-Oued region and the patients with CAD and metabolic syndrome who were chosen from public and private hospitals, were the subjects of the risk factors analysis study. A questionnaire was used to collect all the data. Binary logistic regression was used to evaluate the probability of socio-clinical factors between CAD and the risk factors that are connected with it. Two-sided statistical tests were considered statistically significant if $P < 0.05$. Our biological study involved 120 volunteers subjects divided into three groups (control, CAD and MetS). They are from El Oued (Algeria) region. Some hematological, biochemical and oxidative stress parameters were analyzed. The estimation of sensitivity and specificity of all markers was conducted using a receiver operating characteristics curve (ROC) design.

By analyzing the data from our epidemiological and risk factor studies, we showed that clinical factors like hypertension (OR=154.846, and; P =0.000), the group age over 60 y (OR=76.641, and; P =0.000), and chest pain (OR=42.667, and; P =0.000) all significantly increase the risk of developing CAD in patients compared to healthy individuals (control). In contrast, we demonstrate that the most dangerous socioeconomic factors are alcohol consumption (OR=13.500, and; P =0.001), and obesity (OR=4.495, and; P =0.000), respectively. However, we estimate that the group age less than 40 y,is a significant protective factor for the disease (OR=0.227.6, P 0.014) in patients with CAD as opposed to those with metabolic syndrome. The results showed significant changes ($P<0.05$) in Calcium and inflammatory markers, including an increase in white blood cell (WBC), neutrophil (NEUT), monocyte (MONO), monocyte to lymphocyte ratio (MLR), neutrophil to lymphocyte ratio (NLR), albumin (ALB) and C-reactive protein (CRP) and also significant changes in oxidative stress parameters by increasing in glutathione (GSH) levels with ($P<0.05$) in patients with coronary artery disease compared to patients with syndrome metabolic.

On the other hand, ROC analysis indicated that NLR, MLR, CRP and GSH were significant predictive factors ($P<0.001$) with a specificity (95.2, 90.5,95.2, 20.8 %) AUC (82.8, 78.9, 78.8, 32%) and sensitivity (23.8, 42.9, 27.8, 63.6%) respectively showing strong associations with risk factors associated with coronary artery disease.

Also, there was a negative correlation in CAD group by comparison biochemical and hematological parameters with oxidative stress markers with ($P <0.05$) between (serum SOD / CPK), (serum TAC /NEUT), (serum TAC /NLR), (serum TAC /MLR).

Concerns about public health have been raised by the population's rising incidence of coronary artery disease risk factors, which poses a health danger, particularly in the absence of effective promotion and awareness campaigns. When data for metabolic syndrome patients are evaluated, a high NLR, MLR, CRP and MDA and low vitamin D and calcium may help predict the risk of coronary artery disease, can be recommended and useful as a new marker in monitoring metabolic syndrome patients.

Key words: CAD, Metabolic syndrome, risk factors, inflammation markers, oxidative stress markers, predictive factors.

الملخص

يهدف هذا العمل إلى دراسة مدى انتشار مرض الشريان التاجي وعوامل الخطر المرتبطة به وتقييم العلامات البيوكيميائية والدموية وعلامات الإجهاد التأكسدي من أجل التنبؤ بمرض الشريان التاجي لدى المرضى الذين يعانون من متلازمة التمثيل الغذائي (MetS) في منطقة الوادي بالجزائر. بالنسبة للدراسة الوبائية لأمراض القلب والأوعية الدموية، أجريت على 23422 مريضا. حيث أن المشاركون البالغ عددهم 300 مريض، ينحدرون من مختلف مناطق الوادي والمرضى الذين يعانون من مرض الشريان التاجي ومتلازمة التمثيل الغذائي تم اختيارهم من المستشفيات العامة والخاصة، بالنسبة لدراسة تحليل عوامل الخطر تم استخدام استبيان لجمع كافة البيانات.

حيث تم استخدام الانحدار اللوجستي الثنائي لتقييم احتمالية وجود عوامل اجتماعية وسريرية بين أمراض القلب والأوعية الدموية وعوامل الخطر المرتبطة بها. اعتبرت الاختبارات الإحصائية ذات الوجهين ذات دلالة إحصائية إذا كانت $\mathbf{P < 0.05}$. الدراسة البيولوجية شملت 120 متطوعا مقسمين إلى ثلاث مجموعات الشاهدة ومجموعة المرضى ذوي متلازمة الشريان التاجي ومجموعة مرضى ذوي متلازمة التمثيل الغذائي وهم من منطقة الوادي (الجزائر). تم تحليل بعض عوامل الكيميائية الدموية والحيوية والإجهاد التأكسدي. تم إجراء تقدير معايير الحساسية والخصوصية باستخدام اختبار (ROC). من خلال تحليل بيانات دراستنا الوبائية وعوامل الخطر، أظهرنا أن العوامل السريرية مثل ارتفاع ضغط الدم (OR=154.846, و P =0.000;) وعمر المرضى أكثر من 60 سنة (OR=76.641, و P =0.000;) ، وآلام الصدر(OR=42.667, و P =0.000;) ; كلها تزيد بشكل كبير من خطر الإصابة بأمراض الشريان التاجي لدى المرضى مقارنة بالأفراد الأصحاء (التحكم). في المقابل، أثبتنا أن العوامل الاجتماعية والاقتصادية الأكثر خطورة هي استهلاك الكحول (OR=13.500, و P =0.001;) ، والسمنة (OR=4.495, و P =0.000;) مع ذلك، فإننا نقدر أن عمر المرضى الأقل من 40 سنة (OR=0.227, و P =0.014;) وعمر هو عامل وقائي مهم للمرض لدى المرضى الذين يعانون من متلازمة الشريان التاجي مقارنة بالمرضى الذين يعانون من متلازمة التمثيل الغذائي.

أظهرت النتائج تغيرات كبيرة ($\mathbf{P < 0.05}$) في والكالسيوم وعلامات الالتهابات، بما في ذلك زيادة في خلايا الدم البيضاء (WBC)، (NEUT)،(MONO) ، نسب MLRو NLR والألبومين (ALB) والبروتين الالتهابي (CRP)وكذلك تغييرات كبيرة في علامات الإجهاد التأكسدي عن طريق زيادة مستوى GSH عند المرضى الذين يعانون من متلازمة الشريان التاجي مقارنة مع المرضى الذين يعانون من متلازمة التمثيل الغذائي. من ناحية أخرى، أشار تحليل ROCإلى أن NLR وMLR و CRP و GSH كانت عوامل تنبؤية مهمة ($\mathbf{P < 0.001}$) بخصوصية (95.2, 90.5, 95.2, 20.8%) ، المساحة تحت المنحنى (82.8, 78.9, 78.8, 32%) وحساسية (23.8, 42.9, 27.8, 63.6%) حيث تظهر ارتباطات قوية مع عوامل الخطر المرتبطة بمرض الشريان التاجي.

كذلك، كان هناك ارتباط سلبي في مجموعة متلازمة الشريان التاجي عند مقارنة التحاليل البيوكيميائية وتحاليل الدم مع علامات الاجهاد التأكسدي ($P> 0.05$) بين (مصل SOD /CPK)، (مصل NEUT /TAC)، (مصل NLR /TAC) و (مصل MLR /TAC).

مما سبق نؤكد ان هذه الدراسة تثير المخاوف بشأن معدلات ارتفاع الإصابة بأمراض الشريان التاجي بين السكان في المنطقة مما يشكل خطرا على الصحة العامة، لاسيما في غياب حملات التوعية والترويج الفعالة. عندما يتم تقييم البيانات الخاصة بمرضى متلازمة التمثيل الغذائي، قد يساعد ارتفاع NLR و MLR و CRP و MDA وانخفاض فيتامين د والكالسيوم في التنبؤ بخطر الإصابة بمرض الشريان التاجي، ويمكن التوصية به ومفيد كمؤشر جديد في المراقبة والحد من تعقيدات مرضى متلازمة مرضى متلازمة التمثيل الغذائي.

الكلمات المفتاحية: مرض الشريان التاجي، المتلازمة الأيضية، عوامل الخطر، علامات الالتهاب، علامات الإجهاد التأكسدي، العوامل التنبؤية.

Figures List

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Abbreviation List

AC: Another complication.

ACC: American College of Cardiology.

ACEIs: Angiotensin receptor blockers.

ACS: Acute coronary syndrome.

AF: Arterial fibrillation.

AHA: American heart Association.

ALAT: Alanine Amino Transferase.

ALB: Albumin.

ALP: Phosphatase alkaline.

AMI: Acute myocardial infraction.

AMY: Amylase.

ARBs: Percutaneous coronary intervention.

ARDs: Autoimmune Rheumatic diseases.

ARF: Acute rheumatic fever.

ASAT: Aspartate Amino Transferase.

ATP: Adenosine triphosphate.

AUC: Area under curve.

BASO: Basophils.

BH4: Tetrahydrobiopterin.

BMI: Body mass index.

CAD: Coronary artery disease.

CBC: Complete blood count.

CCTA: Coronary computed tomography angiography.

CD: Cluster of differentiation.

CHD: Chronic heart disease.

CHD: Congenital heart disease.

CI: Confidence interval.

CK: Creatinine kinase.

Ck-MB: Creatinine kinase-myocardial band.

CMS: Cardiometabolic syndrome.

CNS: Central nervous system.

CO_2: Dioxide carbon.

CoQ: Coenzyme Q.

CPE: Cardiogenic acute pulmonary Edema.

CPK: Creatine phosphokinase.

Cr: Creatinine.

CRP: C- reactive protein.

Cu: Copper.

CV: Cardiovascular.

CVA: Cerebral vascular accident.

CVD: Cardiovascular disease.

DBP: Diastolic blood pressure.

DNA: Desoxyribonucleic acid.

DT: Diabetes mellitus.

DTNB: 5,5-Dithiobis (2-Nitro Benzoic Acid).

EDTA: Ethylenediaminetetraacetic acid.

EDTA-Met: EDTA-Methionine.

EKG or **ECG:** Electrocardiogram.

eNOS: Endothelial nitric oxide synthase.

EOS: Eosinophils.

ESC: European Society Cardiology.

FHS: Framingham Heart Study.

FRAP: ferric reducing antioxidant power.

GBD: Global Burden of disease.

GGT: Gamma-glutamyltransferase.

GLY: Glyceamia.

GPx: Glutathione peroxidase.

GSH: Reduced Glutathion.

H+: Hydron.

H_2O_2: Hydrogen peroxide.

Hb: Hemoglobin.

HCS: Health cardiac software.

HCT: Hematocrit.

HD: Heart disease.

HDL-C: High density lipoprotein-cholesterol.

HF: Heart failure.

HIC: high-income countries.

HOCl: Hypochlorous acid.

HSP-60: Heat shock proteins-60.

HTN: Hypertension.

IAA: Include intra-abdominal adiposity.

IC: Intermittent claudication.

ICA: Invasive coronary angiography.

ICAM-1: Intercellular Adhesion Molecule-1.

ICH: Cerebral hemorrhage.

IFN-γ: Interferon gamma.

IHD: Ischemic heart disease.

IL-1 : Interleukine-1.

IL-6: Interleukine-6.

INR: international normalized ratio.

IVC: Interventricular communication.

LDH: Lactate Dehydrogenase.

LDL-C: Low density lipoprotein-cholesterol.

LEAD: Lower extremity artery disease.

LEE: edema of the lower limbs.

LMIC: Middle income nations.

LP: Lipase.

LV: Left ventricle.

LYMPH: Lymphocytes.

MCH: Mean corpuscular hemoglobin.

MCHC: Mean corpuscular hemoglobin concentration.

MCP-1: Monocyte chemoattractant protein-1.

MCV: Mean corpuscular volume.

MDA: Malondialdehyde.

MetS: Metabolic Syndrome.

MI: Myocardial Infarction**.**

MIC: Middle income countries.

miRNA: micro-Ribonucleic acid.

MLR: Monocyte to lymphocyte ratio.

MONO: Monocytes.

MPV: Mean platelet volume.

MRI: Magnetic resonance imaging.

MVO^2: Myocardial oxygen consumption.

NaCl: Sodium Chloride.

NADPH: Nicotinamide adenine dinucleotide phosphate hydrogen.

NBT: Nitro blue tetrazolium test.

NCDs: Non communicable diseases.

NEUT : Neutrophils.

NF-kB: Nuclear factor Kappa.B.

NLR: Neutrophil to lymphocyte ratio.

NO: Nitric oxide.

Nox: NADPH oxidase.

NSTEMI: Non-ST segment elevation myocardial infarction**.**

O2•−: Superoxide anion

OD: Optic density.

OH: Hydroxide.

ONOO-: Peroxynitrite.

OR: Odds Ratio.

P: P- value.

PAD: Peripheral artery disease.

PCI: Percutaneous coronary intervention.

PCT: Procalcitonin**.**

PDGF: Platelet derived growth factor.

PH: Potential of hydrogen.

P-LCR: Platelet larger cell ratio.

PLR: Platelet to lymphocyte ratio.

PLT : Platelets.

PON : Paraxonases.

Prx: Peroxydases.

PT: Prothrombin time.

PURE: Prospective Urban Rural Epidemiology.

PWD: Platelet distribution width.

RAAS: Renin-angiotensin aldosterone system.

RBCs: Red Blood Cells.

RDW-CV: Red cell distribution width- coefficient of variation.

RDW-SD: Red cell distribution width- standard deviation.

RF: Risk factor.

RHD: Rheumatic heart disease.

RNS: Reactive nitrogen species.

ROS: Reactive oxygen species.

SA: Sinoatrial.

SAH: Subarachnoid hemorrhage.

SBP: Systolic blood pressure.

SCAD: Stable coronary artery disease.

SMC: Smooth muscle cell.

SNS: Sympathetic nervous system.

SOD: Super oxide dismutase.

SRs: Scavenger receptors.

STEMI: ST-segment Elevation Myocardial.

TAC: Total antioxidant capacity.

TAHINA: Epidemiological Transition and Health Impact in North Africa.

TBA: Thiobarbituric acid.

TBS: Tris-buffered saline.

TC: Total cholesterol.

TCA: Trichloroacetic acid.

TG: Triglyceride.

TNF-α: Tumor necrosis factor-α.

TP: Total protein.

TRx: Thioredoxin.

UA: Unstable Angina.

VCAM-1: Vascular cell adhesion molecule.

Vit-D 25 (OH): Vitamin-D.

VLDL: Very low-density lipoprotein.

WBC: White blood cell.

WHO: World health organization.

WHO: World health organization.

Zn: Zinc.

Zα/2: The reliability coefficient.

Table of contents

INTROUDUCTION

Introduction

Coronary artery disease or coronary atherosclerosis disease is a type of cardiovascular disease (CVD). It is a mechanism that develops an inflammatory response of the vessel wall from acute to chronic. Various factors such as the combination of hypertension, high blood cholesterol, smoking and diabetes contributed to the development of atherosclerotic plaques (fibrous plaques, atheroma) in the coronary arteries [1].It is a major cause of death globally, obstructive coronary artery disease (CAD) affects both high-income and low- to middle-income nations (LMIC), including many Middle Eastern nations and north Africa [2].The mortality rate due to cardiovascular disease (CVD) shown a steady increase, rising from 12.1 million in 1990 to 18.6 million in 2019. The incidence of total cardiovascular disease (CVD) increased by almost twice, from 271 million cases in 1990 to 523 million cases in 2019 [3].The TAHINA project, which stands for Epidemiological Transition and Health Impact in North Africa, aims to evaluate the prevalence and impact of non-communicable diseases in Algeria. Recent studies indicate a significant epidemic of obesity (21%) and hypertension (24%) in Algeria. Therefore, apart from the increasing rates of cardiovascular mortality, primarily due to ischemic heart disease, the demographic transition in North Africa is also playing a role in the accumulation of cardiovascular risk factors. Consequently, this will lead to a substantial increase in the prevalence of cardiovascular disease in the future [4].Multifactorial lead to behavioural, environmental, social, and cardiometabolic risk factors. The term "cardiometabolic syndrome" (CMS) refers to a group of metabolic disorders that include intra- abdominal adiposity (IAA), insulin resistance, atherogenic dyslipidemia, hypertension, and impaired glucose tolerance. The condition has been referred to by several names, including pluri-metabolic syndrome, insulin resistance syndrome, syndrome X, dysmetabolic syndrome, and CMS [5].The CMS is a well-established and potent risk factor for early and severe CVD and stroke because these metabolic and cardiovascular disorders both alone and jointly contribute to a significant rise in the morbidity and mortality of cardiovascular disease. People with CMS have a much-increased risk of stroke, myocardial infarction (MI), and chronic heart disease (CHD) than people without the condition [6].The most prevalent type of extensive vessel pathology, Atherosclerotic coronary artery disease (CAD) causes syndromes of vital organ ischemia damage , such as myocardial infarction [7].Also it is well-recognized that The disparity between an excess of reactive oxygen species (ROS) and the presence of antioxidants mechanism contribute to increased oxidative stress resulting in the formation of lipid peroxidation

which are as risk factor of atherogenesis. Oxidative stress and Free radicals play significant roles in the progression of atherosclerosis. Free radicals' oxidative modification of LDL has detrimental effects on vascular function, such as a reduction in nitric levels of oxide (NO), endothelial apoptosis, growth in the smooth muscle cells numbers, and the production of molecules that cause inflammation [8].Public policy must be guided by a consistent, comparable, and systematic analysis of long-term trends and patterns in global CVD to give decision-makers benchmarks that the ischemic heart disease (IHD) is the first[9].Our work aims to the determination of clinical and social risk factors for coronary artery disease, to take the necessary prevention tools, to protect people’s life from heart attack disease, which lead to myocardial infarction, and contribute to sudden death, also aims to select the hematological, biochemical and oxidative stress markers as a predictive factor of coronary artery disease in metabolic syndrome patients.

First part
Bibliographic synthesis

I. Cardiovascular system

1. Anatomy and physiology of the cardiovascular system

1.1. Definition

The cardiovascular system as known the circulatory system or blood-vascular, provides the blood supply throughout the body [10]. It can regulate the velocity and amount of blood flow through the vessels by reacting to different stimuli. Numerous factors, such as changing blood volume, hormones, electrolytes, osmolarity, drugs, adrenal glands, kidneys, and much more, can regulate the cardiovascular system. The control of the cardiovascular system is another important function of the parasympathetic and sympathetic nervous systems (Figure 01) [11].

The CV system composed of a muscular pump consisted of cardiac muscle called the Heart also from a closed system of vessels named: arteries, veins and capillaries. The heart and vessels work together with complicated system to provide enough blood flow to all parts of the body [12].

The circulatory system composed of two main loops: the systemic circulation and the pulmonary circulation. The pulmonary circulation between the heart and the lungs, transport the deoxygenated blood to the lungs to get oxygen and then back to the heart, but the systemic circulation transports the oxygenated blood to the cells and tissue after it back to the heart. By this process all the body's cells receive blood, nutriments and oxygen [13].

In addition the waste products resulted metabolic reaction and dioxide carbon (CO^2) are transported by cardiovascular system to the lungs, liver and kidneys to eliminated from the human body [14].

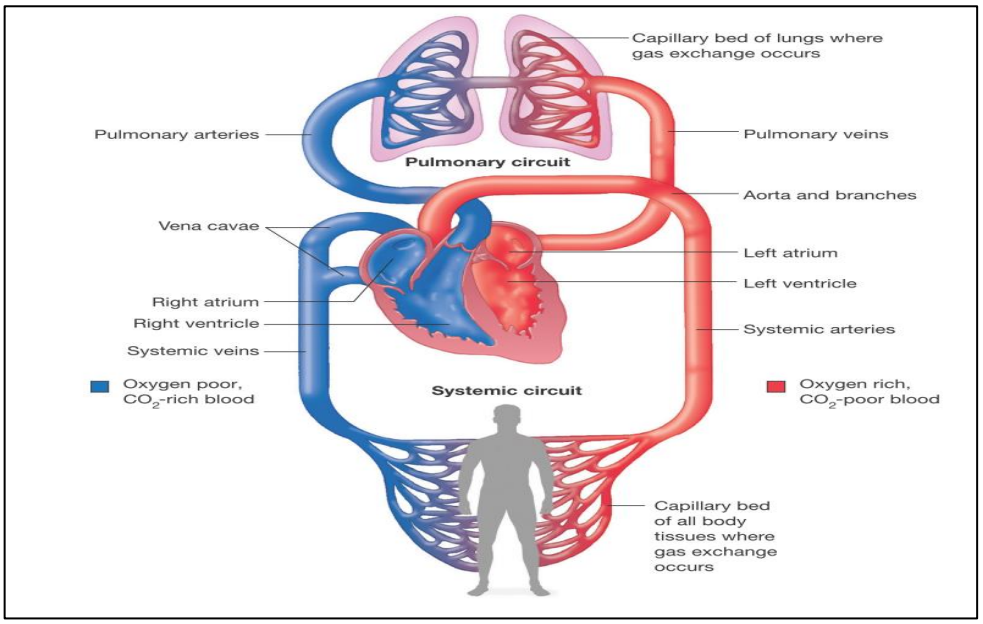

Figure 01: Schematic of cardiovascular system [10].

2. The elements of cardiac system

2.1. Heart

The heart is a muscular pump, consisted of cardiac muscle (myocardium) fibers, The myocardium is a type of involuntary striated muscle found only in the walls of the heart. It beats an average of 60–100 beats per minute (bpm) or about 100,000 times in one day. The heart is located in the left side of the mediastinum than the right in the center of the chest cavity; however, the heart is roughly the size of fist and shaped like an upside-down pear, and it is lies directly behind the sternum. The Apex is the point at the bottom of the heart (Figure 02).[15]

Each time the cardiac muscle contracts; myosin and actin are two types of protein filaments that alternate, are responsible for the striations observed in cardiac muscle. The myocardium contracts as a result of actin filaments sliding past myosin filaments, this action need to sufficient concentration of calcium, sodium and ATP. [16]

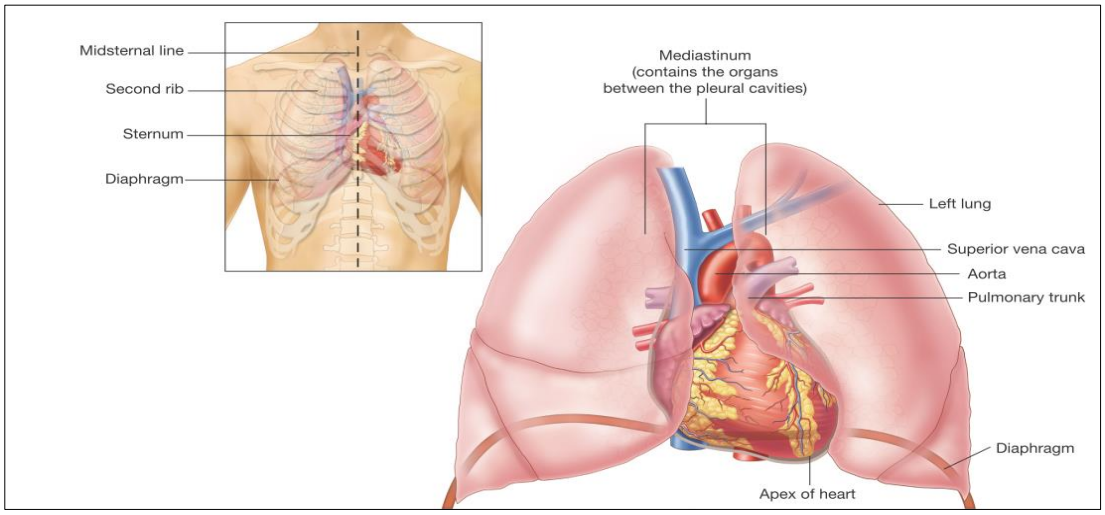

Figure 02: Schematic illustrated the location of the heart within the mediastinum of the thoracic cavity [10].

2.2. Heart chambers

The heart has four chambers or cavities, there are two atria (upper chambers) and two ventricles (lower chambers), these chambers are divided into left and right sides separated by walls named interatrial septum and the interventricular septum. The blood is pumped by the right ventricle into the lungs, where it is oxygenated. The systemic circulation receives blood pumping action from the left ventricle. The right and left atria, which are smaller pumps, transfer blood into the associated ventricles (Figure 03)[17].

2.3. Heart layers

The heart's wall is fairly thick, it made up of three layers (Figure 03):

A. The endocardium: is the inner layer that lines the heart's chambers. It is a very thin, smooth layer that helps to lessen friction when blood flows through the chambers of the heart.

B. The myocardium: is the thick muscular middle layer. This layer of muscle contracts, creating the pressure needed to push blood through blood vessels.

C. The epicardium: is the outer layer of the heart and the inner layer of the sac, or visceral pericardium (double-layered pleural sac), which encloses the heart. The parietal pericardium is the layer that covers the sac's outside. As the heart beats, fluid between the sac's two layers lessens friction.[18]

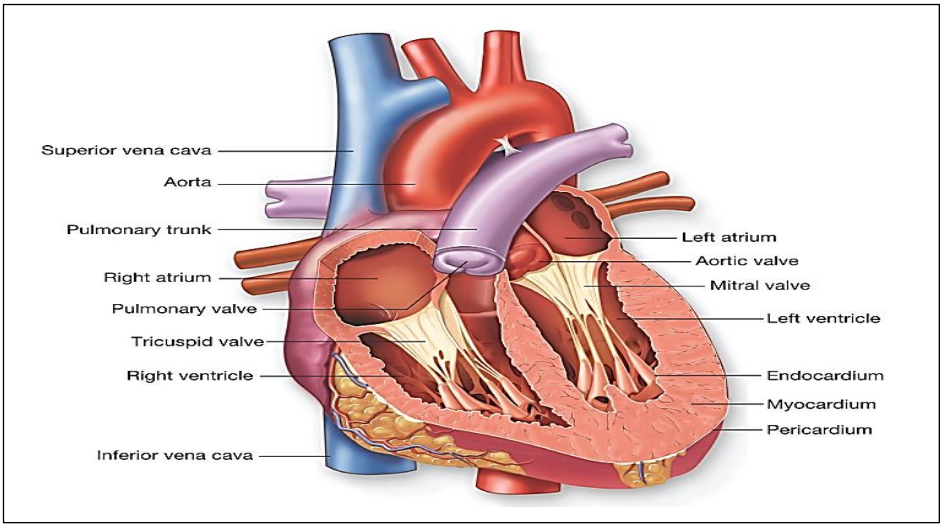

Figure 03: Schematic of internal view of the heart [10].

2.4. Heart valves

The heart has four valves: pulmonary valve, mitral valve, semilunar valve and tricuspid valve, act as restraining gates to regulate the direction of blood flow; they are located at the ventricles' entrances and exits. when the valves are working properly function, allow the blood to flow only forward direction by preventing it from returning to the previous chamber (Figure 04) [19].

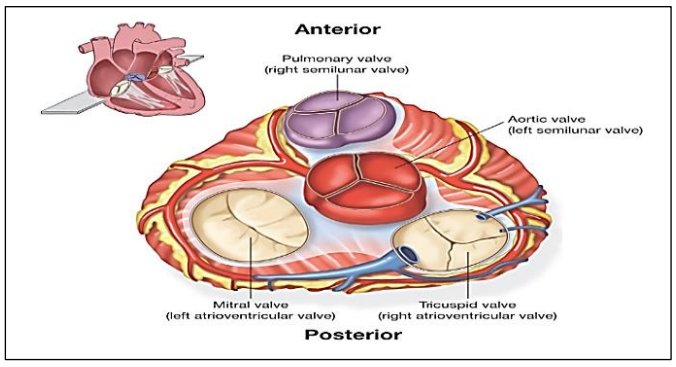

Figure 04: schematic of superior view of the heart valves illustrated the size, position, and shape of each valve[10].

2.5. Blood vessels

There are three types of blood vessels: arteries, capillaries and veins. These are the pipes which distribute the blood throughout the body. The lumen is the channel within blood vessels which allows blood to flows.

2.5.1. Arteries

It is the big, thick-walled vessels that transport blood away from the heart. A thick layer of smooth muscle lines the inside of arteries, and this muscle can contract or relax, contributed to change the size of the arterial lumen. There are three subtype the largest artery is the aorta then the coronary arteries (Figure 05) and the smallest one is the arterioles.[20]

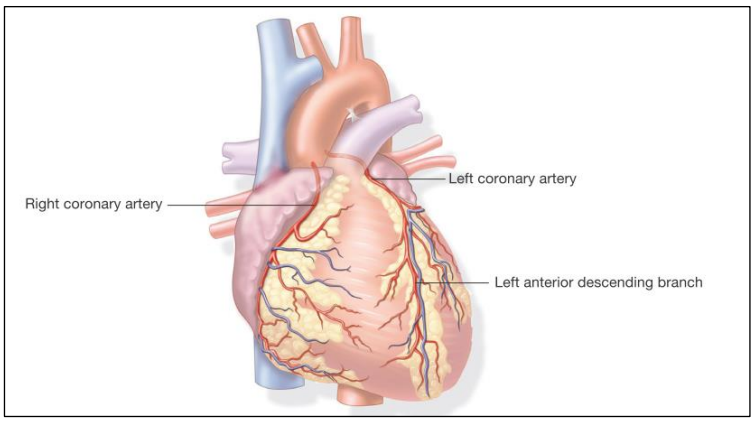

Figure 05: Schematic of coronary arteries[10].

2.5.2. Capillaries

Capillaries are tiny vessels that allow the exchange of oxygen and nutrients, connecting the arterial and venous sections of the vascular system (figure 06). [21]

2.5.3. Veins

The veins carry blood back to the heart, it possess significantly thinner walls compared to arteries, which makes them prone to collapsing with ease.

The veins have also valves that allow the unidirectional flow of blood towards the heart. These valves function to inhibit the backflowing ensuring unidirectional blood flow towards the heart. The heart receives blood from the upper body through the superior vena cava and from the lower body through the inferior vena cava. The blood pressure in the veins is significantly lower compared to that in the arteries. The contraction of skeletal muscles and the muscular action exerted on the veins facilitate the circulation of blood (Figure 06). [22]

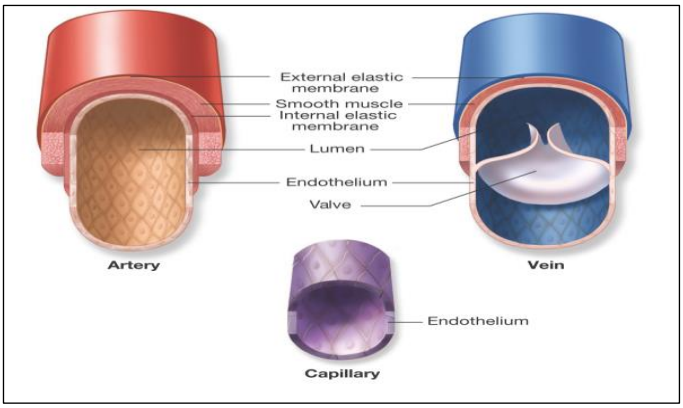

Figure 06: Different structure between arteries, capillaries and veins[10].

3. Blood circulation through the heart

The flow of blood through the heart was very organized; it began by the enter of deoxygenated blood from all tissues of the body, into a relaxed right atrium through two major veins named the superior vena cava and inferior vena cava.

In addition, the right atrium contracts lead to propel the blood through the tricuspid valve into the relaxed right ventricle. Subsequently, the contraction of the right ventricle forces blood through the pulmonary valve into the pulmonary artery, where it is transported to the lungs for oxygenation.

After that the left atrium receives oxygenated blood returning to the heart from the lungs and the blood flows into the relaxed left atrium through the four pulmonary veins.

Then the left atrium contracts and blood passes through the mitral valve into the relaxed left ventricle.

Finally, during the contraction of the left ventricle, blood is propelled past the aortic valve and into the aorta, which is the biggest artery in the body. The aorta transports blood to every part of the body (Figure 07) [23].

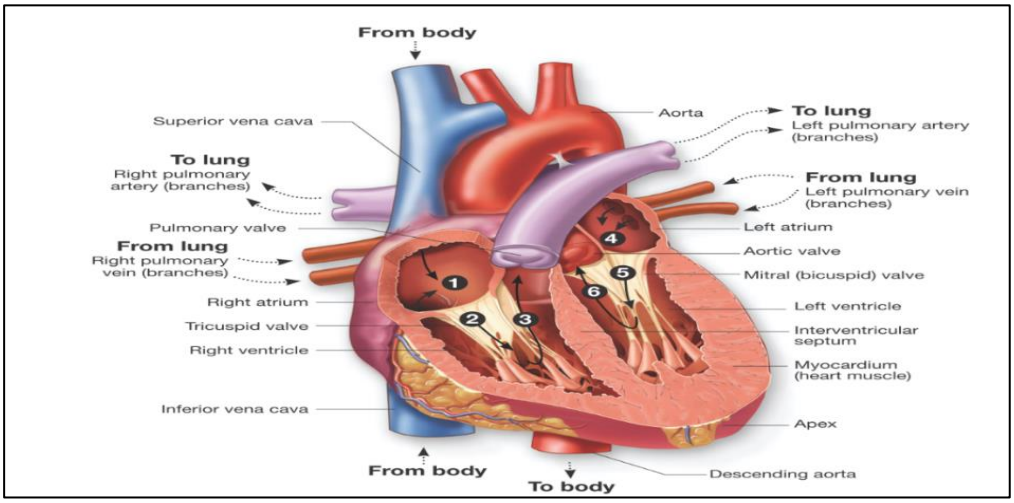

Figure 07: The pathway of blood circulation through the left and right ventricles[10].

4. Blood Pressure

Blood pressure, also known as arterial pressure, refers to the amount of force exerted by blood on the walls of blood vessels. The pulse (P), detected at the wrist or throat is the result of the heart's contraction, which causes a surge of blood. This is why pulse rate is normally equal to heart rate.

The systolic pressure, the peak blood pressure during ventricular systole, results from the forceful contraction of the ventricles exerting pressure on the blood.

During ventricular diastole, the heart does not pump any blood, resulting in a reduction in blood pressure to its lowest point, known as the diastolic pressure.

The normal value of systolic and diastolic was determined by WHO, the systolic was less than 120 mmHg and diastolic less than 80 mmHg.

Additionally, blood pressure is controlled by several additional factors related to the blood and blood vessels, such as arterial flexibility, blood vessel diameter, blood viscosity, blood volume, and resistance to blood flow.[24]

5. Conduction system of the heart

There is no voluntary control over the heart's beating because the autonomic nervous system controls the heart rate, there are a special tissue within the heart conducts an electrical impulse stimuling the various chambers to contract in the correct order. The impulses follow the following path (Figure 08):

A. The electrical impulses began from the sinoatrial (SA) node, also known as the pacemaker. an electrical wave that originates from the sinoatrial node stimule the atria to contract, or enter systole.

B. The stimulation of the atrioventricular node.

C. The stimulation wave is transferred to the atrioventricular bundle (previously known as the bundle of His) by this node.

D. The electrical signal then passes through the interventricular septum's bundle branches.

E. Ventricular systole is the outcome of stimulation of the Purkinje fibers in the ventricular myocardium (figure 09) .[25]

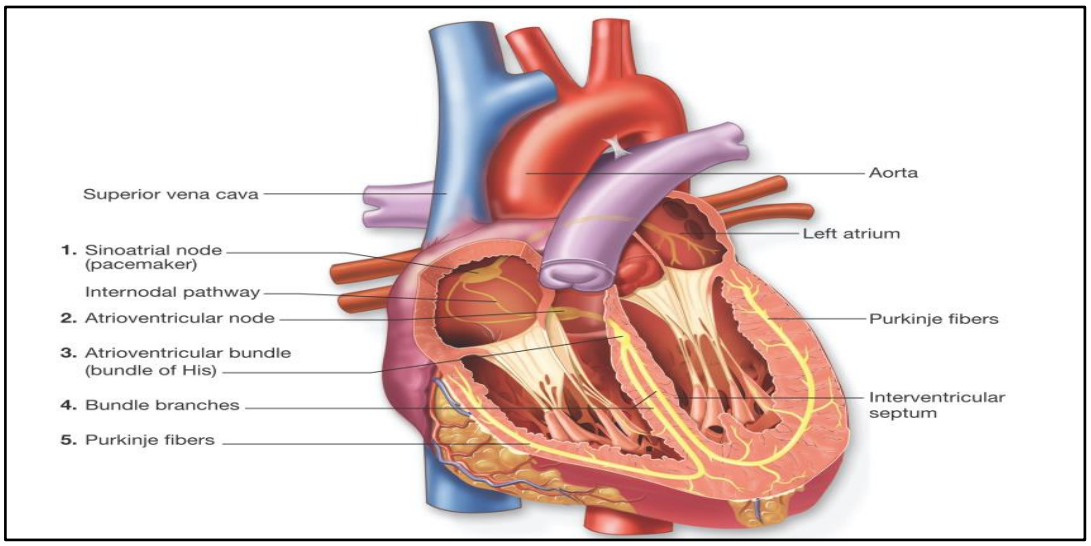

Figure 08: the conducting system of heart [10].

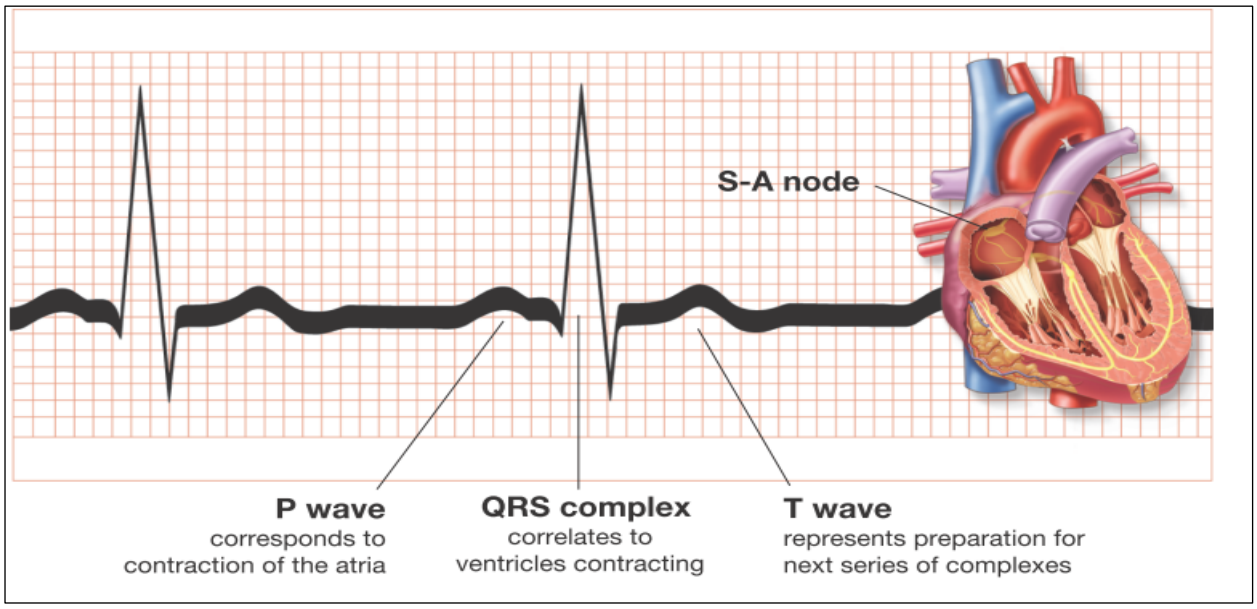

Figure 09: Schematic of an electrocardiogram, (**EKG** or **ECG**) [10].

II. Cardiovascular disease

1. Definition

Cardiovascular diseases (CVDs) involve a variety of disorders affecting the heart and blood vessels, and other conditions (Figure 10), including:

- ❖ coronary heart disease (CAD): stable angina, unstable angina, myocardial infraction, sudden death.
- ❖ Heart failure (HF).
- ❖ Hypertension (HTN).
- ❖ Cerebral vascular accident (CVA): stroke: hemorrhagic, ischemic or transit ischemic attack.
- ❖ Rheumatic heart disease.
- ❖ Congenital cardiovascular disease.
- ❖ Peripheral vascular accident (PAD): lower extremity artery disease (LEAD), aortic aneurysm.
- ❖ Interventricular communication (IVC).

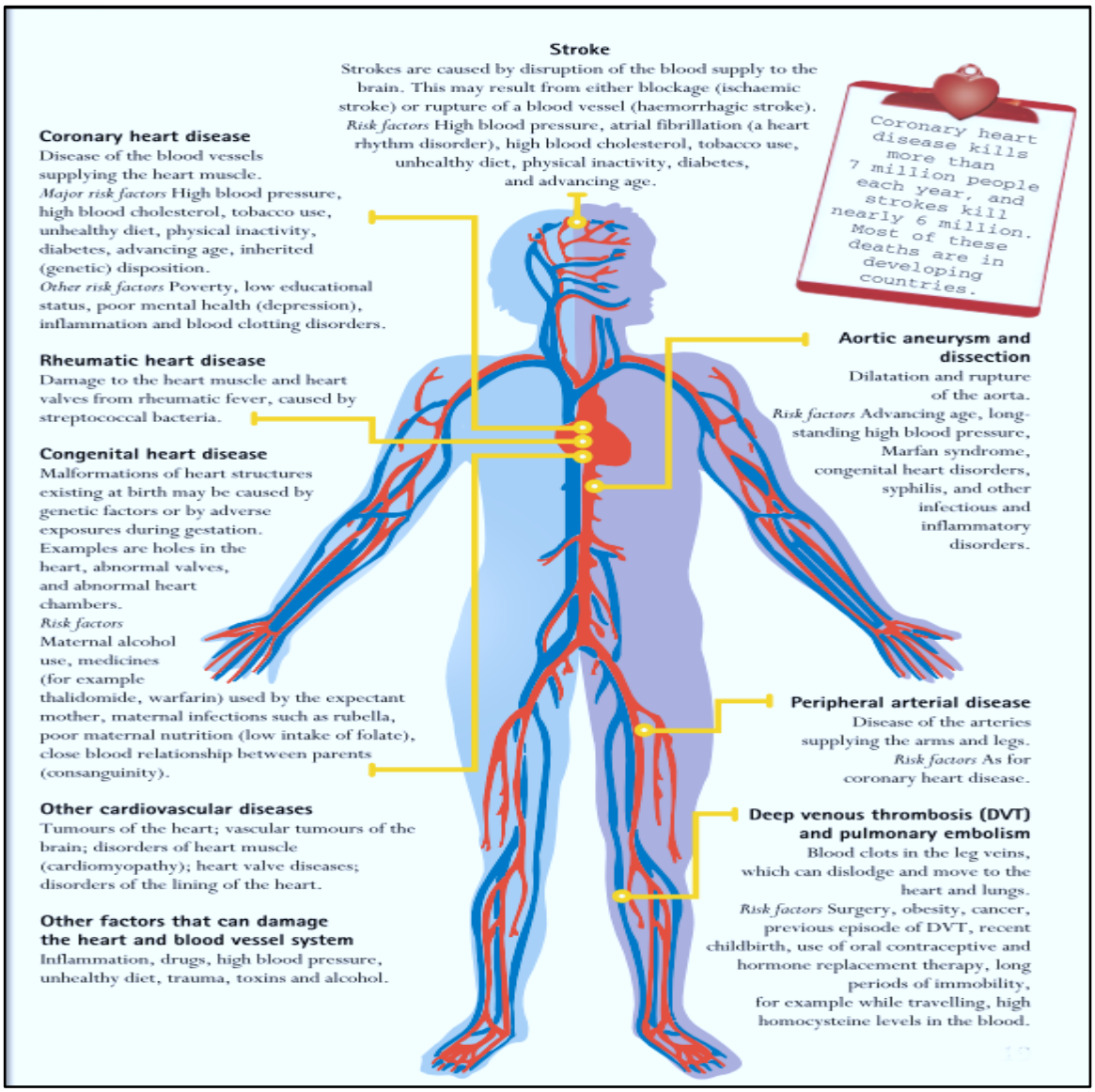

Figure 10: Cardiovascular types[26].

2. Types of CVD

2.1. Coronary artery disease

2.1.1. Definition and classification

CAD known also as ischemic heart disease (IHD), is a burden public health characterized by a high death rate and elevated healthcare expenses [27].

It is the progressive and pathological development of plaque in the interior of lumen and walls of the coronary blood vessels. CAD, or coronary artery disease, leads to a decreased supply of blood to the myocardium, which can cause regional myocardial ischemia and infarction. This can manifest as silent ischemia, angina pectoris, acute coronary syndrome (ACS), or sudden cardiac death [28], [29].

2.1.2. Physiopathology of coronary artery disease

Coronary atherosclerosis is the primary anatomical basis for the various clinical syndromes of coronary heart disease[30]. Atherosclerosis is a focal and chronic disease, a complex progressive characterized by an immune-inflammatory and fibroproliferative response of the artery wall to a long-term, multifactorial insult. This process leads to the production of atherosclerotic plaques (fibrous plaques, atheromas) in the coronary arteries (Figure 11). These plaques are areas of thicker intima and consist of different combinations of fibrous tissue, cells, and fat [31].

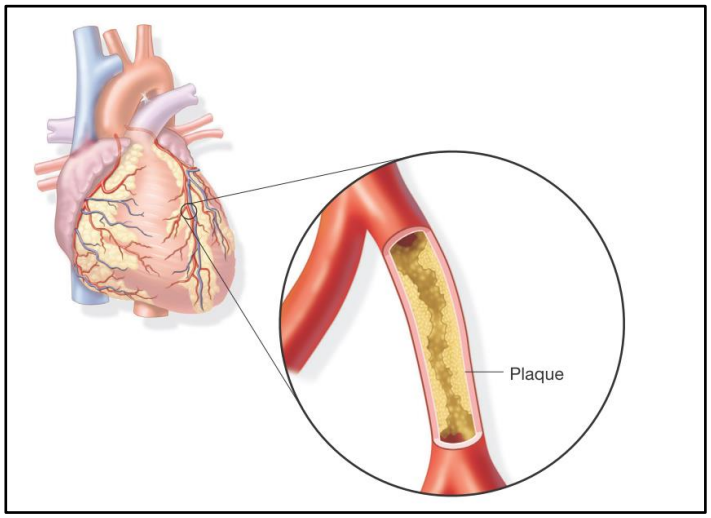

Figure 11: Formation of atherosclerotic plaque in the coronary artery [10].

Atherogenesis is a process that involves complicated interactions between the walls of blood vessels and the soluble and formed components of the blood [32].Important elements lead to the initial atherosclerosis include the process of endothelial injury or dysfunction leads to various subsequent events; the reduction of nitric oxide bioavailability (NO) which synthesized in the Endothelium cells (**EC**) permeates across cell membranes and reaches the smooth muscle tissue of the arterial wall. Nitric

oxide (NO) induces relaxation of smooth muscle fibers, a process referred to as endothelium-dependent vasodilation [33].

Additionally, NO functions as an athero-protective molecule by counteracting the development of atherosclerosis and its associated consequences. Because it is implicated in the decrease of platelet aggregation, tissue oxidation and inflammation, the activation of thrombogenic factors, and cell development, proliferation, and migration[34]. Furthermore, it regulates metabolic balance by decreasing triglyceride levels and steatosis, while increasing insulin production, glucose elimination, and mitochondrial efficiency [35]. However different risk cardiovascular factors such as hyperlipidemia, hypertension, smoking, or diabetes reduced the level of NO as a result of the increase of oxidative stress

Oxidative stress stimulates the production of pro-atherogenic cytokines (TNF-α and interleukins IL-1 and IL-6), adhesion molecules (VCAM-I and ICAM-I), and chemokines (MCP-1) by activating NF-kB through heat-shock proteins (HSP-60). These substances inhibit the function of NOS (Figure 12)[36][37].

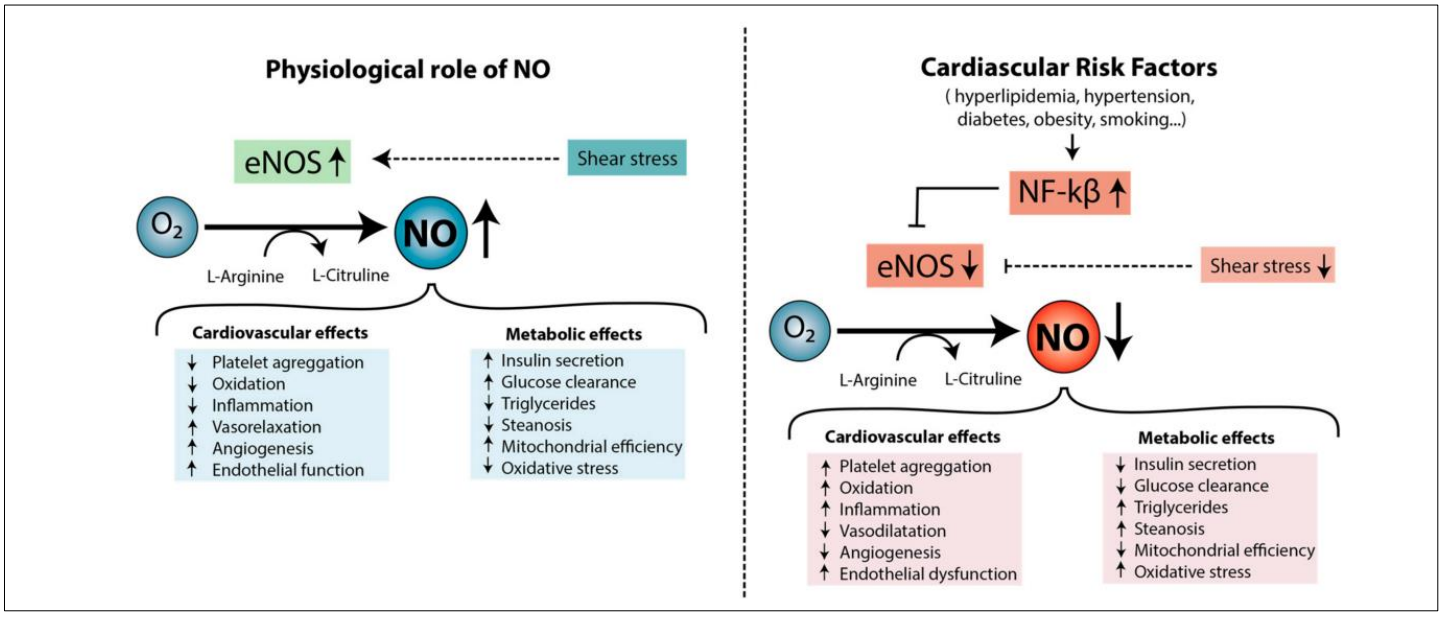

Figure 12: Role of NO in cardiovascular metabolism and disease [30].

Research studied patients with high cholesterol and high hypertension has shown that they have impaired endothelium-dependent vasodilation due to defect in the availability of nitric oxide[38], [39].

The inflammatory process plays an important role in the initiation of the atheroma plaque, a specific pro-adhesion molecule expressed by altered endothelial cells in lesion-prone areas facilitates the recruitment, attachment, and transmigration of T lymphocytes and blood monocytes. Leukocytes become activated macrophages and T lymphocytes as a result of the local environment in the intima, which also facilitates chemical signaling between the two cell types [40].

The macrophages produce cytokines that provide a proinflammatory environment, which promotes the migration of additional inflammatory cells. The generation of additional mediators, such as molecules similar to platelet derived growth factor (PDGF), results in the attraction and multiplication of vascular smooth muscle cells in the lesions. Superoxide anion and other reactive oxygen species cause the oxidation of low-density lipoprotein (LDL). As a result, the uncontrolled absorption of oxidized LDL by macrophages and smooth muscle cells through their scavenger receptors causes the creation of foam cells. As the plaques increase in size, a central area of dead tissue and fatty substances forms due to the programmed cell death of foam cells **(**Figure13) [41].

Smooth muscle cells are responsible for forming the connective tissue matrix that makes up the fibrous capsule of the plaque. Macrophages secrete collagenases and metallo-protenases, which play a crucial role in the degradation and remodeling of the connective tissue matrix [42]. An excessive amount of the degradative enzymes results in the disintegration and weakening of the fibrous capsule (Figure 14).

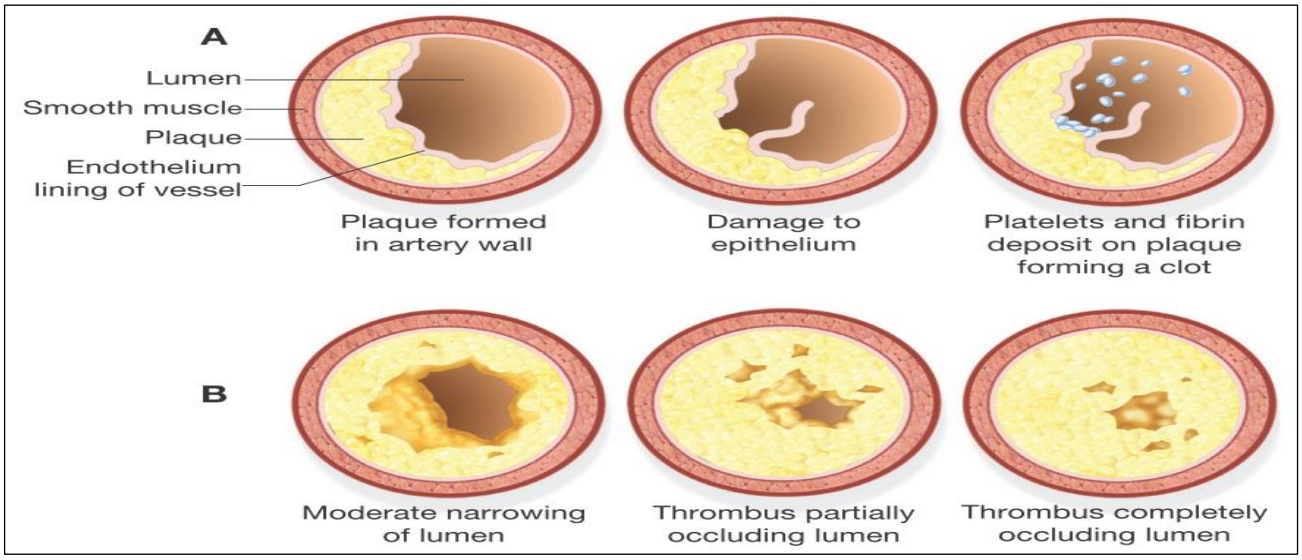

Figure 13: The development of atherosclerosis plaque [10].

Plaques that are likely to rupture and plaques that have already ruptured show signs of inflammation, such as a large number of macrophages and lymphocytes near the plaque capsule, increased levels of inflammatory substances, higher levels of metalloproteinases in the affected area, and significant cell death within the plaque [43][44]. The inflammatory component of atherosclerosis is evident by the association between elevated blood levels of inflammatory markers, particularly high sensitivity C-reactive protein (CRP), and the future occurrence of atherosclerotic disease[45] .

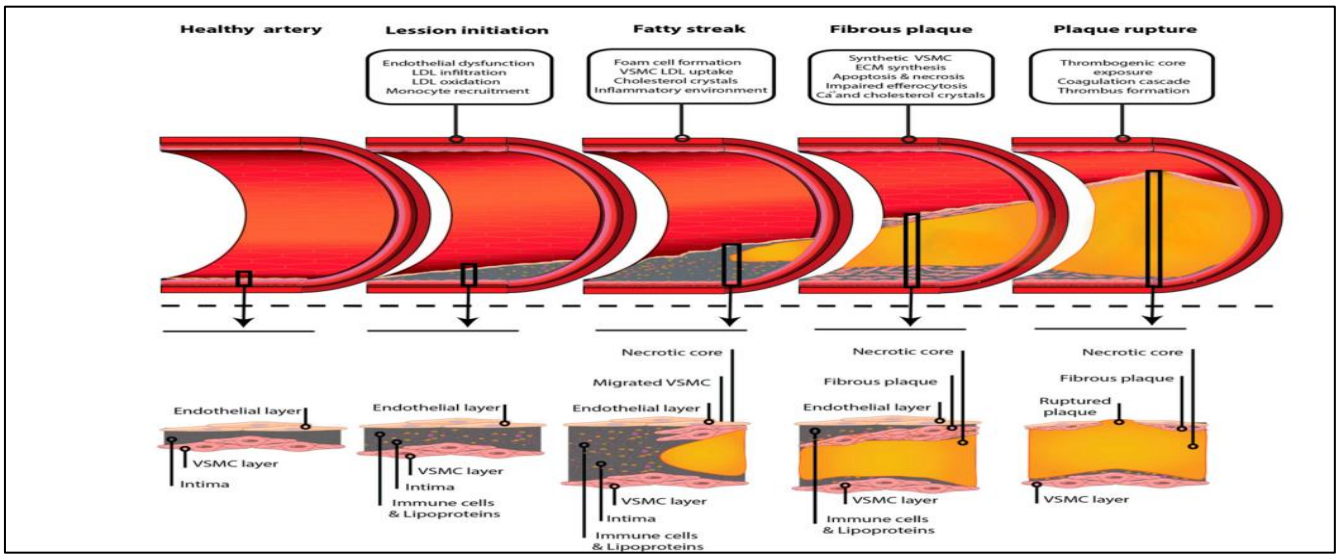

Figure 14: Progression of atheroma plaque formation in an artery[30].

2.1.3. Types of CAD

2.1.3.1. Acute coronary syndrome

Acute coronary syndrome includes a range of clinical symptoms that are compatible with acute myocardial ischemia. This includes Unstable Angina (UA), Non-ST Segment Elevation Myocardial Infarction (NSTEMI), and ST-segment Elevation Myocardial Infarction (STEMI). This situation has similar basic causes, which involve the progression, instability, or rupture of coronary plaques, with or without the presence of luminal thrombosis and vasospasm in the coronary arteries. The primary clinical manifestations include myocardial infarction (MI) and sudden cardiac death [46].

2.1.3.2. Myocardial infraction

Myocardial infarction (MI) is a medical emergency characterized by the death of heart muscle due to severe and prolonged ischemia [47]. The diagnosis is determined by evaluating biochemical criteria, such as elevated troponin levels indicating irreversible cell damage, in addition to clinical evaluation, ECG abnormalities, invasive and noninvasive imaging (Figure 15), and pathological evaluation [48].

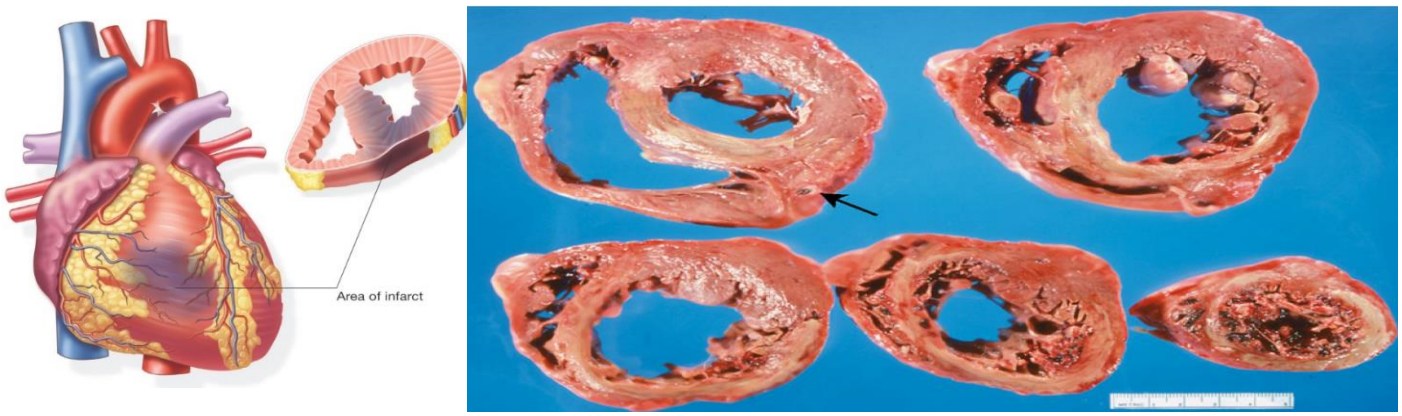

Figure 15: An infarct resulting from a myocardial infarction.[10][30].

2.1.3.3. Nonatherosclerotic Coronary Vascular Diseases

Atherosclerosis-free coronary arteries and a concomitant underlying ailment are present in a small percentage of ischemic heart disease. A wide range of nonatherosclerotic diseases, such as congenital anomalies, dissection, emboli, vasculitis, and other coronary artery disorders, can induce ischemic heart disease [49].

2.1.3.4. Stable coronary artery disease

Stable coronary artery disease refers to several clinical conditions that are defined by the presence of coronary atherosclerosis without acute coronary syndrome [50]. Myocardial demand/supply mismatch refers to episodes of reversible ischemia or hypoxia that can be induced by exercise, emotion, or other stressors [51]. The consequences of ischemia follow a predictable time sequence:

- The concentration of H+ and K+ in the venous blood has increased.
- There are indications of ventricular diastolic dysfunction followed by systolic dysfunction, together with regional wall motion abnormalities.
- ST-T alterations are being developed.
- The individual is experiencing cardiac ischemia pain, also known as angina.[52]

The symptoms in SCAD are reversible, recurring over a period of months to years, and can be relieved by rest or sublingual nitroglycerin. Conditions such as anemia, hypertensive crises, and thyrotoxicosis can worsen the symptoms of angina.

2.1.3.5. Angina Pectoris and Sudden Cardiac Death

Angina pectoris is typically caused by coronary atherosclerosis, which involves the narrowing of one or more of the major coronary arteries [53].

Unstable angina pectoris and related syndromes, such as pre-infarction angina and coronary insufficiency, are frequently accompanied by acute changes in plaques, referred to as "unstable plaques." These unstable plaques often have thrombotic lesions on top of them, which are typically platelet aggregates or nonocclusive thrombi. The presence of macrophages at locations of unstable, fragile plaques suggests the involvement of inflammation in these vascular lesions, as has already been shown in (Figure 16) [43].

Coronary atherosclerosis is the most common anatomic substrate of sudden cardiac mortality.In extensive studies, almost 90% of cases demonstrate severe atherosclerotic narrowing in at least one coronary artery. [54]

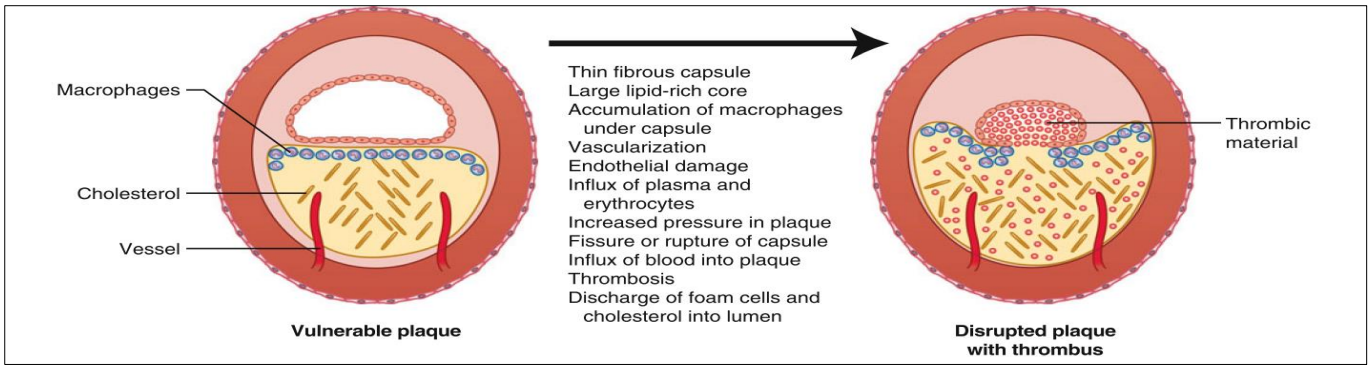

Figure 16: Schematic characteristics of the vulnerable plaque and mechanisms contributing to disruption of the plaque capsule and thrombosis[31].

2.1.4. Strategy diagnostic of CAD

The physical examination is substandard and has low sensitivity. A normal electrocardiogram (ECG) does not definitively rule out the diagnosis, although an irregular resting ECG significantly raises the risk of the diagnosis. It is advisable to do routine laboratory tests in order to assess the extent of the factors' severity. According to the Task members of ESC et al. in 2013, it is recommended to assess hyperglycemia, dyslipidemia, thyroid issue, and renal failure in all patients suspected of having CAD (Figure 17). [55]

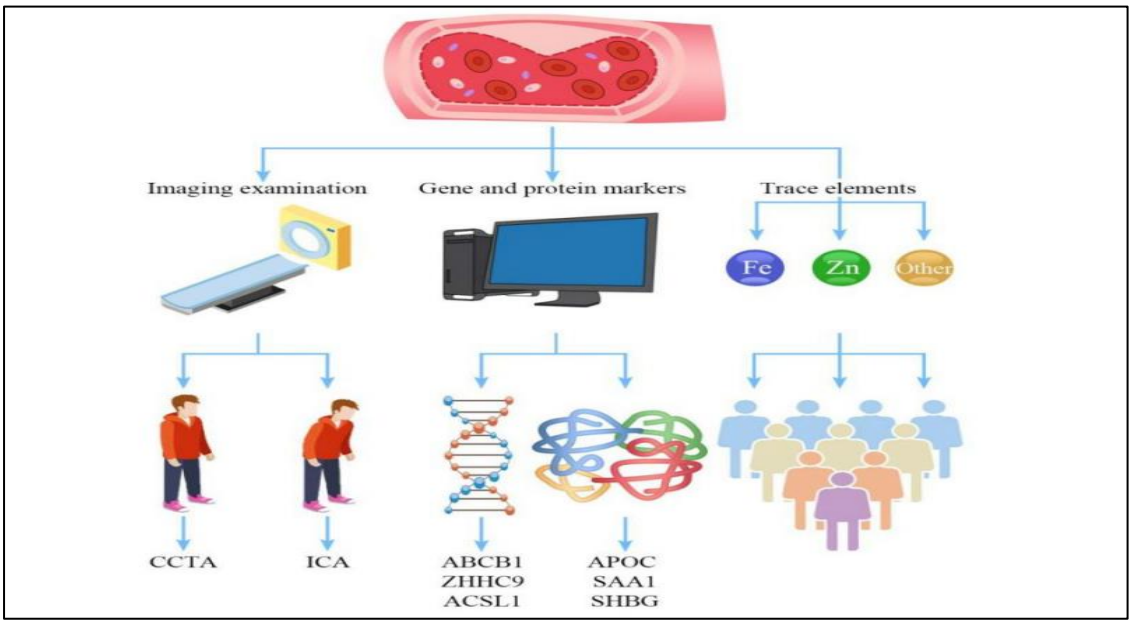

Figure 17: Examination methods for diagnosing coronary atherosclerosis.[56]

2.1.4.1. Electrocardiograms (ECG or ECK)

The electrocardiogram is an important instrument to diagnose the degree, the extent, and severity of myocardial ischemia in order to determine the guide therapy decisions. with a specificity over 90% and a sensitivity below 50%, there is a substantial possibility of false positive results, particularly in females.

The test is often conducted on a treadmill, starting from a state of rest and progressing to maximum effort, following the Bruce protocol. The analysis of ST segment modifications is conducted [57].

2.1.4.2. Serum cardiac markers

Increased levels of cardiac biomarkers, particularly Troponin (I or T), or creatinine kinase (CK) or its isoenzyme MB (CK-MB), indicate damage to the cells of the heart muscle. Troponins have superior clinical sensitivity and specificity compared to conventional cardiac enzymes. Myoglobin lacks specificity in detecting cardiac cell damage [58] .

It is recommended to evaluate troponin levels within the first 6 hours of experiencing pain. The elevation of troponin levels might persist for up to 2 weeks after the commencement of myocardial necrosis, according to Smith et al [59]. The elevation of troponin levels indicates an increase of irreversible death of heart muscle cells [58].Cardiac biomarkers, as stated by Thygesen et al. (2012), lack specificity for acute myocardial infarction (MI). The elevation of cardiac biomarkers is associated with clinical disorders such as pulmonary embolism, heart failure, end stage renal failure, and myocarditis [60]. Also, the dosage of cholesterol, triglyceride concentration and lipoprotein such as low-density lipoprotein (LDL)) and high-density lipoprotein (HDL) are essential to detect the disorder of metabolism lipid which lead to the formation of plaque atheroma.

2.1.4.3. The Multidetector row CT

It enables the identification of coronary calcification. The calculation of calcium scoring involves determining the coronary calcium area based on the maximal plaque density measured in Hounsfield units. The presence of calcified lesions is then assessed using the Agatston score. Calcium scoring is a method used to assess the amount of atherosclerosis present in a person's arteries [61],[62].

2.1.4.4. Coronary computed tomography angiography (CCTA)

Invasive coronary angiography (ICA) with high spatial and temporal resolution is considered the most accurate method for assessing the coronary lumens [63][64].

Due to their high negative predictive value, regular CCTA images can effectively rule out significant coronary artery disease (CAD), reducing the need for further imaging tests and decreasing the need of invasive coronary angiography (ICA) in patients with low and intermediate CAD risk .The National Institutes of Health guidelines in 2016 recommended the use of CCTA as the initial diagnostic test for all patients with suspected stable CAD, due to its cost-efficiency and clinical effectiveness (Figure 18)[65].

The steering committee of the Society of Cardiovascular Computed Tomography has formulated a set of acceptable requirements for the utilization of CCTA in providing guidance to medical practitioners[66].

Figure 18: Device of CCTA [67].

2.1.4.5. Stress echocardiography

Exhibits a greater predictive value compared to the treadmill test. It identifies the variation in wall motion between myocardium affected by reduced ischemic and non-ischemic myocardium, and offers insights into myocardial that is in a state of reduced activity (Figure 19).

Figure 19: Device of stress echocardiography [68].

2.1.4.6. Magnetic resonance imaging (MRI)

Identifies and detects anomalies in the motion of the heart wall (Figure 20).

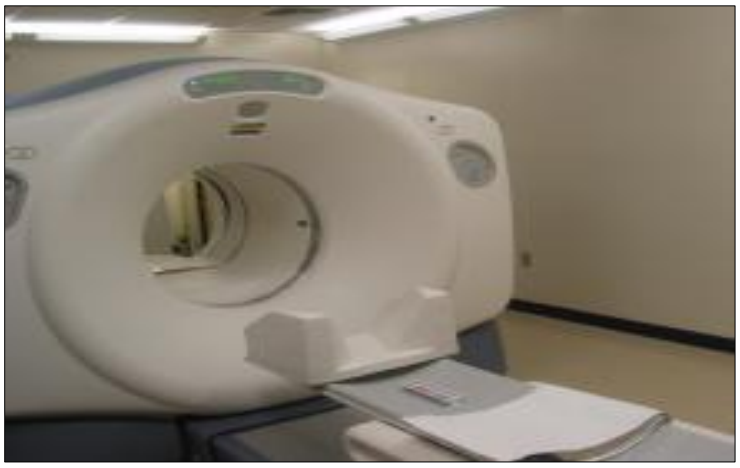

Figure 20: Device of MRI[69].

2.1.4.7. Cardiac coronary angiography

It is the most reliable and widely accepted method (Figure 21). The key indications for ACS or a positive stress test are the presence of significant wall motion anomaly or a lack of response to medical treatment. The text provides a description of the location and quantity of lesions, as well as the kind and severity of stenosis[70].

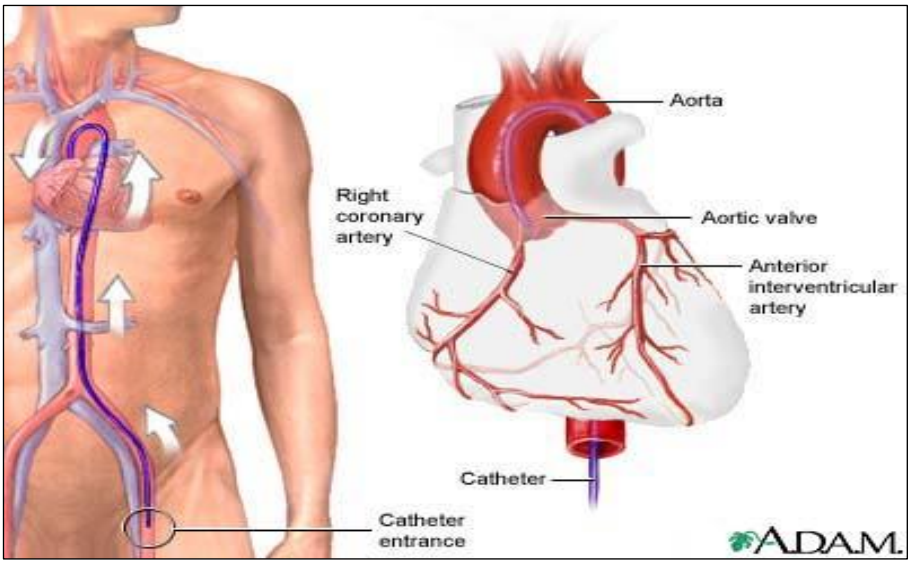

Figure 21: Cardiac coronary angiography[71].

2.1.4.8.Gene and protein levels as new strategy for diagnosis CAD

MicroRNA (miRNA) is a crucial factor in controlling various processes in the body, including cell adhesion, proliferation, lipid uptake, regulate lipoprotein metabolism , metabolic syndrome, obesity , atherosclerosis [72] , and the production of inflammatory mediators. Understanding the role of miRNA in these pathways is essential for studying the effects of coronary atherosclerosis and identifying potential therapeutic strategies. The potential of miRNA as a biomarker for cardiovascular disease, whether for diagnosis, prognosis, or medication response, has been significantly enhanced by the discovery that miRNA can be detected in the bloodstream, even outside of cells [40]. Figure depicts the relationship between genes and proteins (Figure 22).[73]

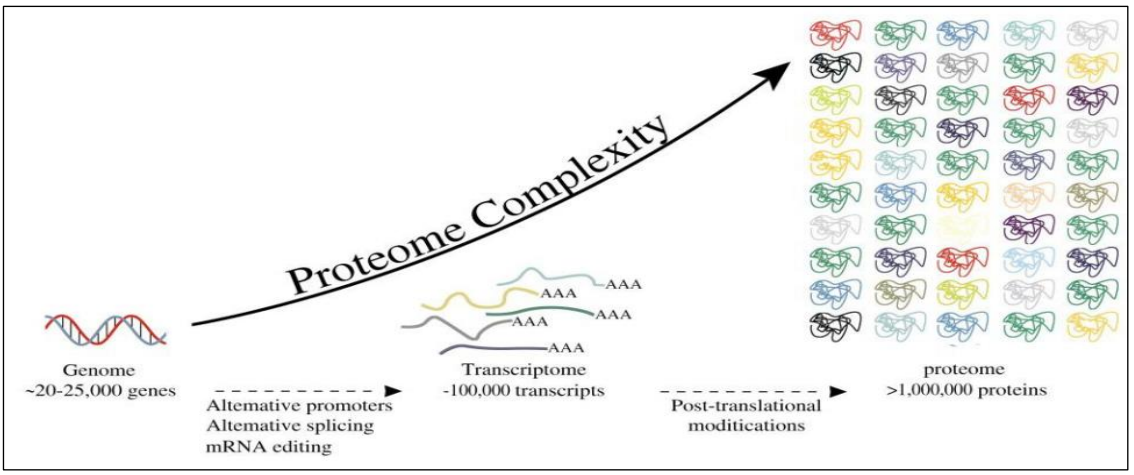

Figure 22: The entire sequence of processes from the expression of a gene to the synthesis of a protein.[56]

2.1.4.9. Trace element

Exploring the disparities in trace element levels in the human body and their associations to coronary heart disease is a valuable endeavor. An analysis indicates that there is a correlation between trace elements in the body and the occurrence of coronary heart disease and other disorders[74].

Therefore, the alterations in the concentrations of trace elements inside the body are regarded as the main factor in the initiation of specific diseases and the transition from a state of good health to a state of illness.

2.1.4.9.1. Zinc ion

The dosage of zinc ions concentration is an important element, because it have a crucial role in regulating several cellular metabolic activities, including the breakdown and utilization of proteins, lipids, and carbohydrates inside the body [75].

Zinc is an essential constituent of more than seventy enzymes, such as superoxide dismutase and glutathione peroxidase. Zinc, as a cofactor of copper-zinc superoxide dismutase (Cu, Zn SOD), has the ability to affect CD. Studies have shown that taking zinc supplements can reduce the effectiveness of copper-zinc superoxide dismutase, as excessive zinc intake interferes with the absorption of copper. Coronary heart disease in non-smoking older people and post-menopausal women, especially women, is linked to a decrease in zinc ion concentration[76]. Patients suffering from coronary artery disease see positive outcomes when they consume zinc ions in the correct dosages[77].

2.1.4.9.2.Iron ion

Iron-containing proteins and enzymes play a crucial role in cellular metabolism. These enzymes and proteins play a crucial role in several cellular processes such as cell growth, cell death, DNA replication, DNA repair, and mitochondrial function [78]. Iron is the primary constituent of hemoglobin, which is

essential for the production of red blood cells and the transportation of oxygen. Iron can be detrimental in high doses because it has the ability to create reactive oxygen species (ROS) and cause damage to biomolecules through the generation of hydroxyl radicals via the Fenton reaction [79]. Iron was initially associated with the development of coronary atherosclerosis [80].

2.1.4.9.3. Other trace elements

Obesity was found to be linked to elevated levels of superoxide dismutase (SOD) and increased quantities of copper in the bloodstream. The presence of metal ions affects the production of leptin in adipocytes by controlling the release of free fatty acids and the uptake of glucose. This emphasizes that obesity is a major risk factor for coronary heart disease [81],[82].

According to Kalita et al., fluctuations in trace elements can enhance insulin resistance in individuals diagnosed with type 2 diabetes. Many enzymes involved in diabetes rely on magnesium and manganese as cofactors. Their inadequate amount increases the likelihood of metabolic syndrome, impairs glucose metabolism, and can result in atherosclerosis [83], [84]. Li et al. found a significant association between the level of selenium in the serum and the risk of death from any cause, in both men and women. This association was particularly strong in women with coronary heart disease. [85].

2.1.5. Prevention of CAD

2.1.5.1. Life style management

2.1.5.1.1. Diet Management of CAD Risk Factors

Appropriate dietary management is a crucial aspect in controlling the risk of coronary artery disease (CAD). The AHA dietary guidelines define population goals, which include adopting a healthy eating pattern, keeping a suitable body weight, and reaching perfect cholesterol levels and blood pressure levels and the importance of aligning energy intake with overall energy needs and achieving a balance between energy expenditure and energy intake (Krauss et al., 2000). In order to maintain BMI, individuals should ensure that their level of physical activity aligns with their energy consumption[86].These goals are described in (Table 01). The AHA guidelines advocate for the intake of a diverse range of foods from all food groups, with a particular focus on fruits and vegetables, fat-free and low-fat dairy products, cereal and grain products, legumes and nuts, and fish, poultry, and lean meats.

Table 01: Overview of nutritional recommendations [87].

	Population goals			
	Overall healthy eating pattern	Appropriate body weight	Desirable cholesterol profile	Desirable blood pressure
Major guidelines	Include a variety of fruit, grains, low-fat or nonfat	Match energy intake to energy needs with	Limit foods high in saturated fat and cholesterol;	Limit salt and alcohol; maintain a healthy body weight

	dairy products, fish, legumes, poultry, lean meat	appropriate changes to achieve weight loss when indicated	and substitute unsaturated fat from vegetables, fish, legumes, nuts	and a diet with emphasis on vegetables, fruits, and low-fat or non-fat dairy products

An analysis of a large randomized controlled study (the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) 5 trials) found that individuals who modify their behavior (by quitting smoking, adjusting their diet, and exercising) after experiencing acute coronary syndrome (ACS) have a reduced risk of experiencing another cardiovascular event in a 6-month period. The advantages of each behavior modification are cumulative, since the individuals who did not make any changes had the highest chance of experiencing another cardiovascular incident (odds ratio [OR] 3.77; 95% confidence interval [CI] 2.40–5.91; $p < 0.0001$)[87].

2.1.6. Strategy therapy for CAD

2.1.6.1.Invasive coronary revascularization

ACS individuals should have prompt evaluation in order to prevent significant cardiac damage and hemodynamic problems. The initial assessment distinguishes patients experiencing a life-threatening emergency from those with a less severe condition. After the diagnosis of STEMI, it is important to promptly create a reperfusion therapeutic approach.

2.1.6.2.Aspiration Thrombectomy

Aspiration thrombectomy is a minimally invasive operation that involves removing a blood clot from a blood vessel using suction with specialized catheterization procedures. This method is a fast and efficient means to eliminate blood clots in the leg arteries below the inguinal ligament in cases of thromboembolic occlusions[88].

2.1.6.3. Antiplatelet and antithrombin therapies

Anticoagulants such as unfractionated heparin and low molecular-weight-heparin are used in combination with antiplatelet during the initial management of ACS, but often not recommended post discharge. [87].

2.1.6.4. Antithrombotic Agents

Antiplatelet therapy decreases the risk of thrombosis by inhibiting platelet release and aggregation. The primary medications commonly employed for the treatment of CAD include Aspirin, adenosine diphosphate P2Y12 receptor antagonists (such as Clopidogrel, prasugrel, and ticagrelor), as well as glycoprotein IIb/IIIa inhibitors (such as abciximab and eptifibatide). Aspirin should be administered

promptly following the diagnosis of ACS, with a dosage of 160-325 mg, and continued at a long-term dosage of 81-100 mg [88]. An oral P2Y12 inhibitor is prescribed for patients who are undergoing primary percutaneous coronary intervention (PCI). Prior to percutaneous coronary intervention (PCI), it is necessary to administer a loading dose, which should then be maintained for a duration of one year .According to O'Gara et al. (2013), administering aspirin at a dosage of 81-150 mg per day in patients with SCAD resulted in a 20-25% decrease in cardiovascular mortality and morbidity [89].

2.1.6.5.B-blocker

These medications lower the amount of oxygen the heart muscle uses, decrease the heart rate, lower blood pressure, and decrease the strength of the heart's contractions. Patients with acute coronary syndrome (ACS) are advised to receive these treatments within 24 hours, unless they have heart failure or cardiogenic shock. [89]

2.1.6.6. Inhibitors of the renin-Angiotensin system

It is recommended to start the administration of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) within the initial 24 hours for patients with acute coronary syndrome (ACS) who have heart failure, a big area of heart muscle damage (massive MI), or a left ventricular ejection fraction (EF) below 40%. These medications decrease the rate of death and illness in specific patients. When using ACE inhibitors or ARBs, it is essential to regularly evaluate serum creatinine levels, potassium levels, and blood pressure [89].

2.1.6.7. Statin

Statin therapy is advised for all patients who have coronary artery disease (CAD). Initiating treatment with a high intensity dose of statin medication in acute coronary syndrome (ACS) results in a 3.9% decrease in the absolute risk of death from any cause, recurrent myocardial infarction (MI), re-hospitalization, and stroke[90].

2.2. Cerebrovascular accident: Stroke

A stroke, also known as a cerebrovascular accident (CVA), is a condition characterized by a sudden focused injury to the central nervous system (CNS) caused by a vascular problem. It is a kind of cardiovascular disease includes the central vessels of nervous system [91].It describes two processes: brain ischemia caused by thrombosis, embolism, or systemic hypoperfusion, and brain hemorrhage caused by intra Cerebral Hemorrhage (ICH) or subarachnoid hemorrhage (SAH). Approximately 80% of strokes in high-income countries (HIC) are caused by ischemic cerebral infarction, whereas the remaining 20% are attributed to brain hemorrhage. [92]

2.2.1. Atherosclerosis and stroke

The development of atherosclerosis is accelerated by significant risk factors, including hypertension, diabetes, obesity, chronic inflammation, and elevated levels of oxidized lipoprotein.

Hemorrhage within the plaque contributes to the gradual constriction of the lumen. The endothelial integrity becomes compromised and unstable, resulting in the adhesion and aggregation of platelets and the formation of a thrombus [92].

2.3. Peripheral artery disease

Peripheral artery disease (PAD) includes all atherosclerotic issues found in all arterial beds, excluding the coronary arteries. The term LEAD is used to refer to conditions that specifically affect the lower limbs [93].

2.3.1. Atherosclerosis and LEAD

LEAD and CAD have a similar etiology, which involves the development of atherosclerotic alterations in three stages: beginning of the lesion, advancement of the lesion, and plaque complication resulting in arterial stenosis. The increase in resistance in the vascular system during exercise, caused by the severity of stenosis, blood viscosity, and flow velocity, leads to a decrease in oxygenation of the muscles. Intermittent claudication (IC) arises as a result of reduced blood flow. Thrombus formation can partially or totally block the blood vessel, resulting in ischemia, claudication, and rest discomfort or ulceration [94]. Chronic ischemia results in the accumulation of lactate and acylcarnitine in the lower extremities, which leads to muscular degeneration, denervation, and atrophy [95].

2.4. Hypertension

Hypertension is a significant global public health issue. Hypertension (HTN) is characterized by a Systolic Blood Pressure (SBP) of 140 mmHg or higher and/or a Diastolic Blood Pressure (DBP) of 90 mmHg or higher. It can also be diagnosed if the individual is taking antihypertensive medicines or has been informed by a healthcare practitioner on at least two occasions that they have HTN (Table 02). Optimal levels of both systolic and diastolic blood pressure are crucial for the proper functioning of important organs such as the heart, brain, and kidneys, as well as for overall health and well-being [96].

Table 02: The classification of blood pressure according to the World Health Organization (WHO)[97].

Normal	Systolic: less than 120 mmHg Diastolic: less than 80 mmHg
A risk (prehypertension)	Systolic: 120-139 mmHg Diastolic: 80-89 mmHg
High	Systolic: 140 mmHg or higher Diastolic: 90 mmHg or higher

2.4.1. Hypertension and CAD

Expansion of vascular smooth muscle cells, leading to constriction of the blood vessel. Angiotensin II, by activating the AT-1 receptor, stimulates the production of inflammatory mediators and reactive oxygen species in the blood vessel wall. Consequently, it actively contributes to the process of inflammation. These mechanisms are all gradual processes that require several years to mature. This data suggests that hypertension is more strongly linked to the development of coronary artery disease (CAD) in later stages rather than in earlier stages [96].

2.5. Heart failure

Heart failure (HF) is a clinical illness that occurs when there is a structural or functional problem with the way the heart fills or pumps blood. Presently, Heart Failure (HF) is categorized into three distinct groups: HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), and HF with midrange ejection fraction (HFmrEF). Despite significant progress in the treatment of heart failure with reduced ejection fraction (HFrEF) during the past few decades, it remains a life-threatening condition [98].

2.5.1. Heart failure and CAD

Heart failure (HF) is a medical condition characterized by abnormalities in the structure and function of the heart muscle, leading to difficulties in the heart's ability to fill with blood or pump it out effectively. Reduced left ventricular myocardial function is the primary cause of HF. However, HF can also be caused by dysfunction of the pericardium, endocardium, heart valves, great arteries, and right ventricular myocardium, either individually or in combination.

Coronary artery disease (CAD) is now recognized as the main risk factor for the development of heart failure (HF), mostly because of better survival rates after acute myocardial infarction (AMI) and a decrease in the number of people with hypertension and valvular heart disease [99]. A recent systematic review of the literature found that ischemic heart disease is the main cause in over 50% of people with heart failure in North America and Europe [100].

2.6. Congenital heart defect

Approximately 1% of all newborns are identified with a congenital heart defect (CHD), which is the most prevalent significant birth abnormality [101]. The population of adult patients with congenital heart disease (ACHD) is steadily expanding due to significant advancements in early diagnosis, medical, and surgical therapy, which enable more children with CHD to reach adulthood and live longer lives [102]. These adult patients with congenital heart disease (CHD) are at risk of developing cardiovascular

disorders, such as coronary artery disease (CAD), cerebrovascular disease, and heart failure, similar to individuals of the same age without CHD[103].

2.6.1. Congenital heart defect with CAD

The presence of coronary anomalies, surgical interventions, endothelial dysfunction, and conventional cardiovascular risk factors are predisposing factors that are likely to interact in certain congenital anomalies to produce coronary artery disease in adults with congenital heart disease. Mounting data indicates that patients with adult congenital heart disease (ACHD) are at a greater risk of developing coronary artery disease (CAD), acute myocardial infarction (AMI), and other acquired cardiovascular diseases (ACVD) compared to individuals without ACHD [104], [105].The findings also indicated a rise in coronary artery disease (CAD) rates, with an increase from 0.3 cases per 1000 patient-years at age 20 to 5.8 cases at age 70 in women, and from 0.5 to 7.8 cases in men. These results highlight that the disparity in ACHD-related risk is greater among females. Furthermore, it is worth mentioning that the overall occurrence of coronary artery disease (CAD) did not show a significant increase in cases of mild congenital heart disease (CHD). However, it was notably elevated by a factor of 2 in cases of moderate CHD and by a factor of 3 in cases of severe CHD. This suggests that the risk of CAD rises in proportion to the severity of the congenital heart defect [106].

A recent study that included 17,189 individuals with adult congenital heart disease (ACHD) and 180,131 controls without congenital heart disease (CHD) found that the risk of acute myocardial infarction was 1.6 times higher in the ACHD group compared to the control group. The risk difference remained significant even after adjusting for exposure to cardiovascular risk factors and increased further with advancing age of the individuals [107].

2.7. Peripheral vascular accident

Peripheral vascular disease (PVD) includes both peripheral artery disease (PAD) and venous disease. PAD is a long-term and increasing condition caused by the buildup of fatty deposits in the arteries, resulting in the narrowing or complete blockage of blood vessels in the limbs. Peripheral artery disease (PAD) commonly impacts the abdominal aorta, iliac arteries, lower limbs, and sometimes the upper extremities.[108]. Peripheral artery disease (PAD) impacts approximately 200 million individuals globally and is becoming increasingly significant on a global scale due to longer life spans and prolonged exposure to risk factors. [109][110] Peripheral artery disease (PAD) is a condition that is comparable to cardiovascular disease. It is characterized by a high risk of both fatal and non-fatal cardiovascular events, including myocardial infarction (heart attack) and stroke.[111].

2.7.1. Peripheral vascular accident and CAD

Peripheral vascular disease is mostly caused by the development of atherosclerotic disease, which results in malfunction of both large and small blood vessels. Peripheral artery disease (PAD) commonly affects the blood vessels in the lower extremities, but it often also affects larger arteries including the abdominal aorta and iliac arteries. Severe disease can include both multilevel and distributed disease. Atherosclerosis is a multifaceted inflammatory response that involves several types of cells in the blood vessels, proteins that promote blood clotting, and substances related to cholesterol and inflammation[112].

2.8.Rheumatic heart disease

Rheumatic heart disease (RHD) is an important contributor to cardiac morbidity and mortality in the children and young adult population. Globally, Rheumatic Heart Disease (RHD) impacts around 15.6 million individuals annually, resulting in approximately 300,000 fatalities each year. 1,2 The eradication of RHD in industrialized countries is mostly attributed to improved living conditions and the extensive utilization of antibiotics. 3 Recent research indicate that globalization, migration, and refugee crises have resulted in the emergence of RHD in industrialized countries, so transforming it into a worldwide health issue[113].

2.8.1.Rheumatic heart and CAD

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are not fully understood. ARF occurs when the immune system mistakenly attacks the throat after infection with group A Streptococcal bacteria, more likely in genetically vulnerable individuals. RHD in autoimmune rheumatic diseases can be attributed to various pathophysiological mechanisms, including inflammation, perfusion defects, abnormal vasoreactivity, myocardial fibrosis, coagulation abnormalities, pulmonary hypertension, and immunomodulatory medication effects. [114][115]

2. 9. Metabolic syndrome

According to (WHO) The metabolic syndrome including visceral obesity, dyslipidemia, hyperglycemia, and hypertension, is a significant global public health issue. It has been linked to cardiovascular risk factors for over 80 years. The concept of syndrome X, introduced by Reaven in 1988, includes insulin resistance, hyperglycemia, hypertension, low HDL-cholesterol, and elevated VLDL-triglycerides. However, Reaven excluded obesity, which is now considered a crucial element, particularly visceral obesity.[116]–[118]

2.9.1. Metabolic syndrome and CAD

Metabolic syndrome is linked to an increase in inflammatory markers, which may predict cardiovascular events like heart attack, stroke, and peripheral artery disease. The enlarged visceral adipose depot stores cytokines and adipokines, which modulate the immune system's interactions with the vascular wall. Atherosclerosis is an inflammatory illness characterized by macrophage and T lymphocyte infiltration into blood vessel walls and lipid accumulation. The immune system's role in atherosclerosis is not fully understood, but recent studies highlight its role in initiating inflammatory pathways when tissue damage occurs. This review focuses on metabolic disturbances that play a crucial role in the intricate interactions between the immune system and the arterial wall in atherosclerosis, focusing on the mechanisms that trigger immunological activation.[119].

III.Epidemiology of Cardiovascular disease and coronary artery disease

1.Estimation framework of IHD

The burden of ischemic heart disease (IHD) was assessed using common epidemiological metrics, such as prevalence, incidence, mortality rates, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life years (DALYs). These parameters were analyzed in relation to age, sex, country, and socio-demographic index (SDI), allowing for comparisons over time. The incidence and prevalence rates were derived from a comprehensive set of population-representative data. The Global Burden of Disease (GBD) utilizes a carefully standardized approach to calculate mortality rates attributed to various causes. This method relies on vital registration data that is classified according to the International Classification of Disease (ICD) codes 1,22. Additionally, verbal autopsy data is incorporated into the Cause of Death Ensemble Model to generate temporal patterns.

YLLs were determined by reducing the age of death from the maximum life expectancy specific to each country. YLDs were calculated by multiplying the prevalence of IHD by its disability weights. DALYs were calculated by adding together the years of life lost (YLLs) and the years lived with disease (YLDs) [120], [121].

2.CAD in Algeria

The most recent Global Burden of Disease study in 2017 identifies ischemic heart disease (IHD), including Acute Myocardial Infarction (AMI), as the primary cause of years of life lost and a significant contributor to morbidity and mortality in Algeria. There has been a substantial and rapid increase in mortality related to these diseases during this period, with the number of deaths rising from 42,528 in 1990 to 79,389 in 2017 [122]. The number of mortality reached 161.300 deaths approximatively 79% in 2022 [123].The rapid advancement in Algeria is associated with a quick and significant shift in the spread of diseases (caused by economic disruptions), unrestrained urban development, and unregulated global integration. There is a lack of research focused on investigating the frequency of these risk factors in these countries, which are seeing a growing impact from this problem.[124]

3.CVD In the world

Non-communicable diseases (NCDs) are the primary cause of death globally. In 2016, they accounted for 71% (41 million) of the total 57 million deaths worldwide. The primary non-communicable diseases (NCDs) that caused these fatalities were cardiovascular diseases, resulting in 17.9 million deaths. This accounts for 44% of all NCD deaths and 31% of all deaths worldwide. [125].

Cardiovascular disease (CVD) is a major problem for the public and is the primary cause of death worldwide, with the exception of Sub-Saharan Africa. According to the World Health Organization (WHO) for the year 2019, the mortality rate attributed to cardiovascular disease in each population reached 90,000.

In the years 2011-2014, the occurrence of cardiovascular disease (CVD) among individuals in the United States who were above the age of 25 was 36.6% [126].In the United Kingdom in 2012, cardiovascular disease (CVD) was the second leading cause of mortality, accounting for 28% of all deaths. Of these deaths, 46% were due to coronary artery disease (CAD) and 26% were due to stroke [127]. It is responsible for 45% of all deaths in Europe and 37% of all deaths in the European Union, as reported by Wilkins et al. in 2017. Although there is a decrease in cardiovascular diseases (CVD) in established countries, emerging countries are experiencing a significant increase in the prevalence of non-communicable diseases (NCDs) in general, including CVDs and their associated risk factors (RF). [128].

According to Benjamin et al. (2017), about 92.1 million adults in the United States have been diagnosed with at least one type of cardiovascular disease (CVD)[129]. According to a study by Heidenreich et al. (2011), it is anticipated that by 2030, 43.9% of the population in the USA will have some type of cardiovascular disease (CVD)[130].

4.In the Arab countries

The Eastern Mediterranean region (EMR) consists of 23 countries, including Arab states in North East Africa (Djibouti, Egypt, Somalia, Sudan), North West Africa (Libya, Morocco, Tunisia, and Algeria), and the Gulf Cooperation Council (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, and Yemen). The second group includes Iraq, Jordan, Lebanon, Palestine, and Syria. The Eastern Mediterranean Region (EMR) contains non-Arab nations such as Afghanistan, Iran, and Pakistan.[127]

The Arab Middle East countries, characterized by a significant proportion of young individuals aged 17-28 years, have experienced fast socioeconomic transformations, political wars, poverty, moderate economic progress, instability, and an evolution in disease epidemiology. [131]

The Arab countries, namely Iraq, Syria, Lebanon, Jordan, Egypt, Yemen, and Turkey, exhibit different levels of mortality related to cardiovascular disease (CVD). The mortality rates vary from 145 deaths per 100,000 inhabitants in Qatar to 548 deaths per 100,000 individuals in Yemen. Significantly, there exist substantial disparities in cardiovascular disease (CVD) mortality rates across urban and rural regions within these nations. [131]

These nations only conducted a limited number of community-based studies. Conversely, Arab Gulf states possess a larger quantity of data pertaining to cardiovascular disease (CVD). These countries have

undergone rapid modernization and socioeconomic progress. Ischemic heart disease and stroke are among the top five primary causes of death in the Arab world. The mortality rate of ischemic heart disease is 90.3 deaths per 100,000 persons, according to Mokdad et al. (2016). [132]

5.Coronary artery disease in the world

CAD accounts for roughly 30% to 50% of all cases of cardiovascular disease (CVD) in the United States. Approximately 7% of the American population, which is equivalent to around 18 million individuals aged 20 and above, suffer from CAD. The prevalence of CAD is 7.4% in males and 6.2% in females. In 2016, the number of deaths attributed to coronary artery disease (CAD) was approximately 360,000 individuals, with over 110,000 deaths directly caused by a myocardial infarction (MI). Approximately 730,000 Americans get a new coronary attack annually, whereas 355,000 Americans suffer recurring attacks. Although CAD continues to be a significant contributor to illness and death, progress has been achieved in reducing both the relative and absolute rates of deaths linked to CAD by around 32% and 15% respectively. [133]

Coronary artery disease (CAD) accounts for around 13.2% of all deaths worldwide. [134]
In the United States of America (USA), it accounts for 25% of all deaths, the prevalence of coronary artery disease (CAD) among adults aged 75 years or older in European countries ranges from 27% to 34%.Coronary artery disease (CAD) was responsible for 16% of male deaths and 10% of female deaths in the United Kingdom (UK). [135].

The mortality rate has decreased in high-income countries (HIC). The death rate linked to acute coronary syndrome (ACS) has decreased in the SWEDEHEART data throughout the last thirty years [136]. The prevalence of coronary artery disease (CAD) in individuals aged 20 years and older in the USA was 6.3%. The prevalence of the condition was 7.4% among males and 5.3% among females [137]. There is a notable association between sudden death and cardiac disease. Autopsies and death certificates have revealed that 62-85% of individuals who passed away outside of a medical facility had a preexisting medical condition known as coronary artery disease (CAD). [138].

In the Middle East, the mortality rate from coronary artery disease (CAD) was higher than in Western countries like the United Kingdom (UK), Germany, and the USA. The INTERHEART study, which examined the factors that contribute to the initial occurrence of a myocardial infarction (heart attack) in 52 nations, found that the Middle East population had a median age of 51 years when experiencing their first heart attack. The age was 12 years below the median age observed in western countries. [139]

6.International studies

6.1. Framingham study

The initiation of the Framingham Heart Study (FHS) occurred in 1948. The study was named after Framingham, a town in eastern Massachusetts that was selected as the study site. The effort was initiated under the supervision of the National Heart, Lung, and Blood Institute in collaboration with the Boston University School of Medicine. The aim of the study was to determine the prevailing risk factors or characteristics that lead to cardiovascular disease (CVD). The study included a majority of the adult population, specifically 5,200 participants from Framingham city, who were between the ages of 30 and 62. In 1972, an extra 5,120 individuals, who were the offspring of the original study participants and their partners, were added to the cohort.

In 2001, a new group of individuals belonging to the third generation was included to the study. This group consists of the descendants of the initial participants. The inclusion of this cohort aims to examine genetic factors and advance the research on cardiovascular disease (CVD). Furthermore, the study incorporated the OMNI 1 and OMNI 2 cohorts in 1994 and 2003, respectively, with the explicit aim of encompassing the diverse racial and ethnic composition of the town of Framingham.

Every two years, the participants in the study got medical checkups and filled out a detailed questionnaire on their lifestyle [140].

In 1961, Dr. William Kannel, the director of FHS, published the first study on the association between coronary heart disease and risk variables including age, male gender, hypertension, high cholesterol, diabetes mellitus, and electrocardiographic left ventricular hypertrophy. In addition, there were papers on hypertension (HTN) and its association with cardiovascular disease (CVD), studies on lipids and their relationship to coronary artery disease (CAD), and the influence of lifestyle factors on CVD. The data collected mentioned here serve as a core knowledge foundation that may be utilized to guide public health programs focused on reducing cardiovascular disease (CVD). [141][142][143].

6.2. The Prospective Urban Rural Epidemiology (PURE) study

The PURE project is extensive epidemiological research that involved 150,000 participants aged 35 to 70. The participants resided in around 600 communities that were selected from 17 nations, comprising 3 high-income countries, 7 middle-income countries, and 7 low-income countries, encompassing different regions of the world. The PURE research was undertaken to collect data on socioeconomic position, medical history, lifestyle behaviors (such as smoking, physical activity, and diet), anthropometric measures, as well as biological and genetic components. [144]

PURE examines countries categorized by socioeconomic level and analyzes the disparities between rural and urban communities [145].

The main discoveries revealed that there is a higher occurrence of severe cardiovascular disease (CVD), fatal CVD, and total mortality in low-income countries (LIC) when compared to high-income countries (HIC).

PURE affirms that the collective impact of cardiovascular disease (CVD) is similar among high-income countries (HIC), middle-income countries (MIC), and low-income countries (LIC). The data from PURE suggest that urban communities saw a reduced prevalence of cardiovascular disease (CVD), but a higher incidence of non-major cardiovascular events in comparison to rural areas. The lower rate of deaths related to heart and blood vessel diseases in cities can be explained by the presence of many hospitals and better access to healthcare services compared to rural areas. • A study conducted by Chow et al. in 2013 found that high-income countries have better management of high blood pressure compared to low-income countries.[146].

VI. Risk factors for CAD

1. Modifiable risk factors

According to the WHO, the primary cause of the rise in non-communicable diseases (NCDs) is the presence of elevated levels of preventable risk factors that are widely prevalent. The four primary non-communicable diseases (cardiovascular disease, cancer, chronic respiratory illness, and diabetes) are directly associated with four prominent behavioral risk factors: tobacco use, excessive alcohol use, physical inactivity, and a poor diet. Consequently, these behaviors result in four significant metabolic/physiological alterations: increased blood pressure, excessive weight/obesity, elevated blood glucose levels, and elevated blood lipid levels. Environmental air pollution is a significant risk factor [147].

1.1. Harmful use of alcohol

Alcohol abuse is a major contributor to early deaths and disabilities on a global scale, leading to many health issues such as heart diseases, cancers, liver diseases, mental and behavioral disorders, non-communicable conditions, and communicable diseases [148]. The Global NCD Action Plan, adopted by the World Health Assembly in 2010, includes a worldwide effort to decrease the detrimental consumption of alcohol [149].

Excessive alcohol consumption ranks as the third most significant factor contributing to premature mortality, following smoking and obesity. [150] whereas consuming 3-5 drinks is linked to a 50% higher mortality rate compared to individuals who do not drink. Alcohol consumption is linked to elevated levels of HDL-C, reduced levels of LDL-C, and decreased fibrinogen levels, resulting in a decrease in platelet aggregability [151].Consuming alcohol in moderation was also linked to a reduced risk of myocardial infarction (MI) [152].

1.2. Smoking

Approximately 30-40% of yearly fatalities have been calculated to be linked to coronary artery disease (CAD), specifically caused by smoking. Case-control and cohort studies, encompassing a total of 20 million individuals, unequivocally demonstrate that smokers have a significantly increased risk of death from coronary artery disease (CAD) compared to non-smokers. particularly when combined with other significant risk factors like diabetes. In patients with established coronary disease, it can cause temporary myocardial ischemia and is a strong risk factor for acute myocardial infarction and sudden cardiac death. Women have greater risks than men, particularly in younger age groups.[153]

Studies have shown that individuals who smoke have a 70% higher risk of dying from coronary artery disease (CAD) compared to those who do not smoke. Smoking has been found to directly or indirectly impact the development of atherosclerotic lesions, leading to increased morbidity and mortality from coronary artery disease (CAD).

Smoking contributes to the blockage of coronary arteries by causing damage to the inner lining of blood vessels and promoting the accumulation of platelets in the layer's underneath. This leads to an increase in the infiltration of fats and the growth of smooth muscle cells, which is mediated by a substance called platelet-derived growth factor (PDGF) .[154] Countries must intensify effective tobacco control initiatives to achieve a global reduction of 30% in tobacco prevalence by 2025.

1.3. Obesity

Obesity, which refers to the excessive buildup of fat in the adipose tissues, is a prevalent factor contributing to cardiovascular fatalities in developed nations .Excessive adipose tissue in the abdomen visceral region can result in the development of atherosclerotic disease [155]. The disruption of the adipocyte-derived endocrine hormones that occurs during overnutrition is believed to contribute to the progression of atherosclerosis [156].

Obesity is strongly correlated with higher rates of coronary artery disease (CAD). However, adiposity is typically accompanied by other risk factors like hypertension, glucose intolerance, and lower levels of HDL-C. Central obesity, commonly measured by the waist-to-hip circumference ratio, is strongly linked to coronary artery disease (CAD). It is also often accompanied by elevated cholesterol levels and insulin resistance, which can further worsen the condition.[157]

1.4. Glucose Intolerance and Diabetes Mellitus

Diabetes is a chronic disease that arises due to insufficient insulin production by the pancreas (type 1 diabetes) or the body's inability to efficiently utilize the insulin it generates (type 2 diabetes). Insulin, being a hormone that controls blood sugar levels, leads to elevated blood glucose in both types of diabetes, which can eventually lead to significant harm to the body. The heart, blood vessels, eyes, kidneys, and nerves are particularly susceptible to the effects of this condition.

Diabetes poses a significant risk to public health and is a major contributor to illness, death, and healthcare expenses worldwide. It is one of the four main non-communicable diseases (NCDs) that world leaders have identified as a priority for intervention, as stated in the 2011 political declaration on NCD prevention and control. The objective of the global non-communicable disease (NCD) aim is to prevent any further increase in the prevalence of diabetes above the levels recorded in 2010 by the year 2025. [158]. Insulin resistance, hyperinsulinemia, and glucose intolerance are all factors that seem to contribute to the development of atherosclerosis. Diabetic individuals possess a higher number of atherogenic risk factors, such as hypertension, hypertriglyceridemia, an increased cholesterol-to-HDL ratio, and elevated levels of plasma fibrinogen, compared to nondiabetic individuals. Consequently, the risk of coronary artery disease (CAD) in diabetic individuals varies significantly depending on the severity of these risk

factors. Patients with diabetes have a 2.6 times higher risk of cardiovascular death compared to patients without diabetes.[159]

1.5. Hypertension

Hypertension, or elevated blood pressure, is a major contributing factor to a range of health problems, such as coronary heart disease, chronic renal disease, and different types of strokes (ischemic and hemorrhagic). [160]

There has been significant diversity in the definition of hypertension. The latest guidelines established by the AHA, American College of Cardiology (ACC), and American Society of Hypertension define hypertension as a systolic blood pressure above 130 mm Hg or a diastolic blood pressure above 80 mm Hg. 20 In contrast, the guidelines of the European Society of Cardiology (ESC) have a stricter definition for hypertension, requiring a systolic blood pressure (BP) above 140 mm Hg or a diastolic BP above 90 mm Hg (Table 03). 21 Irrespective of the exact threshold used to define hypertension, it continues to be a major contributor to illness and death on a global scale [133].The PROCAM study has demonstrated a significant correlation between hypertension and CAD. This study found a high prevalence of hypertension in patients with MI throughout a 4-year follow-up period [161].

There is a pathophysiologic connection between hypertension and CAD, as arterial hypertension can worsen atherosclerosis [162]. The accumulation of lipids and the development of atherosclerotic plaques in the arteries lead to an elevation in transmural pressure. The mechanical stress and endothelial permeability caused by it lead to a reduction in coronary responsiveness [162]. Hypertension is often linked to metabolic diseases such as insulin resistance, hyperinsulinemia, and dyslipidemia. These illnesses are widely recognized as risk factors for coronary artery disease (CAD) [163].

Table 03: Major guideline definitions for HTN [154]**.**

	SBP (mm Hg)		**DBP (mm Hg)**
ACC/AHA Guidelines			
Normal	<120	and	<80
Elevated	120-129	and	<80
Stage 1 HTN	130-139	or	80-89
Stage 2 HTN	≥140	or	≥90
ESC Guidelines			
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 HTN	140-159	and/or	90-99
Grade 2 HTN	160-159	and/or	100-109
Grade 3 HTN	≥180	and/or	≥110
Isolated systolic HTN	≥140	and	<90
ACC (American College of Cardiology); AHA (American Heart Association); DBP (diastolic blood pressure); ESC (European Society of Cardiology); SBP (Systolic blood pressure).			

The objective for hypertension in the global non-communicable disease (NCD) target is to achieve a 25% decrease in the proportion of individuals with elevated blood pressure by the year 2025.

Nevertheless, in some low- and middle-income nations, the rate has remained steady or shown signs of growth. The prevalence of hypertension in adults rose from 594 million in 1975 to 1.13 billion in 2015, primarily observed in low- and middle-income nations. [148]

1.6. Physical inactivity

Lack of physical activity is a major factor in the increase of chronic diseases (NCDs), as insufficient physical exercise raises the chance of death from any cause. Engaging in physical activity also reduces the likelihood of experiencing stroke, hypertension, and depression. In 2013, the World Health Organization (WHO) set a global goal of reducing physical inactivity by 10% by 2025.

Even a modest level of physical activity seems to provide a safeguarding effect against coronary artery disease (CAD). A study conducted on middle-aged men found that engaging in moderately vigorous physical activity was linked to a 23% reduction in the risk of death compared to those with a less active lifestyle. This improvement in survival was found to be equal and additional to other lifestyle factors such as quitting smoking, controlling hypertension, and managing weight. Possible explanations for the advantages of physical activity include increased levels of HDL cholesterol in the blood, decreased blood pressure, weight reduction, and a reduced occurrence of insulin resistance.[164]

1.7. Depression

The impact of stress on individuals varies, resulting in a range of health issues. Psychological stress stimulates the hypothalamic-pituitary-adrenocortical and sympathetic nerve systems, leading to inflammation, blood clotting, and disruption of metabolic and cardiac autonomic regulation. [165] Individuals who experience stress in their professional or personal lives have a 1.1 to 1.6 times higher chance of developing coronary artery disease (CAD) and stroke. Chronic stress induces illnesses in patients with elevated atherosclerotic plaque, resulting in cardiovascular events such as hypertension, insulin resistance, arrhythmia, myocardial ischemia, cardiac failure, and stroke (Figure 23).[44]

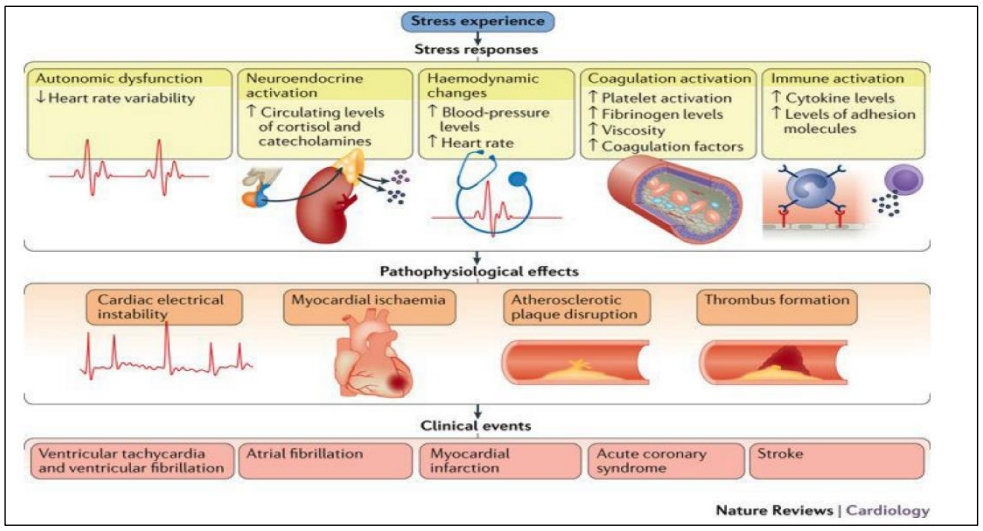

Figure 23: Effects of stress on the development of atherosclerosis [166].

1.8. Dyslipidemia

Dyslipidemia is a medical disorder marked by abnormal levels of lipids in the blood, specifically cholesterol and triglycerides, which are the primary lipoproteins. There is no empirical evidence to suggest that fasting is more effective than non-fasting when assessing a lipid profile for the purpose of predicting cardiovascular risk. Several nations are presently revising their protocols for assessing a lipid profile in the non-fasting condition to simplify blood sampling for patients, laboratory personnel, and doctors [167].

The serum's total cholesterol content is a significant and unequivocal risk factor for CAD. The Multiple Risk Factor Intervention Trial (MRFIT) conducted on a sample size of over 350,000 middle-aged American males revealed a direct correlation between greater levels of serum total cholesterol and an escalating risk of coronary artery disease (CAD). [168] Furthermore, findings from the Framingham Heart Study indicate that there is a significant negative correlation between HDL and CAD risk, a

significant positive correlation between LDL and CAD risk, and a weak correlation between triglycerides and CAD risk. Twenty-nine Over the past 35 years, it has been established that there is a direct correlation between lowering LDL levels and reducing negative health outcomes. Specifically, for every 38 mg/dL decrease in LDL, there is an approximate 23% decrease in major cardiovascular events. These findings were initially observed in the MRFIT study. [169] Among patients who have experienced many cardiac episodes, the most vulnerable group, it has been observed that significant decreases in LDL cholesterol levels, reaching as low as 30 and 50 mg/dL, continue to demonstrate a consistent and proportional connection, even at extremely low LDL levels [169].

Measuring triglycerides is crucial for assessing the risk of cardiovascular disease (CVD), particularly in those with diabetes, glucose intolerance, and insulin resistance. In both the Copenhagen City Heart Study and the Women's Health Study, there was a significant correlation between an increase in non-fasting triglyceride concentration of 5mmol/l or more, compared to less than 1mmol/l, and a substantial increase in adjusted age risks. Specifically, the risk of myocardial infarction (MI) increased by 17 times, the risk of ischemic heart disease (IHD) increased by 6 times, the risk of ischemic stroke increased by 5 times, and the risk of mortality from any cause increased by 4 times in women. Non-HDL cholesterol, also known as Non-HDL-C, is the second target to be achieved after LDL-C in individuals with diabetes[170].

1.9. Life style and Dietary Factors

An unhealthy diet is rich in calories, characterized by excessive consumption of fat, fat, sugar, carbs, high-fat meats, limited intake of fruits and vegetables, and whole grains, and insufficient amounts of vitamins and minerals and cholesterol is a contributing factor to the development of other risk factors, including obesity, hyperlipidemia, and diabetes, which increase the likelihood of developing coronary artery disease (CAD). Consuming red meat is also linked to a higher risk of overall, cardiovascular, and cancer-related death.[169][171]

Multiple studies have demonstrated a substantial correlation between diets that are rich in fiber and reduced risks of cardiovascular disease, including stroke and coronary artery disease .A recent study conducted among a sample of 65,226 individuals in England revealed that consuming seven or more servings of fruits and vegetables on a daily basis resulted in a 31% decrease in the risk of dying from heart disease [172]. Furthermore, reducing the amount of salt consumed in one's diet from 9-12 grams per day to the recommended level of 5 grams per day will significantly affect blood pressure and cardiovascular disease [173].

2. Non modifiable risk factors

2.1. Age

The aging process has a significant impact on the cardiovascular system, causing a gradual decline in the structure and function of the heart and blood vessels. This deterioration contributes to the development of cardiovascular disease (CVD) . [173]

Epidemiological studies have shown that the risk of cardiovascular events can vary greatly (4-5 times) at any age, depending on the presence of associated risk factors.

By the year 2030, the proportion of individuals aged over 65 years will reach 20% of the total population. Cardiovascular disease (CVD) will cause 40% of all deaths in this age range and will be the primary cause, according to North and Sinclair (2012).[174]

2.2. Gender

Cardiovascular disease (CVD), previously regarded as mostly affecting men, has been discovered to be more common in women than men within the European population. The disparity in cardiovascular risk arises from variations in gene expression and the functioning of the circulatory system. Over time, males encounter an elevated risk of cardiovascular issues and atherosclerosis. [174]

On the other hand, women are shielded from atherosclerosis while they are in their reproductive years due to the presence of estrogens, which have a beneficial impact on the cardiovascular system.

In the last fifty years, there has been a rise in the prevalence of coronary heart disease (CAD) and stroke in both males and females. The increased susceptibility to stroke in females is associated with their longer lifespan. [175]

Common risk factors for cardiovascular disease (CVD) include advancing age, high blood pressure, elevated total cholesterol and LDL-C levels, menopause, high systolic blood pressure, smoking, diabetes, elevated triglyceride levels, and low HDL-C levels.

Menopause, systolic arterial hypertension, smoking, diabetes, triglycerides, and HDL-C are the primary factors affecting women. Each 10 mmHg increase in systolic blood pressure (SBP) was found to be linked with a 15% higher risk of coronary artery disease (CAD) and a 25% higher risk of stroke in both males and females. Diabetes significantly raises the risk of cardiovascular disease by 3-7 times in women and 2-3 times in men. [175]

2.3. Family history

The presence of a familial history of heart attack in both parents significantly raises the likelihood of developing coronary artery disease (CAD), especially if one parent experiences a premature coronary event before the age of 50. (men below the age of 55 years and women below 65 years) [176]**.**

Research has demonstrated that having a family history of cardiovascular disease (CVD) raises the likelihood of developing CVD by 45% in both males and females [177].According to a recent study on individuals with premature ACS, 28% of females and 20% of males had a familial predisposition to CAD.

Individuals who have a family history of coronary artery disease (CAD) are more likely to have a greater occurrence of common cardiovascular disease (CVD) risk factors, including hypertension (HTN), diabetes mellitus (DM), dyslipidemia, and obesity. [178]

2.4. Menopause

The incidence of coronary artery disease is uncommon prior to menopause, with mortality rates of 1022 women under the age of 55 compared to 4600 males in the year 2000. Given that atherosclerosis is a disease that progresses slowly, it is probable that it begins before menopause. The premenopausal phase is

essential for lowering cardiac risk factors. The premenopausal female gender advantage may be diminished by trends in risk factor behavior, such as the rising prevalence of smoking among younger women. Estrogen, a type of female sex hormone, is believed to have a preventive effect against atherosclerosis in premenopausal women. However, there is currently no conclusive evidence to support a direct athero-protective action of estrogen. Exogenous sex hormones, such as combination oral contraceptives, pose a distinct risk factor for myocardial infarction in premenopausal women. [179]

Menopause is a natural process that indicates a change from reproductive to non-reproductive life, and is accompanied by physiological and hormonal alterations. The danger associated with post menopause is mostly attributed to a rapid decline in estrogen hormone levels, which play a crucial role in protecting lipid, glucose metabolism, and blood vessels [180].

2.5. Genetic risk factors

The significance of genetic risk factors in coronary artery disease (CAD) has increased due to the identification of the proprotein convertase subtilisin kexin type 9 (PCSK9) enzyme, which plays a crucial role in controlling cholesterol metabolism [181], [182]. PCSK9 gene mutations that result in increased function may be correlated with elevated cholesterol levels and an increased likelihood of cardiovascular diseases (CVDs). Conversely, mutations that lead to decreased function are connected with lower blood cholesterol levels and a decreased risk of CVDs, without any known negative consequences [183]. This involved a comprehensive evaluation of markers within the community, which utilized several research methods and included a total of 48,421 individuals and 3,477 events [183].

3. Another marker risk factors

3.1.Homocystinuria

Homocystinuria is a hereditary recessive disease that occurs due to a defect in the metabolism of methionine. Elevated levels of circulation homocysteine and urine homocysteine have been documented in this illness .Individuals afflicted with such problems have been discovered to be susceptible to early start of cardiovascular ailments. [184] Homocysteine has been implicated in the pathogenesis of atherosclerosis. Research indicates that homocysteine may have an impact on the coagulation system, and it has been observed that the endothelium is resistant to thrombosis[185].

3.2.Hyperuricemia

Hyperuricemia is commonly characterized as the presence of an abnormally high concentration of urate in the bloodstream. Serum uric acid is the result of the breakdown of purines in the body[186]. When the quantity of serum uric acid exceeds 6.8 mg/dl, it leads to hyperuricemia[187]. Research has shown a correlation between hyperuricemia and the risk of coronary artery disease (CAD) [188]

Several plausible mechanisms have been proposed to explain the association between uric acid and various factors. These mechanisms suggest that uric acid may stimulate the proliferation of vascular smooth cells, reduce the production and activity of nitric oxide in blood vessels, and potentially be linked to insulin resistance [189].

Nevertheless, the validity of these suggested pathways in establishing the association between serum uric acid and CAD risk is still a subject of debate. However, studies have shown that serum uric acid is positively linked to artery intima-media thickness, a forerunner of atherosclerosis .[190]

V.Oxidative stress

1. Definition

"Oxidative stress" is a widely recognized concept in the fields of redox biology and medicine. Oxidative stress was first defined in 1985 by Helmut Sies as "an imbalance in the levels of pro-oxidant and antioxidant substances, favoring the oxidant species leading to potential damage [191]. Oxidative stress is currently defined as the state of imbalance between the production of reactive oxygen/nitrogen species (ROS/RNS) and an organism's ability to counteract their harmful effects via antioxidative defense systems.The imbalance between an excess of reactive chemicals and a deficiency in natural defensive mechanisms results in harm to cellular structures and molecules, including lipids, proteins, and DNA. This ultimately plays a role in the development of various diseases. [192]

2.Physiology action of free radical

ROS, when present in optimal concentrations, function as signal transduction molecules that regulate cellular functions and offer cellular protection [193] Free radicals serve multiple advantageous functions for the organism. They are necessary for the synthesis of certain cellular structures and are utilized by the host defense system to eradicate pathogens. The crucial significance of reactive oxygen species (ROS) for the immune system is clearly demonstrated by patients suffering from granulomatous disease. These individuals have a faulty NADPH oxidase system, which prevents them from producing $O_2^{\bullet -}$. As a result, they are highly susceptible to multiple and often long-lasting infections [194], [195]. Free radicals have a crucial regulatory function in intracellular signaling cascades in various cell types, including fibroblasts, endothelial cells, vascular smooth muscle cells, cardiac myocytes, and thyroid tissue. Nitric oxide (NO) is well recognized as the most prominent free radical functioning as a signaling molecule. It serves as a vital intercellular messenger that is necessary for regulating blood flow, plays a role in the formation of blood clots, and is essential for appropriate neurological function [196]. It plays a role in general host defense, as it is necessary for the elimination of intracellular infections and tumor cells. Free radicals also have the ability to stimulate cell division, a process known as mitogenic response[197]. low or moderate quantities of free radicals is vital for human health.

3.The Adverse Impact of Free Radicals on Human Health

However, if ROS is produced excessively, such as in the case of inflammation, it can stimulate the generation of more highly reactive substances [198]. Of utmost importance is the oxidative modification of crucial enzymes or regulatory sites, which, when modified by redox reactions, leads to changes in cell signaling and programmed cell death. Oxidative stress and inflammation are strongly linked. Oxidative stress can lead to inflammation, which in turn triggers additional oxidative stress, creating an unhealthy cycle [199][200]. This cycle ultimately causes damage to cells and contributes to the development of a

pro-inflammatory environment [201]. Literature data confirm the key role of oxidative stress in etiology of numerous and different diseases, such as metabolic syndrome, atherosclerosis, cardiovascular disease, cancer, neurodegenerative disorders, diabetes, infertility, renal diseases, and gastrointestinal and hepatic diseases (Figure 24) [202].

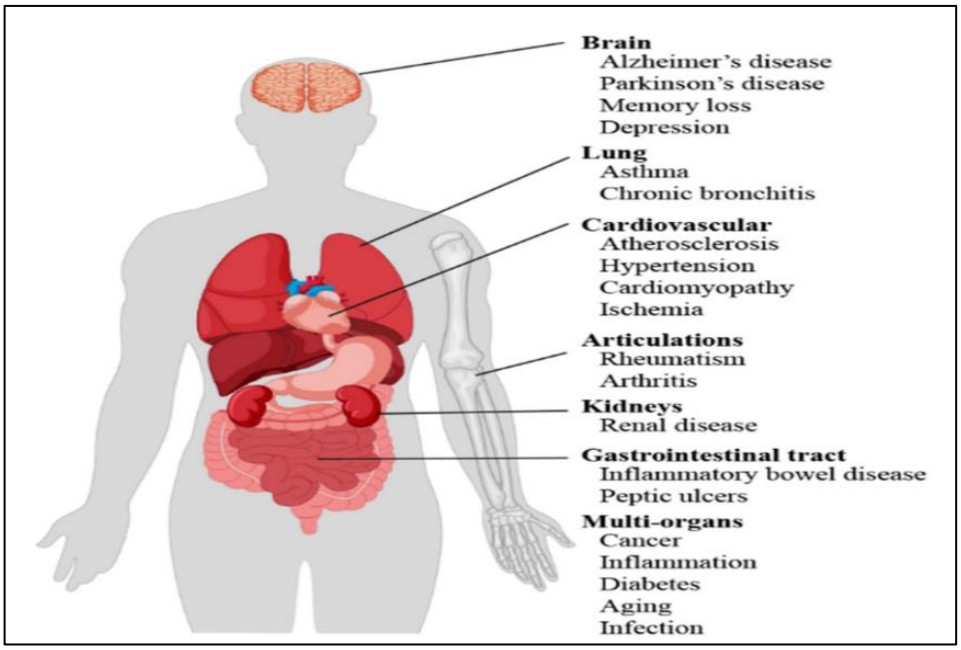

Figure 24: Pathophysiology of oxidative stress induced to disease in human [202].

4.Types of ROS

Pro-oxidant compounds can be classified into two categories: free radical species or non-radical species, Free radicals are molecules that possess one or more unpaired electrons, which contribute to the molecule's reactivity. When two free radicals combine and share their unpaired electrons, they produce nonradical molecules. that facilitate peroxidation. There are two primary groups: ROS (reactive oxygen species) and RNS (reactive nitrogen species)[204] .

The principal reactive oxygen species (ROS) are generated via the process of regular cellular metabolism using molecular oxygen. it has physiological significance are the superoxide anion (O2-), hydroxyl radical (OH•), and hydrogen peroxide (H2O2)[205]. These can generate more intricate compounds, such as peroxynitrite (ONOO-), hypochlorous acid (HOCl), and lipid peroxyl radicals. Peroxynitrite has the potential to undergo further reactions with carbon dioxide, resulting in the formation of a highly reactive compound called nitrosperoxycarbonate (Figure 25)[206].

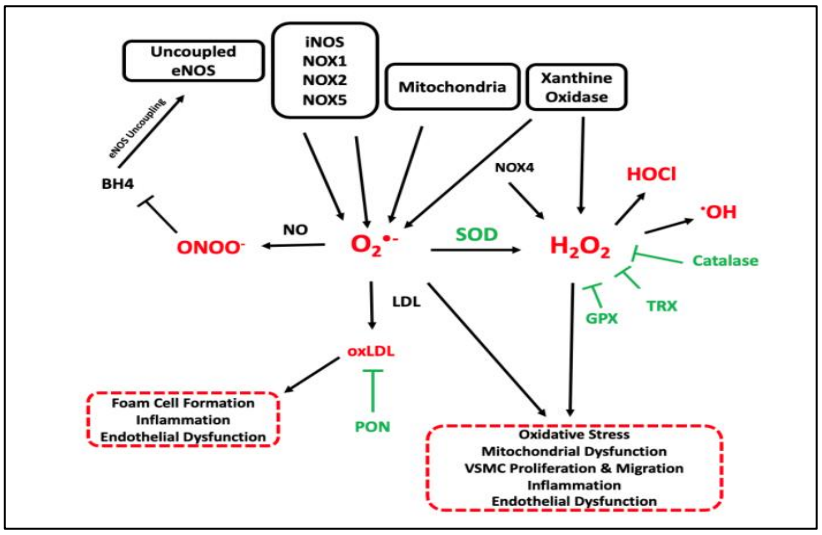

Figure 25: Schematic illustrate an overview of the vascular origins and roles of reactive oxygen species (ROS) in the development of atherosclerosis[207].

5. Source of ROS

5.1. Oxidant

The vascular wall contains various ROS-producing systems, such as NADPH oxidases, xanthine oxidase, mitochondrial respiratory chain enzymes, and uncoupled endothelial NO synthase (eNOS). These systems have mechanisms of cross-regulation, with ROS sources categorized into initial and secondary sources. The "kindling-bonfire radicals" theory suggests that primary ROS from NADH oxidase kindle the production of secondary sources and a tertiary source, the mitochondria, resulting in a "bonfire" of radicals and oxidative stress. This cascade of ROS production is identified as an inflammasome activator and an important mechanism underlying human inflammatory disorders[208], [209].

5.1.1. NADPH Oxidases

NADPH oxidases are complex enzymes composed of several subunits that generate superoxide by utilizing molecular oxygen and NADPH as the electron source. Their composition includes two subunits enclosed by membranes, namely p22phox and a Nox homologue, along with many regulatory subunits [210] found in the cytoplasm. Nox was initially discovered in the membrane of professional phagocytic cells of the immune system, but subsequent investigations revealed its existence in nonphagocytic cells such as endothelial cells and smooth muscle cells [211]. There are seven distinct kinds of Nox found in humans, specifically Nox1, Nox2, Nox3, Nox4, Nox5, Duox1, and Duox2. Out of all of them, only Nox1, Nox2, Nox4, and Nox5 are present in endothelium, vascular smooth muscle cells (SMCs), fibroblasts, or perivascular adipocytes at notable quantities. Nox homologues have significant roles in the development

of atherosclerosis [212], with Nox1 and Nox2 promoting atherosclerosis and Nox4 exhibiting an anti-atherosclerotic action. The Nox5 gene is not present in the rodent genome and represents the most difficult homologue to investigate36. Increased expression of Nox5 was detected in human atherosclerotic lesions and was linked to hypertension and diabetic nephropathy [213]. Transgenic mice expressing human Nox5 specifically in their podocytes developed early renal impairment[214].

5.1.2. Xanthine Oxidases

Xanthine oxidases are enzymes that produce hydrogen peroxide and superoxide anions, which are found in endothelial cells and blood plasma. They are elevated in atherosclerotic plaques and have been linked to the progression of atherosclerosis [215]. Oscillatory shear stress and angiotensin II therapy can enhance the expression and activity of endothelium xanthine oxidases. Studies have shown that xanthine oxidase inhibitors can reduce atherosclerosis development in mice lacking the apoE gene. Suppression of xanthine oxidase can decrease endothelial dysfunction in smokers [216], [217]. Xanthine oxidases also activate LOX-1 and CD-36 in macrophages and vascular smooth muscle cells. High concentrations of uric acid in the blood can cause gout and increase the occurrence of atherosclerosis-related events[218].

5.1.3. Uncoupled Endothelial Nitric Oxide Synthase

eNOS, an enzyme that generates nitric oxide (NO), is crucial for endothelial protection. However, oxidative stress [219] can impair the enzyme's function, leading to endothelial dysfunction. Excessive superoxide inactivates NO, causing eNOS to become uncoupled, generating superoxide instead of NO. Factors contributing to this uncoupling include a lack of eNOS cofactor tetrahydrobiopterin (BH4), a shortage of eNOS substrate l-arginine, and eNOS S-glutathionylation. Peroxynitrite, formed when nitric oxide reacts with superoxide, can oxidize BH4 [220], leading to a deficiency in BH4. In animals lacking the apoE gene, BH4 breakdown increases and eNOS function is disrupted, causing oxidative damage. ROS production by uncoupled eNOS has been observed in patients with atherosclerosis, hypercholesterolemia, hypertension, diabetes mellitus, and chronic smokers [221], [222].

5.2. Antioxidant

An antioxidant is a substance that has the ability to counteract the process of oxidation caused by reactive oxygen species (ROS), preventing them from interacting with cellular macromolecules and altering their structure or function [223], [224].The antioxidant defense mechanism operates at two levels:

The Primary defense mechanism system functions by directly neutralizing free radicals to prevent them from causing harm to biomolecules within cells, therefore inhibiting oxidative damage. Endogenous enzymes are crucial in this phase [225], [226].

5.2.1. Endogenous enzymatic antioxidant

5.2.1.1. Superoxide Dismutase (SOD)

The humans possess three isoforms of SOD [227]: cytosolic copper and zinc-containing enzyme (Cu-Zn-SOD), found in the space between mitochondrial membranes; manganese-requiring mitochondrial enzyme (Mn-SOD), found in the mitochondrial matrix; and extracellular copper and zinc-containing SOD (EC-SOD). Superoxide dismutase (SOD) reduce the extent of atherosclerotic lesions by decreasing the amounts of F2-isoprostanes and isofurans in the aorta. It also inhibits any participation of MCP-1 and VCAM-1.[228], [229]. Additionally, it converts the superoxide radical generating hydrogen peroxide (H2O2), so the inhibiting generation of peroxynitrite ($ONOO^-$) and the reduction of transition-metal ions[230].

$$O_2^- + O_2^- + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2$$

5.2.1.2. Catalase

Catalase is present in peroxisomes and it catalyze the decomposition of hydrogen peroxide (H2O2), into water (H2O) inside the cell [116]. Research has shown that catalases may improve the development of atherosclerosis in mice models that are fed a high-fat diet [117]. Research conducted on $apoE^{-/-}$ mice shown that reducing the amount of F2-isoprostanes in the aorta and improving the condition of atherosclerosis were observed when catalases were overexpressed in conjunction with SOD-1. The foam cells derived from atherosclerotic lesions in rabbit aortas exhibited increased catalase activity. In addition, this enzyme also causes a decrease in the proliferation of vascular smooth muscle cells (VSMCs) [118]. Nevertheless, the precise mechanisms behind this athero-protective action are yet unknown [234].

$$2H_2O_2 \xrightarrow{Catalase} 2H_2O + O_2$$

5.2.1.3. Thioredoxin

The Thioredoxin system comprises Thioredoxin (Trx) and Thioredoxin reductase (TrxR), which have the ability to decrease hydrogen peroxide and interact with specific proteins. The two mammalian isoforms of Trx (Trx1 and Trx2) and three izoenzymes of TrxR (Trx1-3) are widely distributed and can be found both within and outside of cells. Oxidant scavenging is carried out by Trx peroxidases or peroxiredoxins (Prx) [235].Clinical and experimental research have further confirmed the role of the Trx system in atherogenesis at various stages. The system has been demonstrated to have a significant impact on the control of metabolic processes, insulin signaling, blood pressure management, and inflammation.

Plasma Trx levels were shown to be elevated in patients with atherothrombosis. The inhibition of the cytosolic isoform of thioredoxin, Trx1, has been demonstrated to suppress the production of VCAM-1 and ICAM-1, hence preventing the start of atherosclerosis [236]. The inhibition of the mitochondrial isoform of thioredoxin, Trx2, could be responsible for the prothrombotic phenotype observed in mouse models, as well as the endothelial dysfunction [237]. The Trx system may regulate the inflammatory and chemotactic activities of macrophages throughout different stages of atherosclerotic plaque development, hence modulating their phenotypes [238]. As TrxR is an enzyme containing selenium, it could play a role in transmitting the positive effects of selenium supplementation on the development of atherosclerosis [239].

5.2.2. Endogenous Non-Enzymatic Antioxidants

Endogenous non-enzymatic antioxidants are small molecules that are present intra or extracellular of in lipid or water-based environment.

5.2.2.1. Glutathione Peroxidase (GPX)

Glutathione is selenocysteine enzyme, soluble in water, it is a significant antioxidant found in cells it plays a crucial role in regulating oxidative stress, inflammation and lipid hydroperoxides, to the corresponding alcohols. There are four known isoforms of GPXs in humans, each containing selenocysteine in the active site [240].Glutathione plays a significant role in atherosclerosis by controlling the growth of atherosclerotic lesions in the aortic arch by the removal of hydroxide (OH), hypochlorous acid (HOCl), and peroxynitrite (ONOO-)[241].

5.2.2.2. Coenzyme Q (CoQ)

Coenzyme Q is found in cellular membranes. Coenzyme Q10 is the primary form of a lipophilic antioxidant with anti-inflammatory effects that is present in humans. CoQ functions as an inhibitor of lipid and protein oxidation and decreases the conversion of α-tocopheroxyl radical to α-tocopherol. It has the ability to scavenge peroxyl radicals, which in turn enhances endothelial function.[242]

5.2.2.3. Paraoxonases

Paraoxonases (PON) are a group of enzymes that consist of three isoforms: PON1, PON2, and PON3. These enzymes shown the ability to decrease oxidative stress, decrease lipid peroxidation, and decrease the occurrence of atherosclerosis in animal models [243]. PON1 is linked to high-density lipoprotein (HDL), and when it is expressed at higher levels, it provides protection against atherosclerosis in mice lacking the apoE gene [244]. PON2 is produced by the endothelial cells of the vascular wall. Within the cell, it is located within the membranes of the endoplasmic reticulum (ER) and mitochondria.

PON2 possesses the capability to reduce the production of superoxide. The study demonstrated that it relocated to the plasma membrane in response to lipid peroxidation and reduced oxidative stress in mice models [245]. The expression of PON3 was observed to be diminished in vascular smooth muscle cells (SMCs) derived from atherosclerotic plaques, indicating its potential function in providing protection. In addition, PON3 has the ability to suppress the production of mitochondrial superoxide [246].

5.2.2.4. Nitric Oxide Synthases

Nitric oxide synthases (NOS) have the ability to either promote or inhibit oxidation processes in atherosclerosis. Endothelial nitric oxide synthase (eNOS) produces nitric oxide (NO) which is consistently expressed in endothelial cells. NO has the ability to hinder LDL oxidation, leukocyte adhesion and migration, vascular smooth muscle cell (SMC) proliferation, and platelet aggregation [247]. The removal of eNOS increased the development of atherosclerosis in mice lacking the apoE gene[248]. Neuronal NO synthases are naturally present in both central and peripheral nerve cells, as well as in the arterial wall. This suggests that nNOS may have a potential function in preventing the development of atherosclerosis. Inducible nitric oxide synthase (iNOS), is triggered in response to inflammation, sepsis, and oxidative stress, and functions in a manner that promotes the development of atherosclerosis. The production of a pro-atherosclerotic oxidant called peroxynitrite by iNOS is believed to have a significant impact on the pro-atherogenic effect of iNOS [249].

5.2.2.5. Bilirubin

Bilirubin, a naturally occurring antioxidant, eliminates harmful substances, prevents protein damage, reduces inflammation and malfunction of blood vessels, and prevents the attachment of white blood cells to the inner lining of blood vessels[250], [251].

5.2.2.6. Uric Acid

Uric acid is the last result of the decomposition of purines. The process involves two consecutive precursors, hypoxanthine and xanthine, which are both converted by the enzyme xanthine oxidase. Uric acid enhances the generation of cytokines, acts as a scavenger for hydroxyl radicals (OH) and hypochlorous acid (HOCl), and triggers inflammatory responses, smooth muscle cell proliferation, endothelial dysfunction, and instability of plaque[252].

5.2.2.7. Lipoic Acid

Lipoic acid, synthesized by mitochondria, is a cofactor for α-ketoacid dehydrogenases and inhibits atherosclerotic lesion development. It also scavengers ONOO-, HOCl, and peroxyl radicals, attenuates endothelial dysfunction, decreases inflammatory markers, and increases eNOS activity[253], [254].

5.2.3. Exogenous Non-Enzymatic Antioxidants (Natural Antioxidants)

Vitamin C, vitamin E, and uric acid play a secondary defense mechanism by scavenging free radicals and participating in DNA repair. These antioxidants also protect against oxidative damage caused by oxygen free radicals, as shown in Table 04.

5.2.3.1. Vitamin C

Vitamin C, found in fruits and vegetables like citrus fruits, kiwi, and strawberries, is an antioxidant that helps control blood vessel dilation, improve blood vessel cell functionality, inhibit cyclooxygenase enzyme, and prevent LDL cholesterol oxidation. It also regenerates other antioxidants, prevents white blood cell clumping, and removes reactive oxygen species. However, The British Regional Heart Study show no significant correlation between vitamin C content and endothelium dysfunction in males without a history of cardiovascular disease or diabetes[255].

5.2.3.2. B Vitamins

B vitamins play a crucial role in the metabolism of essential amino acids, particularly homocysteine and glutathione[256]. They also scavenge hydroxyl and lipid peroxyl radicals, improve endothelial function, and improve NO synthase coupling through tetrahydrobiopterin[257], [258]. Clinical studies show that folate, hydroxocobalamin, and pyridoxine supplements can decrease serum homocysteine in patients with venous thrombosis on reducing coronary events or cardiovascular death[259].

5.2.3.4. Vitamin A and Carotenoids

Carotenoids, found in fruits and vegetables, are lipid-soluble substances that scavenge free radicals and prevent LDL peroxidation. They can decrease plasma cholesterol levels by inhibiting HMG-CoA reductase. Carotenoids also increase macrophage LDL receptor activity, reducing circulating LDL, inflammation, oxidative stress, and endothelial dysfunction [260]. However, a clinical study suggests an inverse relationship between β-carotene or retinol intake and cardiovascular disease risk [261]. The US Preventative Task Force does not recommend β-carotene for cardiovascular disease prevention [262]. Additionally, β-carotene and vitamin A significantly increase all-cause mortality [263].

5.2.3.5. Polyphenols

Polyphenols are abundant natural antioxidants found in in fruit (especially apples), grains, vegetables, cereals, olive oil, dry legumes, chocolate and beverages such as tea, coffee and wine. They are divided into several classes, including flavonoids, phenolic acids, stilbenes, and lignans. Flavonoids are subclassified as flavonols, flavones, flavanones, flalavan-3-ols, isoflavones, and anthocyanins [264]. They

have various mechanistic effects, including suppressing reactive oxygen species (ROS), increasing the expression of eNOS and reducing NO oxidation, blocking the action of xanthine oxidase and protein kinase C, and protecting vascular endothelial cells and NO from oxidation. They also decrease redox-sensitive gene activation, prevent the expression of pro-angiogenic factors, increase vasodilatory factors, inhibit angiogenesis, and reduce platelet aggregation and hypertension [265], [266]. Resveratrol, a stilbene polyphenol found in grapes, red wine, and Polygonum cuspidatum, has established antioxidant properties, including inhibition of lipid oxidation, regulation of vasodilator and vasoconstrictor production, inhibition of platelet aggregation. Clinical studies have shown a significant inverse association between flavonoid intake and coronary heart disease after 5 years of consumption [267].

Table 04.: Type of antioxidants and their mechanism [259].

Antioxidants	Type of Antioxidants		Action Mechanism
Enzymatic	Endogenous	Superoxide Dismutase	Preventing peroxynitrite formation, reducing levels of F2-isoprostanes and isofurans in the aorta and reduction of transition-metal ions
		Catalase	Reducing vascular smooth muscle cell (VSMC) proliferation
		Glutathione peroxidase	Inhibition of H_2O_2 mediated expression of MCP-1 and VCAM-1
		Thioredoxin Reductase	Increasing NO bioavailability and decreasing oxidative stress
Non enzymatic	Endogenous	Glutathione	Modulation of the size of atherosclerotic lesions in the aortic arch
		Uric acid	Increasing cytokine production, scavenging OH, plaque instability, attenuating endothelial activation and SMC proliferation
		Bilirubin	Scavenging oxidants, inhibiting protein oxidation, attenuating endothelial activation/ dysfunction and SMC proliferation
		Coenzyme Q	Inhibiting lipid and protein oxidation, scavenging peroxyl radicals and improving endothelial function
		Lipoic acid	Inhibition atherosclerotic lesion development, increasing in eNOS activity
	Exogenous	Vitamin E	Preventing foam cell formation and endothelial dysfunction, scavenging free radicals, diminishing the oxidation of LDL and modulating endothelial cells
		Vitamin C	Enhancement of NOS activity, inhibition of cyclooxygenase, diminishing cell-cell adhesion, improvement of endothelial dysfunction and vasodilation
		B vitamins	Scavenging hydroxyl and lipid peroxyl radicals, improving endothelial function
		Vitamins A and Carotenoids	Prevention LDL peroxidation, reducing inflammation, oxidative stress and endothelial

			dysfunction.
		Polyphenols	Suppressing ROS formation, increasing the expression level of eNOS, inhibiting angiogenesis, reducing platelet aggregation and hypertension

6.Oxidative stress with atherosclerosis

ROS can be produced by various enzyme systems present in the vascular system. The main producers of reactive oxygen species (ROS) in blood vessels include the mitochondrial electron transport chain, oxidizing enzymes like nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase (XO), nitric oxide synthase (NOS), and uncoupled endothelial nitric oxide synthetase (eNOS) are present in macrophages, vascular smooth muscle cells, and endothelial cells, involved in smooth muscle cell proliferation, ROS/RNS production, and LDL oxidation [268], [269].

In general, these enzymes facilitate the process of reducing oxygen by transferring electrons from their substrates to oxygen molecules. Cellular homeostasis and signaling necessitate basal levels of reactive oxygen species (ROS). Increased levels of reactive oxygen species (ROS) can have positive effects, particularly in the process of macrophage oxidative burst, which is necessary for eliminating pathogens. However, if there is an abundance of reactive oxygen species (ROS), which can occur as a result of increased ROS production and/or reduced antioxidant capacity, it leads to oxidative stress[207].

ROS, or reactive oxygen species, are a significant intracellular source of inflammation and can damage the cellular functions of biomolecules such as lipids, proteins, and carbohydrates. They can be initiated by hyperglycemia or hyperglyceridemia, leading to lipid peroxidation and LDL oxidation. The oxidation of lipoproteins is an initial phase in the development of atherosclerosis, which has deleterious and toxic effects on endothelial cells. Ox-LDL may induce endothelial dysfunction, the expression of adhesion molecules, migration and proliferation of smooth muscle cells, and foam cell formation [270], [271]. Atherosclerosis has three important stages: fatty streak formation, induction of atheroma, and atherosclerotic plaques, ultimately leading to atherothrombosis [272], [273]. Lipoproteins, particularly low-density lipoprotein (LDL-C), accumulate in the intimal layer of the arteries, and certain risk factors facilitate their penetration into the vascular intima. ROS and RNS convert LDL-C to reactive Ox-LDL, which remains in the vascular intima[274], [275].

Endothelial cells are activated by cytokines such as tumor necrosis factor (TNF-α), interleukin-1,-4, and -6 (IL-1, IL-4, IL-6) and interferon gamma (IFN-γ) and oxidized lipids, stimulate the expression of leukocyte and monocyte adhesion molecules, particularly VCAM, ICAM, and E-selectin, on the endothelial surface [276], [277].

Monocytes and T lymphocytes accumulate in the vascular wall intima mediated by these adhesion molecules. Specific chemokines cause smooth muscle cell migration from media to intima and cellular proliferation [181]. Monocytes differentiate into macrophages through chemotactic proteins, The cells identify and absorb Ox-LDL molecules through "scavenger" receptors (SRs) and mononuclear phagocytosis occurs in the foam cell formation stage (Figure 26).

Finally, macrophages transform into foam cells, and the accumulation of these yellow foam cells on the walls of arteries results in the formation of fatty streaks. Foam cells undergo apoptosis, a form of programmed cell death, during the formation of atherosclerotic lesions. A necrotic core is created by apoptotic foam cell death, serving as a repository for cellular debris and lipids [182].

A fibrous atherosclerotic plaque cap is created during the migration of smooth muscle cells from media to intima vascular layers and the induction of extracellular matrix production in atheroma formation [280]. Macrophages and T lymphocytes secrete metalloproteinase and TNF-α to lyse the fibrous cap extracellular matrix and inhibit collagen synthesis in the smooth muscle cells. This lysis leads to the destruction of the fibrous cap, causing coagulation, blood clot formation, platelet adhesion, and thrombus formation, which may completely block the arteries [281], [282].

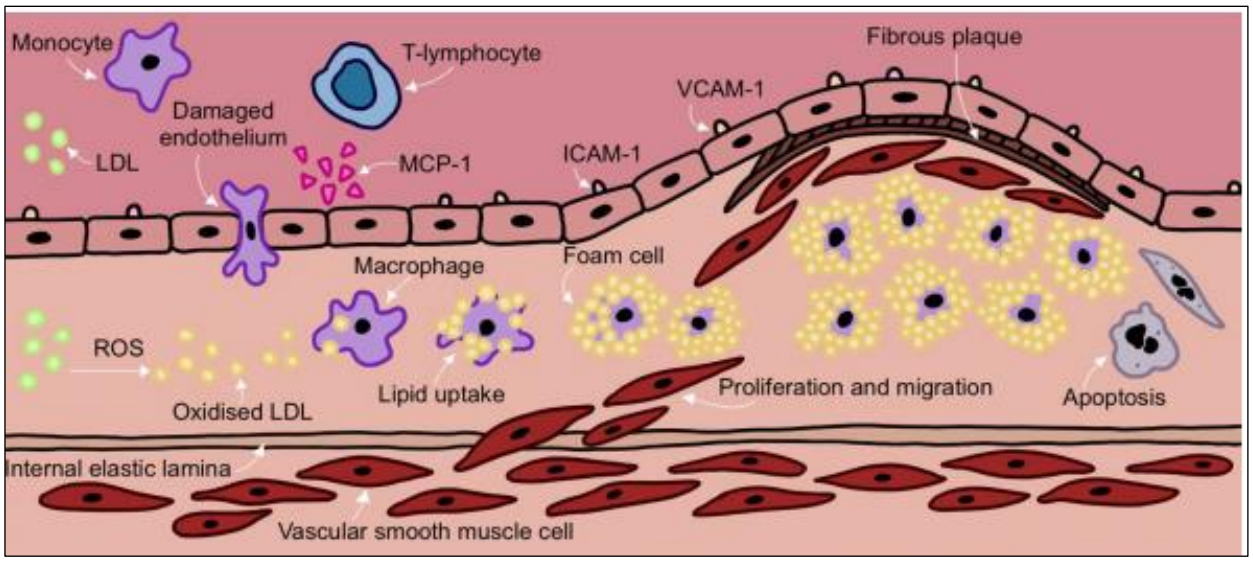

Figure 26: The development of Atherosclerosis[283].

7.Reasons for Failing Antioxidant Strategies Related to Atherosclerosis in Humans

Several antioxidants have been tested in animal models for potential treatment of atherosclerosis, but studies in humans are limited or have not revealed positive effects. Traditional antioxidant therapy in humans may fail due to factors such as long-term use, instigation before full disease onset, potential loss of beneficial effects through oxidation, and the incomplete oxidant theory of atherogenesis.

Antioxidants that pass through the mitochondrial membrane have superior effectiveness compared to traditional antioxidants. Combination antioxidant therapies may be more effective overall [271].

Diet plays a crucial role in preventing atherosclerosis and other cardiovascular diseases, lifestyle habits, nutritional quality, and acquired eating patterns can reduce the risk of atherosclerosis. A balanced diet and lifestyle, including a diet rich in vegetables, fruits, whole-grain cereals, extra-virgin oil, nuts, moderate consumption of fish and poultry, low intake of dairy products, red meat, and sweets, and moderate consumption of red wine, are recommended [170] .

Reducing trans-fat, saturated fat, cholesterol, and hydrogenated fats, consuming plant sterol/stanol esters, supplementing with vitamin C, high doses of resveratrol, adequate micronutrients like potassium, magnesium, and zinc, daily consumption of soy protein and soluble fiber, adequate vitamins like vitamin E, vitamin C, and vitamin D, and consumption of dark chocolate, flavanols, and quercetin, is also essential. Drinking black or green tea daily and supplementing with standardized colored plants like maqui berry may also be beneficial [171].

Second part Experimental part

Materials & Methods

I. Materials & Methods

1.Materials

1.1. Geographic of El Oued

The region of El Oued is located in south-eastern Algeria with a diameter area of 54573 square kilometers. The geographical coordinates of El Oued are as follows: latitude 33.3683° and longitude 6.8674° with a mean altitude of 60 m. It covers an area estimated 54 573 km² and has a 28 commune, and 12 districts (Figure 27). The total population of the wilaya was estimated around 731930 inhabitants, a density more than 12 inhabitants per km^2. El Oued has a socioeconomic development in Algeria especially in agricultural domain.

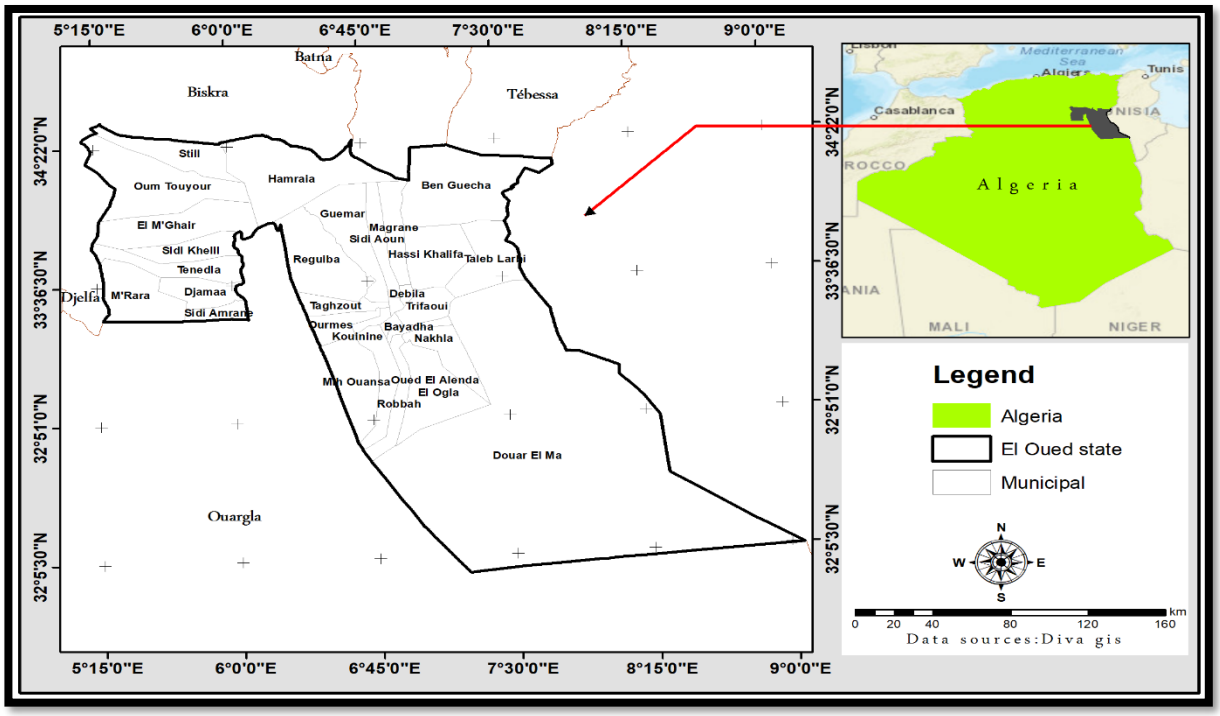

Figure 27: Schematic illustrated the geographical location of El Oued State with its various municipalities and district.

1.2. Sample size

Our epidemiological part cover 23422 cardiovascular patients, 3936 of them with CADs as we found in the archive service of hospital Echahid Djilani Ben Amor and Dr Salhi cardiac clinic, their epi-info was extracted from their medical files, also in our second part which questionary included 300, who agreed to participate in our study, divided into three groups CAD group; metabolic syndrome group and healthy group each group contain 100 persons (50 women and 50 men).

In the third part; blood sampling we used the following formula equation [286] to calculated the sample size in our research work, the sample size will be selected in order to determine the estimated prevalence of CAD with a 95% confidence interval. Approximately 14% is the expected prevalence of CAD. The sample size n calculated is satisfied the relation given above.

$$n=(Z\alpha/2)^2 (P) (1-P)/ e^2$$

The reliability coefficient ($Z\alpha/2$) = 1.96

Estimated prevalence of CAD patients (P) = 0.14

Estimated prevalence of no CAD patients (1-P) = 0.86

The margin of error (e) = 0.05

$n= (1.96)^2 (0.07) (0.93)/ (0.05)^2=185.01$ persons

We estimated that a total of 80 patients would be required to detect the difference between groups after filtering out the patients who were present in this study.

1.3. Selection criteria

1.3.1. Inclusion criteria

- The subjects selected in the research must be live in El Oued.
- CAD and MetS group clinical diagnosis confirmed by cardiologist and internist doctors.
- CAD patients were confirmed their diagnosis by ECG and Troponin test.
- Control subject must be in good health and did not consume any drug at least 2 weeks.
- Patients must suffer for at least two months.
- Subjects selected aged 20 and more.

1.3.2. Exclusion criteria

- Subjects with deafness or muteness without possibility of translation.
- People who live outside El Oued.
- Control group who suffers from any chronic or acute diseases and consume drugs for 3 months.
- CAD and MetS patients had suffered for any types of cardiac diseases.
- Absent subjects of the survey area during the entire duration of the investigation.
- Subjects refusing to participate in the survey.
- Persons with mental disorder.
- Pregnant women and kids.

1.4. Study design

We selected randomly 200 volunteers, both the sex women and men aged between [24-75] years old who were hospitalized in the Hospital of Echahid Benamor Djilani in El Oued, from 01 October 2022 to 15 Mars 2023. These patients reported to the clinical study service (NCT00000508). A number of 120 subjects men and women were selected randomly who are agree to participate in our study, divided into three groups each one contain 40 subjects (CAD, Mets and healthy group). In our study we collected the contact information for 200 women and men, initially who are interested to participate in the work research. Unfortunately, after that we lost the contact with some of them (25 persons) also a (20 persons) refuse to continue the participation in the study and (29 persons) didn't complete their medical visits.

We reached out 120 women and men, who were enrolled in the study, equally divided between the groups **(**Figure 23). Ethical approval was requested and approved by the Ethics Committee referenced (14EC/DCMB/FNSL/EU2023) of the Department of Cellular and Molecular Biology, Faculty of Natural Sciences and Life, university of El Oued. All the volunteers selected (control and patients' groups) in this study live in the El Oued region which located in the southeast of Algeria (Figure 28).

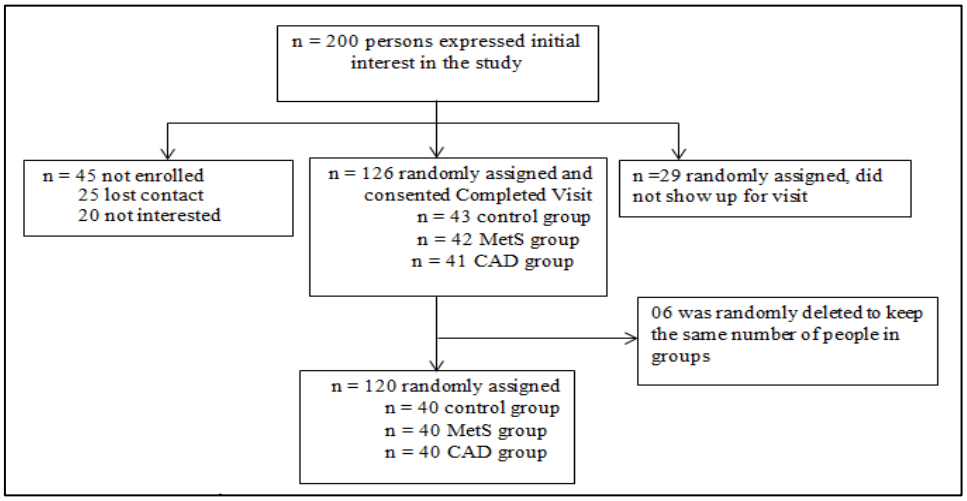

Figure 28: Flowchart of subject recruitment, enrollment, and retention from patients.

1.5.Data collection

The research was carried out in compliance with the World Health Organization's STEP-wise strategy for surveillance chronic disease risk factors (WHO 2001). The data collection involves three steps:

1.5.1. Epidemiology study

The epidemiological information's (Age, Gender, weight, residence address, kind of CVD, chronic disease antecedent, smoking, dyslipidemia), were collected from patients' files of Echahid Ben Amor Djilani hospital also from Dr Salhi cardiac clinic, the data period was from October 2010 to December 2021.

1.5.2. Risk factors study

We used a structured questionnaire to assess study participants' self-reported behavioral about their epi-info (anthropometric measurements (weight, height, body mass index (BMI)), blood type, address residence, social case, professional case) and lifestyle risk factors for CAD.

The number of participants involve 300 subjects (women and men), divided into three equal groups, each one included 100 persons (50 women and 50 men): the first group included CAD patients, the second group was MetS patients and the third one was healthy subjects. The participants were interviewed face-to-face in hospital, private medical clinics and homes to fill out questionnaires, take physical measurements and take blood samples. During the field work, we used the Arabic version to conduct interviews with participants.

The questionary used (Appendix 01and 02; English and Arabic version) was based at the international standards according to WHO, a rose angina questionnaire (Appendix 03 and 04; English and Arabic version) used to make the questions about CAD patients and a questionnaire of physical activity for the measurements of body activity also the questionnaire of depression and epileptic crisis, our study period was from December 2021 to March 2022.

1.5.3. Paraclinical study

We did an echocardiogram (ECG) to confirm the diagnosis of subject with CAD.

1.5.4. Biological study

1.5.4.1. Study design

we carried out on 120 subjects volunteers, aged between 20-100 years, were divided into three groups, each one contain 40 subjects; the first group include healthy persons (control), the second group with metabolic syndrome and the third with coronary syndrome disease.

1.5.4.2. Laboratory investigation

Blood samples for three groups were done in the morning fasting. it was taken by nurses from venous, drawn into tubes, stored in a cool box (2°C to 8°C), and then sent to the laboratory for analysis using standard methods. Blood samples is collected in two tubes, the first tubes with anticoagulant (EDTA) are mixed well for hematological markers.

The second tubes with anticoagulant (HEPARIN) is mixed well and centrifuged at 2500 rpm for 10 minutes, then obtained the serum to achieve the dosage of oxidative stress markers (MDA, GSH, SOD, GPX and ORAC) and biochemical parameters; Glycemia, lipidic markers (total cholesterol,

triglyceride, HDL-C, LDL-C and VLDL), renal markers (Urea and Creatinine), hepatic markers (ASAT, ALAT, total protein, Albumin, calcemia, C-reactive protein, vitamin -OH 25 and phosphor), enzymatic markers (phosphatase alkaline, amylase, lipase, CK-Mb, LDH and troponin), electrolyte markers (sodium, potassium, chlorine).

II.Methods

1.Biochemical parameters assay

The most biochemical parameters were determined by Auto analysis (Mindray BS-240), the lipidic markers, LDH and CPK were determined by semi-Auto chemistry Analyzer (BA-88A), and the electrolyte markers were determined by EasyLyte® PLUS REF 2121.Use commercial kits from Spinreact for (total protein-10012991, GGT), and commercial kits from DiaScan (Urea-CH35.04.125, CREA-CH-68.06.050, CAL-CH-69.06.050, TRG-CH-33.10.020, ALB-CH-02.02.250, THROMBOPLASTIN-HS01) also commercial kits from Diagnofarm (Glycemia-), also commercial kits from ElitechGroup (AST-ASSL-0510, ALT-ALSL-0510, CHOL-CHSL-0570, PAL-21-0790).

2.Hematological analysis

Hematological analysis for complete blood count (CBC) is performed by the hematology Auto analyzer (Sysmex XT-2000i).

3.Estimating oxidative stress parameters

3.1. Malondialdehyde assay (MDA)

MDA was measured according to the method described by Yagi, 1976 [287].Thiobarbituric acid 0.67% (w/v) was added to aliquots of the sample previously precipitated with 10% trichloroacetic acid (w/v). Then the mixture was centrifuged, and the supernatant was heated (100°C) for 15 min in a boiling water bath. Then cool in a cold-water bath for 30 minutes, leaving the tubes open to allow evacuation of the gases formed during the reaction and the absorbance was measured at 532 nm using a spectrophotometer. The concentration of TBARS was determined using the molecular extinction coefficient of MDA.

($A=1.53 \times 10^5 M^{-1}. Cm^{-1}$ The results were expressed in µmol / l).

MDA (µmol/mg of HGB) = (OD of sample/1.53 x 10^5) /mg of HGB.

3.2. Glutathione peroxidase activity (GPX)

GPX was measured according to the method described by Fohe L and all. A 0.4 ml of GSH (0.1 mM) and a 0.2 ml of buffer solution TBS (Tris 50 mM, NaCl 150 mM, pH 7.4), were added to a 0.2 ml of sample after the mixture incubated in water bath at 25°C, for 5 min, then a 0.2ml of H2O2 (1.3 mM) to initiate the reaction, after leave it to act for 10 minutes, and addition of 1 ml of TCA (1%) to stop the reaction, then put the mixture in ice for 30 minutes, and after centrifuge for 10 minutes at 3000 rpm, after that we take a 0.48 ml of supernatant and add a 2.2 ml of buffer solution TBS and a 0.32 ml of DTNB (1.0 mM), finally mixture and leave for 5 minutes, the optical density was measured at 412 nm using a spectrophotometer [288].

$$\text{GPX (µMGSH / Mg of HGB)} = \frac{\text{(OD of sample - OD of standard)}}{\text{OD of standard}} \text{ X } 0.04$$

3.3. Determination of Reduced glutathione level (GSH)

The determination of the reduced glutathione concentration by measuring the optical density results from the formation of 2-nitro-5-mercocapturic acid from the reduction of dithio-bis-2-nitrobenzoic acid, which is called reagent of Ellman with SH groupings exist in GSH briefly, 800 µL of homogenate are added to 200 µL of salicylic acid (0.25%) and centrifuge at 1000 rpm for 5 minutes. 500 ml of supernatant are then mixed with 1000 µL of tris buffer (tris 0.4 mol, NaCl 0.02 mol, pH = 8.9) and 25 µL of DTNB (0.01 mol. L-1). After 5 minutes of incubation, the absorbance is read at 412 nm [289].

$$\text{GSH (}\boldsymbol{n}\text{M / Mg of HGB)} = \frac{\text{D x 1 x1.525}}{\text{13133 x 0.8 x 0.5 x mg of HGB}} \text{ X d}$$

13133: Absorption constant of SH groups at 412 nm.

OD: The absorbance reader by the spectrophotometer.

521.1ml: Total volume of blend.

521ml: Volume of solution float.

1: Volume of protein mixture.

0.8 ml: Volume of homogeneous solution without protein exists in 1ml.

GSH: Concentration of glutathione.

3.4. Determination of superoxide dismutase activity assay (SOD)

The assay method of SOD activity using the NBT by the method Beauchamp & Fridovich,1971, the superoxide anion (O^2), is used as a basis for detecting of presence of SOD by measuring the pectro-photometrically absorbance at 560 nm [290].

Table 05: Superoxide dismutase activity assay.

Collect in tubes	Blanc	Sample
EDTA-Met 0.1Mm EDTA-13Mm met	1000µl	1000 µl
Phosphate buffer(50Mm)	892.2 µl	892.2 µl
Sample	0	50 µl
Phosphate buffer	1000 µl	950 µl
NBT (75 µM)	85.2 µl	85.2 µl
Riboflavin (2 µM)	22.6 µl	22.6 µl

Expression of results

$$\textbf{IP (\%)} = \frac{\text{(OD of blanc - OD of stample)}}{\text{OD of blanc}} \quad X\ 100$$

1 UI of SOD ⟶ 50%

3.5. Determination total antioxidant capacity (TAC) or FRAP assay

The Antioxidants are determined to samples by colorimetry. The ferric-tripyridyltriazine complex is reduced to the ferrous-tripyridyltriazine in presence of the antioxidants; the complex loses its yellow color to a dark blue. This coloration measured at 595 nm is proportional to the concentration of antioxidants present in the samples. The method is starting by Taken 500µl of sample, then we Add to it 1.25ml of the buffer solution (0.2 M, PH = 6.6), then the mixture was incubated 20 min in a water bath at 50 ° C, after that we Add 1.25ml of the aqueous TCA solution (10%) to stop the reaction and put it in Centrifugation at 3000 rpm for 5 minutes. 1.25 ml of supernatant are then mixed with 1.25 ml distilled water and 250 µl FeCl (0.1%). Finally, was measured at 700 nm against a blank. The results expired by IC50, after calculating of the ferric reducing antioxidant power values according to Oyaizu, 1986 [289] as follows:

$$TAC\ (\%) = 100 - (OD\ control\ /OD\ sample) \times 100$$

4.Statistical analysis

Sample size was calculated by using Epi-info (epidemiological information, statistical program, IBM, SPSS STATISTIC version 22). Statistical analysis is performed by Minitab 18 Statistical Software and IBM SPSS Statistics 28.0.0.0 software results comparisons were carried out by using the Student T test to compare means among the groups, Correlation analysis was carried out using Pearson Correlation test and regression analysis was used for other analysis and statistical data. Differences were considered statically significant at $P < 0.05$.

Results

III.Results

1.Epidemiology study of coronary artery disease

Our study carried out 23422 cardiovascular patients, who were diagnosed and hospitalized in the hospital and private cardiac clinic in different regions of El Oued from October 2010 to December 2021.

1.1. Distribution of cardiovascular diseases in El Oued by type and Sex

Our outcomes show that the most common kind of cardiovascular disease in women than men with (59.3%, 40.7%) respectively (Figure 30), also we observed that the high percent CVD is hypertension and coronary artery disease with total percent 74,40 % and 16,63% respectively HTN (47,48% for women and 26,92% for men), CAD (7,13% for women and 9,5% for men). In our study HTN was affected the women more than men, the opposite of CAD which was affected the men than women. In the other side the other cardiovascular kind were distributed from the high to the less percent respectively through the elven years ago (Figure 29).

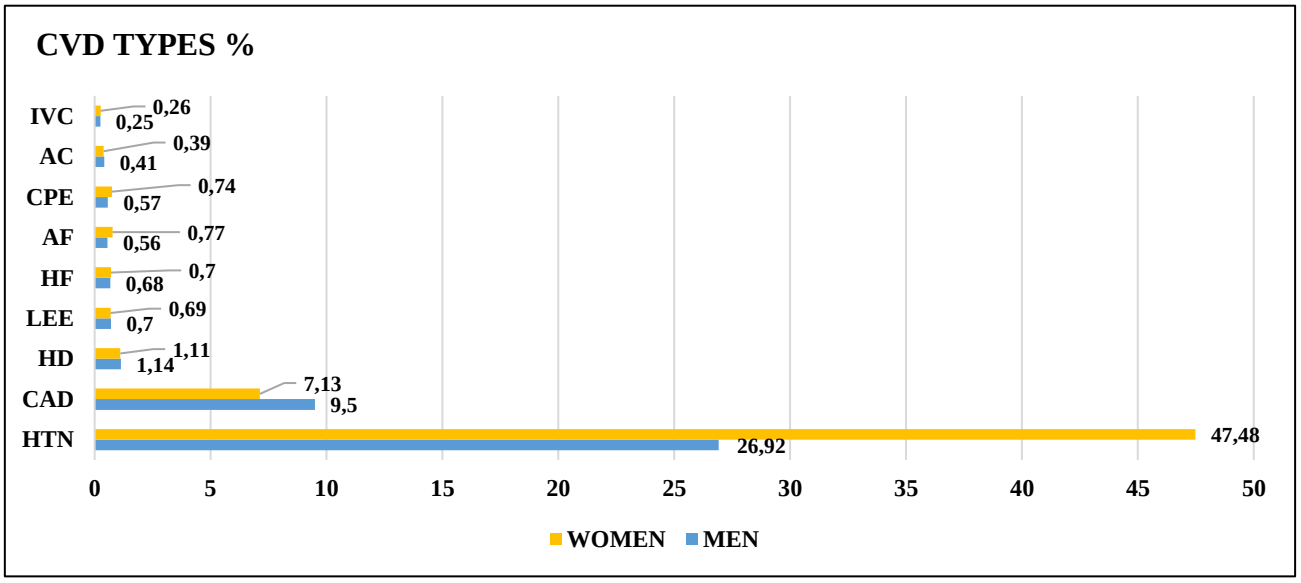

Figure 29: Distribution of CVD in El Oued region according to CVDs type and sex.

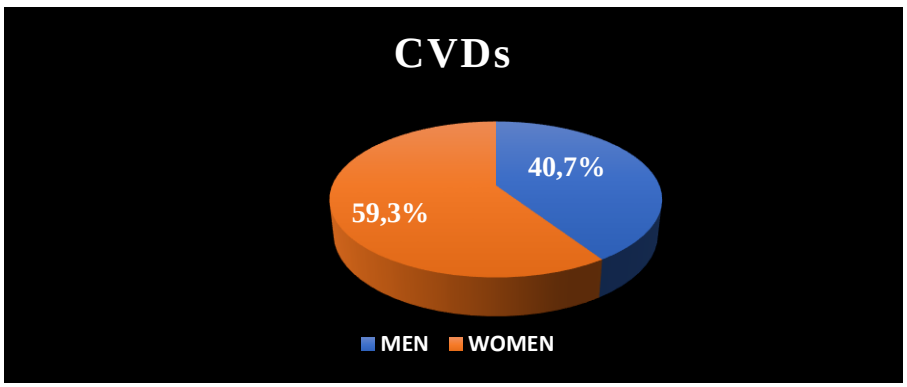

Figure 30: Distribution of CVDs among women and men in El Oued.

1.2. Distribution of cardiovascular patients in El Oued by Age, Sex and year

The results show that the most age affected with CVD among men and women is between 51 to 60, and it is spread in the center with 65.14% than the other sides, and in 2019, the largest number of people with coronary artery disease was recorded (Figures 31, 32 and 33).

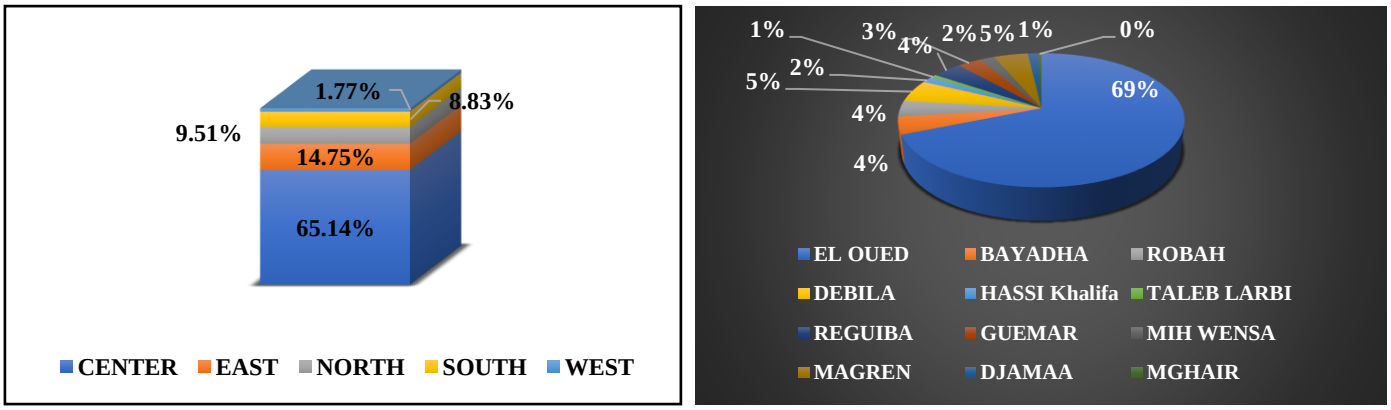

Figure 31: Distribution of CVD patients among women and men in El Oued areas.

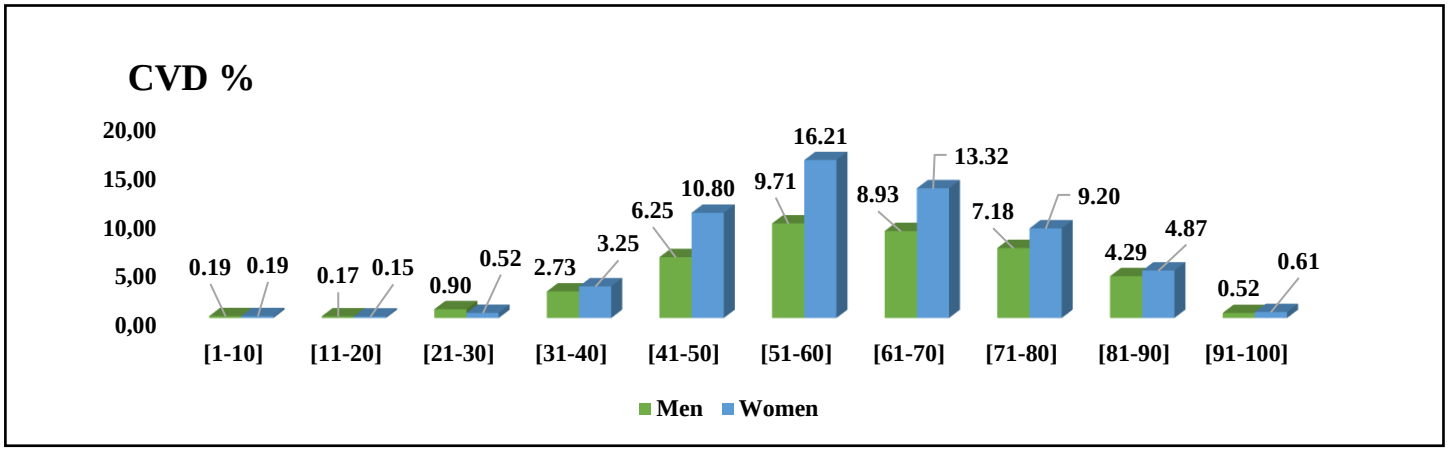

Figure 32: Distribution of CVD patients among women and men in El Oued according to age and Sex.

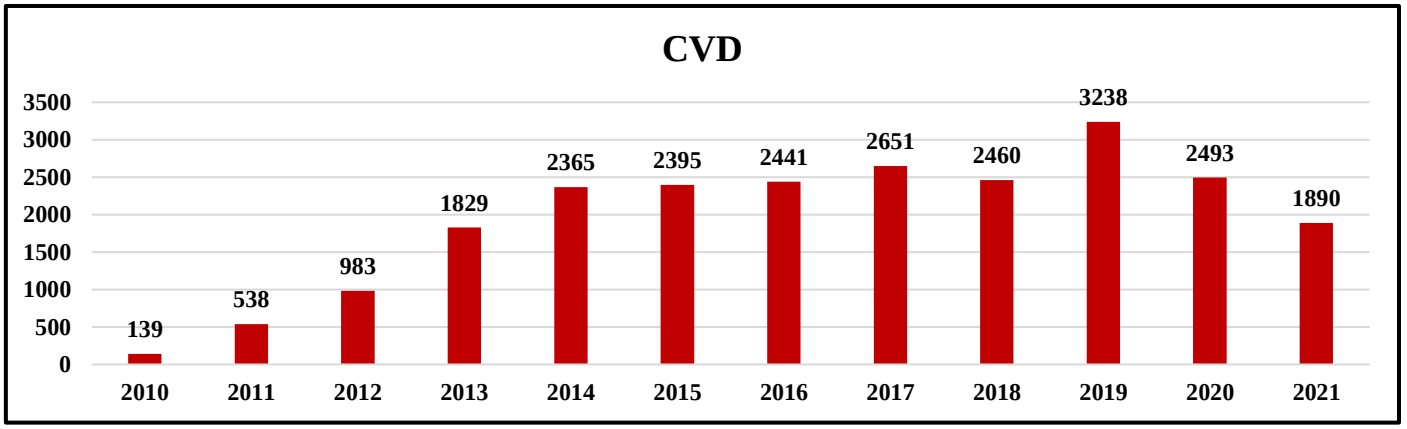

Figure 33: Distribution of CVD among women and men in El Oued from October 2010 to December 2021.

1.3. Distribution of coronary artery disease patients in El Oued by year and regions

In our study concerning the CAD among women and men, we found that the numbers through eleven years was growing, it reached the maximum in 2019 with 16.87% (Figure 34), also the most common region affected in El Oued' center with 68.78% than the other areas (Figure 35).

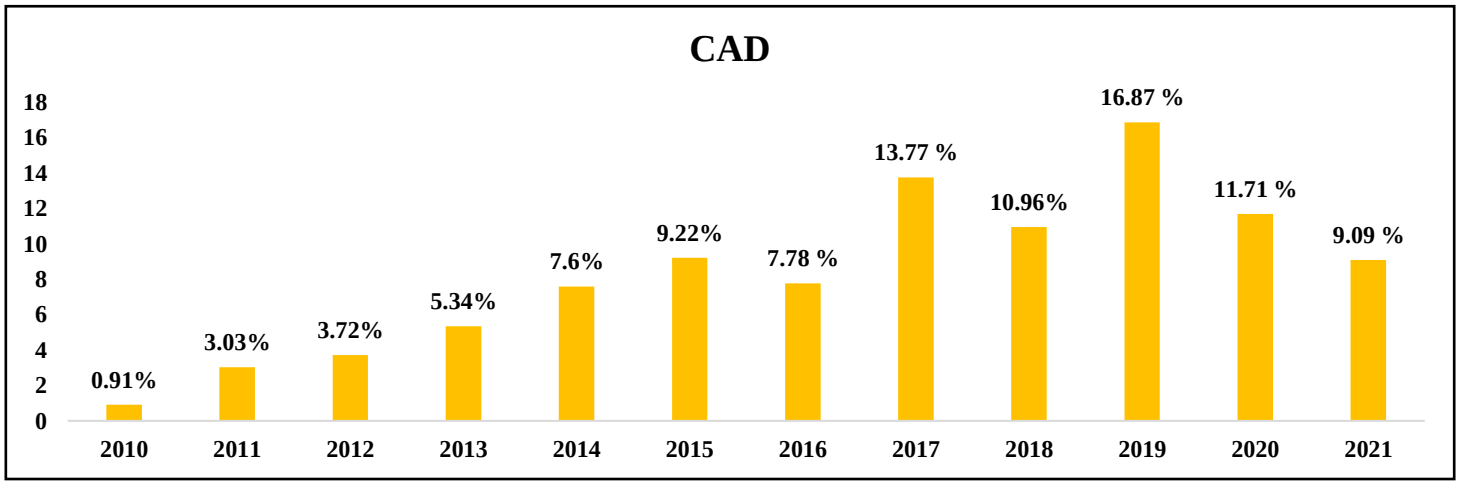

Figure 34: Distribution of CAD among women and men in El Oued from October 2010 to December 2021.

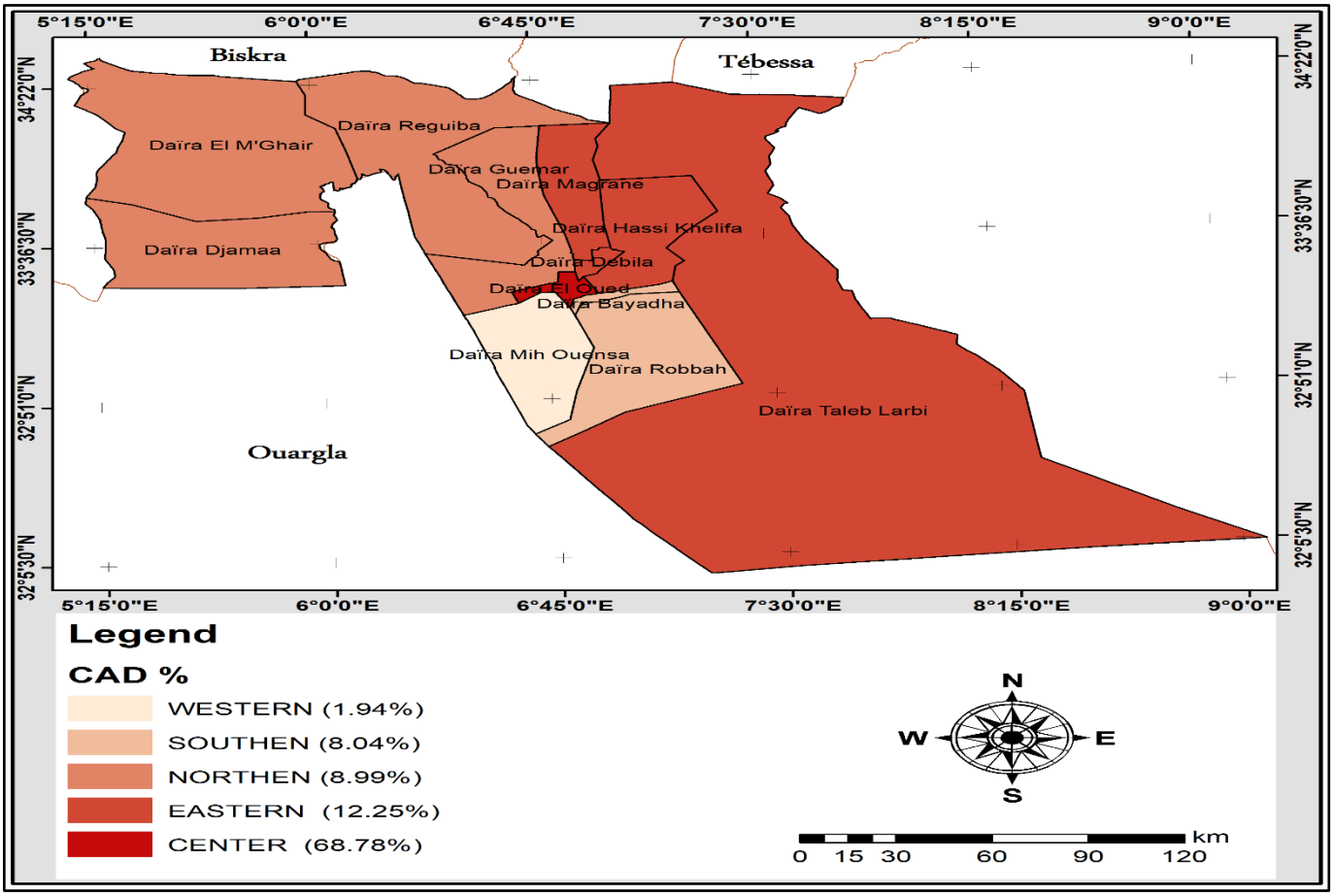

Figure 35: Schematic illustrated the CAD epidemiology in El Oued State.

1.4. Distribution of coronary artery disease patients in El Oued by age and sex

The results show that the CAD affected the men than women with 58% (Figure 36), and it spread in the age between 51 to 60 (Figure 37).

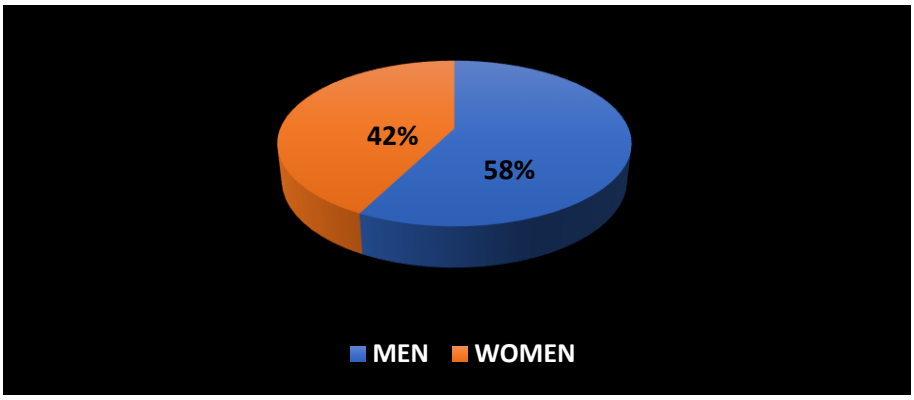

Figure 36: Distribution of CAD among women and men in El Oued according to sex.

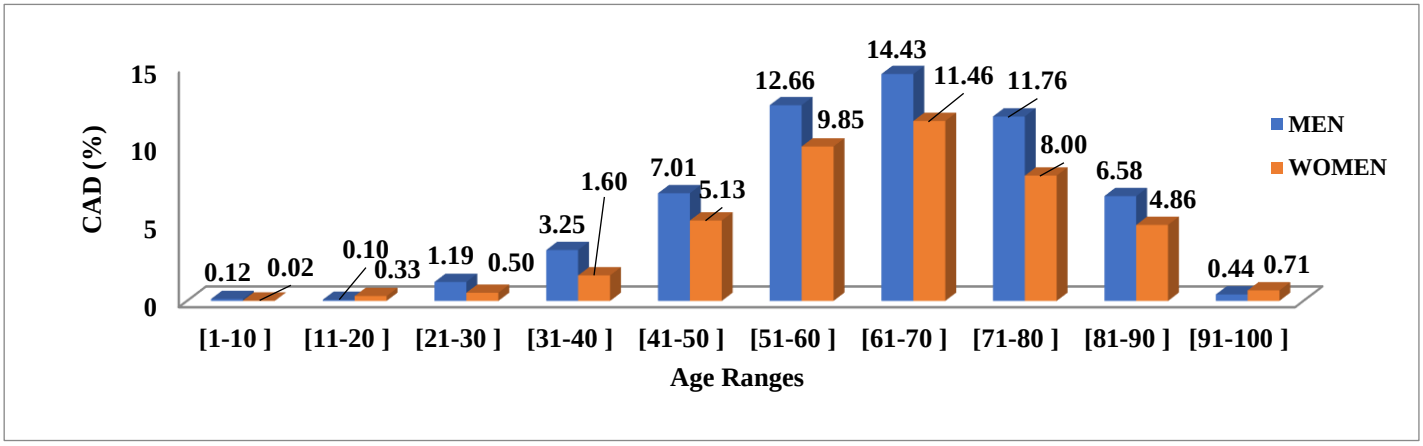

Figure 37: Distribution of CAD among women and men in El Oued according to age.

1. 5. Distribution of coronary artery disease patients in El Oued according to weight and dyslipidemia

In our population study, we observed the weight and dyslipidemia and weight among CAD patients represented a low percent with 4.24%, 8% respectively compared to the total patients with 3936 (Figure 38).

Figure 38: Distribution of CAD among women and men in El Oued according to weight and dyslipidemia.

1.6. Distribution of coronary artery disease patients in El Oued according to smoking

We found the smokers or passive smoking patients that it represented a 9.63%, in the other hand the no smoking with 90.37% (Figure 39).

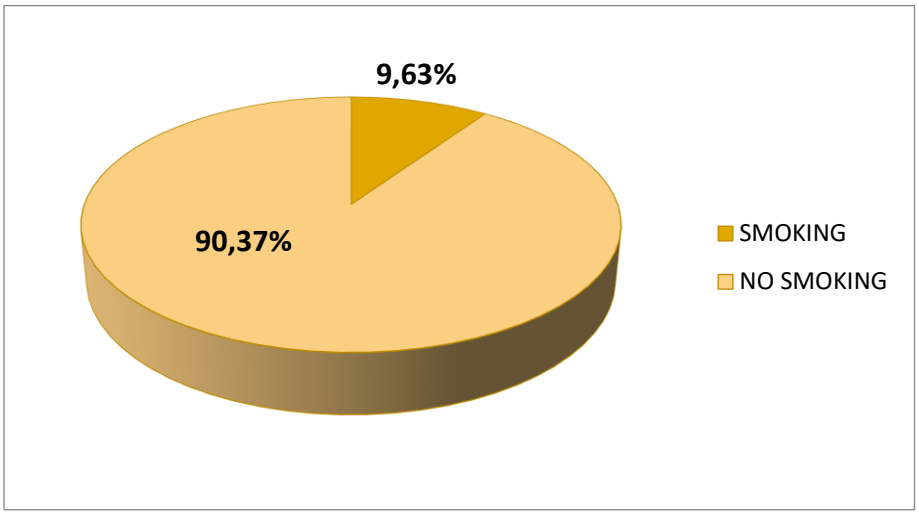

Figure 39: Distribution of CAD among women and men in El Oued according weight and smoking.

1.7. Distribution of coronary artery disease patients in El Oued according to hypertension and diabetes mellitus

A total number of CAD patient with 3936 subjects, we found a different percent distributed among men and women with hypertension and diabetes also without HTA and DT (Figure 40).

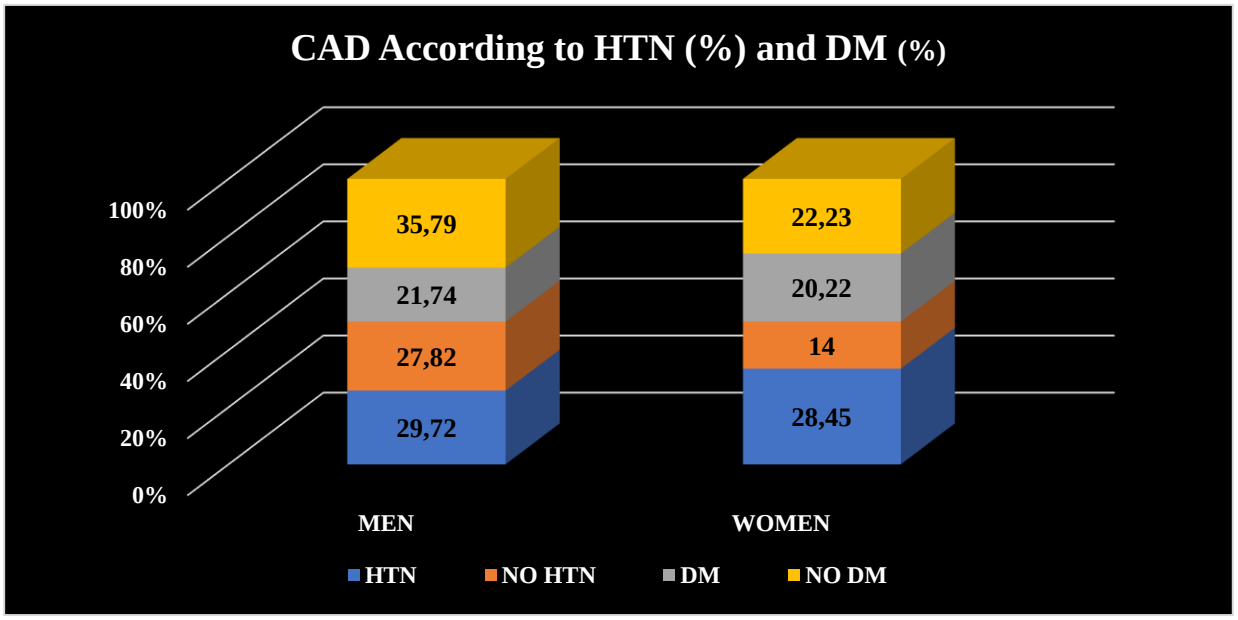

Figure 40: Distribution of CAD among women and men in El Oued according to DM and HTN.

2. Study of risk factors

2.1. Description of study population

The table below represented the characteristic of our population‘s study included 300 volunteers among women and men from El Oued regions, they divided to three groups each one contained 100 subjects, (controls, MetS, CAD). The data contained epi-info (age, blood group, job, social case, educational level, weight, length, BMI, address living and SARS-Covid19). The results obtained are homogenous in the three groups (Table 06).

Table 06: Description of study population.

		control group	MetS group	CAD group
Age (years)		35.5 ± 1.02	57.32 ± 1.48	63.01±1.24
Length		1.67± 0.01	1.64 ± 0.01	1.64 ± 0.01
Weight (kg)		76.79 ± 1.69	78.48 ± 1.62	74.39 ± 1.24
Body mass index (BMI) (kg/m^2)		27.26 ± 0.51	29.18 ± 0.62	27.68 ± 0.49
Job %	Worker	79	37	24
	Unworked	18	47	51
	Retired	3	16	25
Educational Level %	Illiterate	3	35	50
	Primary	3	20	16
	Medium–Secondary	50	30	33
	High School	44	15	1
Address (living)	Urban	61	61	46
	Rural	39	39	54
Blood types %	O	50	59	54
	A	30	25	23
	B	17	11	19
	AB	3	5	4
SARS-COVID 19%	Exposed	60,3	59.2	40.8
	Not exposed	43,4	44.4	55.6
Troponin Test analysis	Positive	0	0	100
	Negative	100	100	0
Tension measurement	SBP (mm Hg)	11.87 ± 1.11	13.26 ± 0.21	13.87 ± 0.26
	DBP (mm Hg)	7.68 ± 0.06	7.88 ± 0.10	7.94 ± 0.12

2.2. Socioeconomic and clinic factors

2.2.1. Comparative study between CAD and control group

Odds ratio of clinic-pathological in (Table 07) and socioeconomic factors in (Table 08) show that medicinal herbs as alternative treatment, salt consumption, depression and stress, surgery operation, smoke, obesity, kidney disease, abdominal obesity ,medication consumption, heart disease, inflammatory and stroke, are a significative risk factors with (OR=2.347; P=0.008, OR=2.509; P=0.008, OR=2.630; P=0.001, OR=3.144; P=0.000, OR=3.296; P=0.001, OR=4.495; P=0.000, OR=4.831; P=0.008, OR=5.667; P=0.000, OR=5.924;P=0.000,OR=7.452; P=0.032, OR=8.877; P=0.000, OR=9.791; P=0.009).

In addition, breathing dysfunction, alcohol consumption, gallbladder dysfunction, rheumatism, cardio surgery, chest pain, age > 60 years old, diabetes mellitus, chronic diseases and HTN represent a high-risk factor in our study population with (OR=10.756; P=0.000, OR=13.500; P=0.001, OR=12.236; P=0.002, OR=23.222; P=0.000, OR=24.750; P=0.000, OR=42.667; P=0.000, OR=76.641; P=0.000, OR=116.217; P=0.000, OR=132.481; P=0.000, OR=154.486; P=0.000) respectively.

In contrast, the age < 40 years old is considered as protective factor with (OR=0.014; P=0.000).

On the other hand, CAD heredity, liver disease, tonsillectomy, infection disease, anemia, age between [40-60] years old, sudden death family history, passive smoke, epileptic crisis, sport practice, consumption of milk and dairy products, sweets consumption, bread consumption, pastries consumption, red meat consumption and canned food consumption are not considered as predictor risk factors for CAD population through the OR value and P-Value which are not significative.

Table 07: Comparative study of clinical factors between CAD and control group (N=200).

Risk factors	Control group (%)	CAD Group (%)	OR	CI 95%	*P-value*
CAD Heredity					
Positive	50.9	49.1	0.952	0.515-1.759	0.500
Negative	49.7	50.3			
Chronic disease					
Positive	2.7	97.3	**132.481**	30.524-575.003	**0.000**
Negative	78.4	21.6			
Kidney disease					
Positive	18.8	81.3	**4.831**	1.332-17.522	**0.008**
Negative	52.7	47.3			
Liver disease					
Positive	33.3	66.7	2.020	0.180- 22.645	0.500
Negative	50.3	49.7			
Tonsillectomy					
Positive	85.7	14.3	0.158	0.019-1.339	0.059
Negative	48.7	51.3			
Gallbladder dysfunction					
Positive	8.3	91.7	**12.236**	1.549-96.681	**0.002**
Negative	52.7	47.3			
Infection disease					
Positive	50.0	50.0	1.000	0.138-7.245	0.689
Negative	50.0	50.0			
Anaemia					
Positive	40.5	59.5	1.598	0.774-3.299	0.137
Negative	52.1	47.9			
Surgery operation					
Positive	31.9	68.1	**3.144**	1.700-5.815	**0.000**
Negative	59.5	40.5			
Heart disease					
Positive	12,5	87,5	**7,452**	0,900-61,729	**0,032**
Negative	51,6	48,4			
Stroke					
Positive	10	90	**9,791**	1,217-78,806	**0,009**
Negative	52,1	47,9			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

Risk factors	Control group (%)	CAD group (%)	OR	CI 95%	*P-value*
Cardio surgery					
Positive	4.8	95.2	**24.750**	3.251-188.423	**0.000**
Negative	55.3	44.7			
HTN					
Positive	1.6	98.4	**154.846**	20.739-1156.136	**0.000**
Negative	71.7	28.3			
Diabetes mellitus					
Positive	1.8	98.2	**116.217**	15.592-866.248	**0.000**
Negative	68.3	31.7			
Inflammatory					
Positive	12.9	87.1	**8.877**	2.975-26.489	**0.000**
Negative	56.8	43.2			
Rheumatism					
Positive	5.0	95.0	**23.222**	3.047-177.207	**0.000**
Negative	55.0	45.0			
Chest pain					
Positive	5.9	94.1	**42.667**	14.485-125.681	**0.000**
Negative	72.7	27.3			
AGE					
<40 years old	95.8	4.2	**0.014**	0.004-0.047	**0.000**
Positive	24.2	75.8			
Negative					
{40-60} years old					
Positive	45.5	54.5	1.313	0.727 – 2.371	0.226
Negative	52.2	47.8			
>60 years old	3 .2	98.8	**76.641**	17.861 – 328.861	**0.000**
Positive	71.5	28.5			
Negative					
Sudden death family history	55.2	44.8	0.784	0.356 - 1.730	0.344
Positive	49.1	50.9			
Negative					
Breathing dysfunction					
Positive	10.0	90.0	**10.756**	2.424 - 47.727	**0.000**
Negative	54.4	45.6			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

Table 08: Comparative study of socioeconomic factors between CAD and control group (N=200).

Risk factors	Control group (%)	CAD group (%)	OR	CI 95%	*P-value*
Passive Smoke					
Positive	47.6	52.4	1.128	0.571-2.229	0.431
Negative	50.6	49.4			
Smoke					
Positive	28.3	71.7	**3.296**	1.610-6.748	**0.001**
Negative	56.5	43.5			
Alcohol consumption					
Positive	7.7	92.3	**13.500**	1.720-105.932	**0.001**
Negative	52.9	47.1			
Depression and stress					
Positive	34.3	65.7	**2.630**	1.428-4.844	**0.001**
Negative	57.9	42.1			
Epileptic crisis					
Positive	36.4	63.6	1.949	0.901-4.217	0.063
Negative	52.7	47.3			
Sport practice					
Positive	65.5	34.5	0.474	0.208-1.078	0.053
Negative	47.4	52.6			
Obesity					
Positive	24.0	76.0	**4.495**	2.175-9.288	**0.000**
Negative	58.7	41.3			
Consumption of milk and dairy products					
Positive	47.8	52.2	1.144	0.636-2.059	0.382
Negative	51.1	48.9			
Medicinal herbs as alternative medicines					
Positive	34.6	65.4	**2.347**	1.217-4.526	**0.008**
Negative	55.4	44.6			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

Risk factors	Control group (%)	CAD group (%)	OR	CI 95%	*P-value*
Sweets consumption					
Positive	57.7	42.3	0.602	0.339-1.068	0.055
Negative	45.1	54.9			
Salt consumption					
Positive	32.6	67.4	**2.509**	1.232-5.109	**0.008**
Negative	54.8	45.2			
Bread consumption					
Positive	49.4	50.6	1.041	0.596-1.819	0.500
Negative	50.5	49.5			
Pastries consumption					
Positive	45.9	54.1	1.332	0.759-2.338	0.195
Negative	53.0	47.0			
Red Meat consumption					
Positive	50.0	50.0	1.000	0.493-2.027	0.571
Negative	50.0	50.0			
Medication consumption					
Positive	19.0	81.0	**5.924**	2.577-13.621	**0.000**
Negative	58.2	41.8			
Canned food consumption					
Positive	47.4	52.6	1.139	0.561-2.310	0.429
Negative	50.6	49.4			
Abdominal obesity					
Positive	23.1	76.9	**5.667**	2.887-11.124	**0.000**
Negative	63.0	37.0			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

2.2.2. Comparative study between CAD and MetS group

Odds ratio of clinic-pathological factors (Table 09) and socioeconomic (Table 10) show that abdominal obesity, age > 60, chest pain and cardio surgery represent a significative risk factor with (OR= 1.162; P= 0.000, OR= 1.836; P= 0.023, OR= 5.333; P= 0.000, OR= 8.083; P= 0.000).
In contrast the age < 40 years old represents a protective factor with (OR= 0.227; P= 0.014).

On the other hand, CAD heredity, chronic disease, kidney disease, liver disease, tonsillectomy, gallbladder dysfunction, infection disease, anemia, surgery operation, heart disease, stroke, HTN, diabetes mellitus, inflammatory, rheumatism, Age between [40-60], sudden death family history, breathing dysfunction, passive smoke, smoke, alcohol consumption, depression and stress, epileptic crisis, sport practice, obesity, consumption of milk and dairy products, medicinal herbs as alternative medicines, sweets consumption, salt consumption, bread consumption, pastries consumption, red meat consumption, medication consumption, and canned food consumption are not considered as predictor risk factors for CAD population through the OR value and P-Value which are not significative.

Table 09: Comparative study of clinical factors between CAD and MetS group (N=200).

Risk factors	MetS group (%)	CAD group (%)	OR	CI 95%	*P-value*
CAD Heredity					
Positive	49.1	50.9	1.051	0.565-1.956	0.500
Negative	50.3	49.7			
Chronic disease					
Positive	51.7	48.3	1.311	0.687-2.505	0.256
Negative	44.9	55.1			
kidney disease					
Positive	48.0	52.0	1.096	0.474-2.535	0.500
Negative	50.3	49.7			
Liver disease					
Positive	50.0	50.0	1.000	0.138-7.242	0.689
Negative	50.0	50.0			
Tonsillectomy					
Positive	83.3	16.7	0.192	0.022-1.673	0.106
Negative	49.0	51.0			
Gallbladder dysfunction					
Positive	38.9	61.1	1.642	0.609-4.424	0.230
Negative	51.1	48.9			
Infection disease					
Positive	50.0	50.0	1.000	0.243-4.114	0.640
Negative	50.0	50.0			
Anaemia					
Positive	51.1	48.9	0.942	0.480-1.851	0.500
Negative	49.6	50.4			
Surgery operation					
Positive	48.4	51.6	1.129	0.647-1.970	0.388
Negative	51.4	48.6			
Heart disease					
Positive	61.1	38.9	0.609	0.226-1.641	0.230
Negative	48.9	51.1			
Stroke					
Positive	47.1	52.9	1.137	0.420-3.078	0.500
Negative	50.3	49.7			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

Risk factors	MetS group (%)	CAD group (%)	OR	CI 95%	*P-value*
Cardio surgery					
Positive	13.0	87.0	**8.083**	2.318-28.187	**0.000**
Negative	54.8	45.2			
HTN					
Positive	50.0	50.0	1.000	0.566-1.765	0.558
Negative	50.0	50.0			
Diabetes mellitus					
Positive	51.4	48.6	0.886	0.507-1.547	0.388
Negative	48.3	51.7			
Inflammatory					
Positive	57.1	42.9	0.658	0.360-1.200	0.112
Negative	46.7	53.3			
Rheumatism					
Positive	54.8	45.2	0.785	0.397-1.555	0.301
Negative	48.7	51.3			
Chest pain					
Positive	28.1	71.9	**5.333**	2.899-9.812	**0.000**
Negative	67.6	32.4			
AGE					
<40 years old					
Positive	80.0	20.0	**0.227**	0.062-0.830	**0.014**
Negative	47.6	52.4			
{40-60} years old					
Positive	53.8	46.2	0.777	0.439-1.373	0.234
Negative	47.5	52.5			
>60 years old					
Positive	43.0	57.0	**1.836**	1.046-3.222	**0.023**
Negative	58.1	41.9			
Sudden death family					
Positive	61.8	38.2	0.562	0.264-1.197	0.094
Negative	47.6	52.4			
Breathing dysfunction					
Positive	43.8	56.3	1.348	0.630-2.887	0.282
Negative	51.2	48.8			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

Table 10: Comparative socioeconomic factors between CAD and MetS group (N=200).

Risk factors	MetS group (%)	CAD group (%)	OR	CI 95%	*P-value*
Passive Smoke					
Positive	48.8	51.2	1.061	0.540-2.084	0.500
Negative	50.3	49.7			
Smoke					
Positive	43.1	56.9	1.478	0.799-2.734	0.138
Negative	52.8	47.2			
Alcohol consumption					
Positive	29.4	70.6	2.591	0.877-7.651	0.063
Negative	51.9	48.1			
Depression and stress					
Positive	47.0	53.0	1.229	0.700-2.159	0.283
Negative	52.1	47.9			
Epileptic crisis					
Positive	36.4	63.6	1.949	0.901-4.217	0.063
Negative	52.7	47.3			
Sport practice					
Positive	47.4	52.6	1.123	0.436-2.895	0.500
Negative	50.3	49.7			
Obesity					
Positive	47.9	52.1	1.138	0.640-2.025	0.385
Negative	51.2	48.8			
Consumption of milk and dairy products					
Positive	51.4	48.6	0.917	0.515-1.634	0.441
Negative	49.2	50.8			
Medicinal herbs as alternative medicines					
Positive	42.4	57.6	1.545	0.837-2.854	0.107
Negative	53.2	46.8			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

Risk factors	MetS group(%)	CAD group (%)	OR	CI 95%	*P-value*
Sweets consumption					
Positive	50.7	49.3	0.956	0. 531-1.720	0.500
Negative	49.6	50.4			
Salt consumption					
Positive	47.3	52.7	1.163	0.624-2.164	0.376
Negative	51.0	49.0			
Bread consumption					
Positive	52.1	47.9	0.852	0.488-1.485	0.335
Negative	48.1	51.9			
Pastries consumption					
Positive	47.7	52.3	1.176	0.673-2.057	0.335
Negative	51.8	48.2			
Red Meat consumption					
Positive	60.4	39.6	0.574	0.297-1.112	0.068
Negative	46.7	53.3			
Medication consumption					
Positive	50.0	50.0	1.000	0.557-1.795	0.559
Negative	50.0	50.0			
Canned food consumption					
Positive	58.3	41.7	0.643	0.334-1.239	0.123
Negative	47.4	52.6			
Abdominal obesity					
Positive	78.7	21.3	**1.162**	0.080-0.327	**0.000**
Negative	37.4	62.6			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

2.2.3. Comparative study between MetS and control group

Odds ratio of clinic-pathological (Table 11) and socioeconomic factors (Table 12) show that depression and stress, salt consumption, smoke, surgery operation, obesity, kidney disease, medication consumption, abdominal obesity, gallbladder dysfunction, chest pain, rheumatism, breath dysfunction and stroke with

(OR=2.140; P=0.011, OR=2.158; P=0.025, OR=2.231; P=0.023, OR=2.786; P=0.001, OR=3.949; P=0.000, OR=4.409; P=0.014, OR=5.667; P=0.000, OR=5.924; P=0.000, OR=7.452; P=0.032, OR=8.000; P=0.000, OR=8.239; P=0.000, OR=8.308; P=0.000, OR=8.609; P=0.017) represent a risk factors.

Heart disease, inflammatory, Age > 60 , diabetes mellitus, HTN, and chronic disease respectively with (OR=12.236; P=0.002, OR=13.500; P=0.000, OR=84.333; P=0.000, OR=131.233; P=0.000, OR=154.846; P=0.000, OR=173.727; P=0.000) represent are high significative risk factors.

Also, Age <40 years old and sport practice with (OR=0.061; P=0.000, OR=0.422; P=0.033) considered as protective factors.

On the other hand, CAD heredity, liver disease, tonsillectomy, infection disease, anemia, cardio surgery, Age between [40-60], sudden death family history, passive smoke, alcohol consumption, epileptic crisis, consumption of milk and dairy products, medicinal herbs as alternative medicines, sweets consumption, bread consumption, pastries consumption, red meat consumption and canned food consumption are not considered as predictor risk factors for CAD population through the OR value and P-Value which are not significative.

Table 11: Comparative study of clinical factors between MetS and control group (N=200).

Risk factors	Control group (%)	MetS group (%)	OR	CI 95%	*P-value*
CAD Heredity					
Positive	51.8	48.2	0.906	0.488-1.679	0.437
Negative	49.3	50.7			
Chronic disease					
Positive	2.5	97.5	**173.727**	39.635-761.471	**0.000**
Negative	81.7	18.3			
kidney disease					
Positive	20.0	80.0	**4.409**	1.204-16.140	**0.014**
Negative	52.4	47.6			
Liver disease					
Positive	33.3	66.7	2.020	0.108-22.645	0.500
Negative	50.3	49.7			
Tonsillectomy					
Positive	54.5	45.5	0.825	0.243-2.795	0.500
Negative	12.5	87.5			
Gallbladder dysfunction					
Positive	12.5	87.5	**7.452**	0.900-61.729	**0.032**
Negative	51.6	48.4			
Infection disease					
Positive	50.0	50.0	1.000	0.138-7.242	0.689
Negative	50.0	50.0			
Anaemia					
Positive	39.5	60.5	1.693	0.824-3.477	0.103
Negative	52.5	47.5			
Surgery operation					
Positive	33.3	66.7	**2.786**	1.504-5.159	**0.001**
Negative	58.2	41.8			
Heart disease					
Positive	8.3	91.7	**12.236**	1.549-96.681	**0.002**
Negative	52.7	47.3			
Stroke					
Positive	11.1	88.9	**8.609**	1.056-70.170	**0.017**
Negative	51.8	48.2			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

Risk factors	Control group (%)	MetS group (%)	OR	CI 95%	*P-value*
Cardio surgery					
Positive	25.0	75.0	3.062	0.313-29.948	0.311
Negative	50.5	49.5			
HTN					
Positive	1.6	98.4	**154.846**	20.739-1156.136	**0.000**
Negative	71.7	28.3			
Diabetes mellitus					
Positive	1.7	98.3	**131.233**	17.597-978.673	**0.000**
Negative	69.7	30.3			
Inflammatory					
Positive	10.0	90.0	**13.500**	4.583-39.766	**0.000**
Negative	60.0	40.0			
Rheumatism					
Positive	14.8	85.2	**8.239**	2.724-24.917	**0.000**
Negative	58.9	41.1			
Chest pain					
Positive	13.8	86.2	**8.000**	2.669-23.982	**0.000**
Negative	56.1	43.9			
AGE					
<40 years old	85.2	14.8	**0.061**	0.029-0.128	**0.000**
Positive	26.1	73.9			
Negative					
{40-60} years old					
Positive	41.7	58.3	1.690	0.943-3.029	0.052
Negative	54.7	45.3			
>60 years old					
Positive	2.1	97.9	**84.333**	11.314-628.594	**0.000**
Negative	64.7	35.3			
Sudden death family					
Positive					
Negative	43.2	56.8	1.396	0.680-2.865	0.233
	51.5	48.5			
Breath dysfunction					
Positive					
Negative	17.2	82.8	**8.308**	3.877-17.801	**0.000**
	63.4	36.6			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

Table 12: Comparative study of socioeconomic factors between MetS and control group (N=200).

Risk factors	Control group (%)	MetS group (%)	OR	CI 95%	*P-value*
Passive Smoke					
Positive	48.8	51.2	1.063	0.535-2.113	0.500
Negative	50.3	49.7			
Smoke					
Positive	34.2	65.8	**2.231**	1.067-4.666	**0.023**
Negative	53.7	46.3			
Alcohol consumption					
Positive	83.3	16.7	5.211	0.598-45.426	0.106
Negative	49.0	51.0			
Depression and stress					
Positive	37.1	62.9	**2.140**	1.157-3.960	**0.011**
Negative	55.8	44.2			
Epileptic crisis					
Positive	50.0	50.0	1.000	0.425-2.355	0.586
Negative	50.0	50.0			
Sport practice					
Positive	67.9	32.1	**0.422**	0.181-0.984	**0.033**
Negative	47.1	52.9			
Obesity					
Positive	25.5	74.5	**3.949**	1.903-8.192	**0.000**
Negative	57.5	42.5			
Consumption of milk and dairy products					
Positive	46.4	53.6	1.248	0.696-2.238	0.276
Negative	51.9	48.1			
Medicinal herbs as alternative medicines					
Positive	41.9	58.1	1.519	0.768-3.003	0.151
Negative	52.2	47.8			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

Risk factors	Control group (%)	MetS group (%)	OR	CI 95%	*P-value*
Sweets consumption					
Positive	57.0	43.0	0.630	0.356-1.115	0.074
Negative	45.5	54.5			
Salt consumption					
Positive	35.0	65.0	**2.158**	1.050-4.435	**0.025**
Negative	53.8	46.3			
Bread consumption					
Positive	47.3	52.7	1.223	0.701-2.133	0.285
Negative	52.3	47.7			
Pastries consumption					
Positive	48.1	51.9	1.133	0.644-1.993	0.387
Negative	51.3	48.7			
Red Meat consumption					
Positive	39.6	60.4	1.741	0.900-3.371	0.068
Negative	53.3	46.7			
Medication consumption					
Positive	19.0	81.0	**5.924**	2.577-13.621	**0.000**
Negative	58.2	41.8			
Canned food consumption					
Positive	39.1	60.9	1.772	0.905-3.467	0.065
Negative	53.2	46.8			
Abdominal obesity					
Positive	17.2	82.8	**5.667**	2.887-11.124	**0.000**
Negative	63.4	36.6			

***OR** > **1** and **P** < **0.05** indicate a risk factor. ***OR** < **1** and **P** < **0.05** indicate a protective factor.

3. Paraclinical study

The following figures show images of ECG, for a person with myocardial infarction (MI) and a healthy subject (Figure 41 and 42) respectively.

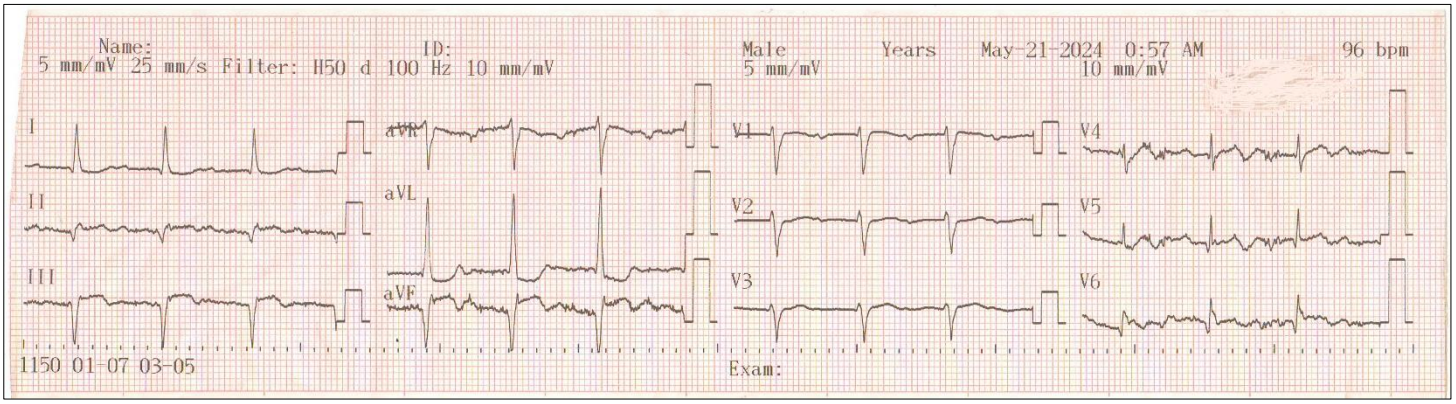

Figure 41: A picture of an echo-cardiogram of subject with myocardium infractus (MI).

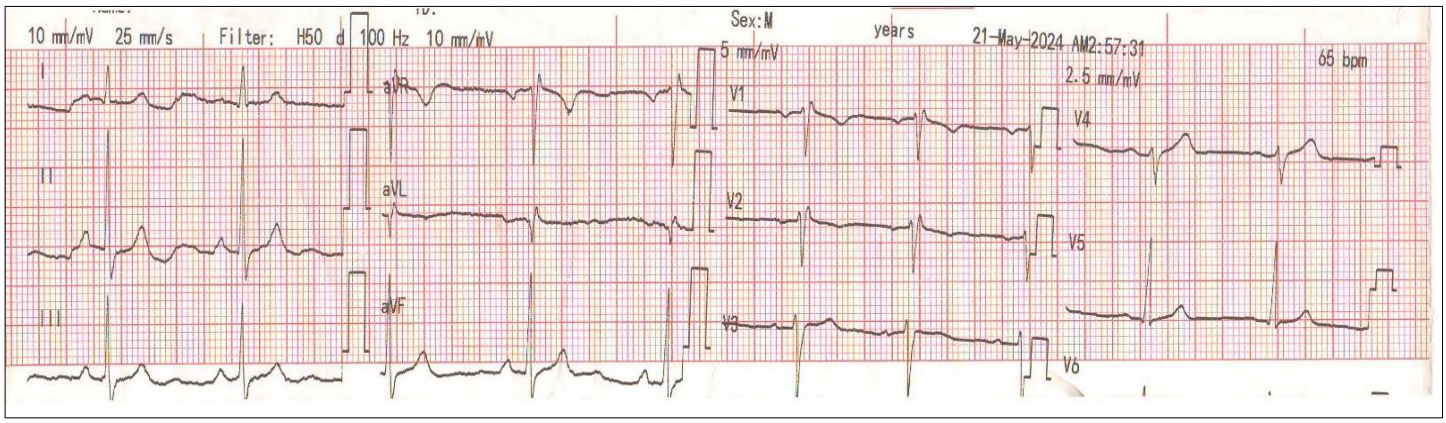

Figure 42: A picture of an echo-cardiogram of healthy subject.

4. Study of biological markers and predictive factors

4.1. Hematological markers

The results of hematological analysis for control, metabolic syndrome and coronary artery syndrome are illustrated in (Table 13, 14 and 15).

The outcomes of MetS patients as compared to healthy group show the leukocyte lineage (white blood cell, neutrophils) is significant increase ($P \leq 0.01$), but there is no significant difference in the other markers red blood cell, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width- standard deviation, red cell distribution width- coefficient of variation, lymphocytes, monocytes, eosinophils, basophils, procalcitonin, neutrophils to lymphocytes ratio, monocytes to lymphocytes ratio, platelets, men platelet volume, platelet larger cell ratio and platelet distribution width with ($P > 0.05$).

Table 13: Erythrocyte line in control, MetS and CAD groups.

Erythrocyte line	Control group	MetS group	CAD group
RBC {10^6/uL}	4.63 ± 0.07	4.68 ± 0.06 ^{NS}	4.49 ± 0.10 $^{NS, NS}$
Hb {g/dL}	12.82 ± 0.29	13.00 ± 0.20 ^{NS}	12.51 ± 0.25 $^{NS, NS}$
HCT {%}	40.28 ± 0.75	40.75 ± 0.57 ^{NS}	38.97 ± 0.75 $^{NS, NS}$
MCV {fL}	86.85 ± 1.03	86.47 ± 1.29 ^{NS}	87.26 ± 1.06 $^{NS, NS}$
MCH {Pg}	27.60 ± 0.43	27.80 ± 0.25 ^{NS}	28.02 ± 0.36 $^{NS, NS}$
MCHC {g/dL}	31.64 ± 0.25	31.89 ± 0.17 ^{NS}	32.13 ± 0.26 $^{NS, NS}$
RDW-SD {fL}	41.39 ± 0.51	42.17 ± 0.76 ^{NS}	42.54 ± 0.65 $^{NS, NS}$
RDW-CV {%}	13.37 ± 0.28	13.66 ± 0.25 ^{NS}	13.68 ± 0.15 $^{NS, NS}$

(NS) P> 0.05, **(*,#)** P≤0.05, **(**, ##)** P≤0.01, **(***, ###)** P≤0.001. *** (**between patient (CAD, Metabolic syndrome), and control group**). # (**between patient; CAD, and Syndrome Metabolic group**).**

Table 14: Leukocyte line in control, MetS and CAD groups.

Leukocyte line	Control group	MetS group	CAD group
WBC {10^3/uL}	6.20 ± 0.25	7.35 ± 0.38 **	11.03± 0.80 $^{***,###}$
NEUT {10^3/uL}	3.38 ± 0.20	4.35 ± 0.33 **	8.04 ± 0.73 $^{***,###}$
LYMPH {10^3/uL}	2.21 ± 0.07	2.31 ± 0.11 ^{NS}	2.11 ± 0.13 $^{NS, NS}$
MONO {10^3/uL}	0.41 ± 0.01	0.43 ± 0.02 ^{NS}	0.66 ± 0.04 $^{***,###}$
EOS {10^3/uL}	0.17 ± 0.02	0.23 ± 0.05 ^{NS}	0.20 ± 0.09 $^{NS, NS}$
BASO {10^3/uL}	0.018 ± 0.002	0.021 ± 0.002 ^{NS}	0.020 ± 0.002 $^{NS, NS}$
PCT {%}	0.28 ± 0.01	0.28 ± 0.01 ^{NS}	0.30 ± 0.01 $^{NS, NS}$
NLR	1.56 ± 0.08	2.26 ± 0.42 ^{NS}	4.84 ± 0.73 $^{***,###}$
MLR	0.19 ± 0.01	0.20 ± 0.02 ^{NS}	0.35 ± 0.03 $^{***,###}$
PLR	124.07 ± 6.04	127.47 ± 8.29 ^{NS}	151.60 ± 15.40 $^{NS, NS}$

(NS) P> 0.05, **(*,#)** P≤0.05, **(**, ##)** P≤0.01, **(***, ###)** P≤0.001. *** (**between patient (CAD, Metabolic syndrome), and control group**). # (**between patient; CAD, and Syndrome Metabolic group**).**

Table 15: Platelet line in control , MetS and CAD groups.

Platelet line	Control group	MetS group	CAD group
PLT {10^3/uL}	263.20 ± 10.30	266.10 ± 11.40 ^{NS}	265.00 ± 15.00 $^{NS\,,\,NS}$
MPV {fL}	10.91 ± 0.14	10.72 ± 0.14 ^{NS}	10,97 ± 0,13$^{NS\,,\,NS}$
P-LCR {%}	32.25 ± 1.03	30.5 ± 1.02 ^{NS}	36,63 ± 5.07 $^{NS\,,\,NS}$
PWD {fL}	13.65 ± 0.32	13.33 ± 0.31 ^{NS}	16,11 ± 2.58 $^{NS\,,\,NS}$

(NS) P> 0.05, **(*,#)** P≤0.05, **(**, ##)** P≤0.01, **(***, ###)** P≤0.001. *** (**between patient (CAD, Metabolic syndrome), and control group**). # (**between patient; CAD, and Syndrome Metabolic group**).**

Regarding the CAD patients as compared to the healthy groups show that leukocyte lineage (WBC, NEUT, MONO, NLR and MLR) is significantly increased with (P≤0.001) but there is no significant difference in RBC, HB, HCT, MCV, MCH, MCHC, RDW-SD, RDW-CV, LYMPH, EOS, BASO, PCT, PLR, PLT, MPV, P-LCR and PDW with (P > 0.05).

The CAD patients as compared to the MetS groups show that the leukocyte lineage (WBC, NEUT, MONO, NLR and MLR) is significant increase (P≤0.001). but there is no significant difference in RBC, HB, HCT, MCV, MCH, MCHC, RDW-SD, RDW-CV LYMPH, EOS, BASO, PCT, PLR, PLT, MPV, P-LCR and PDW with (P > 0.05).

4.2. Biochemical markers

Concerning biochemical markers for control, metabolic syndrome and coronary artery disease are illustrated in (Table 16).

For the MetS patients compared to the healthy group our results demonstrated that a significant increase (P≤0.001) in glycaemia, triglyceride, high density lipoprotein cholesterol, very low lipoprotein density, aspartate aminotransferase, alanine aminotransferase, phosphorus and amylase also with (P ≤ 0.01) in total cholesterol, albumin, gamma glutamyl transferase, total protein, lipase and C-reactive protein and with (P ≤ 0.05) in phosphatase alkaline.

Regarding the low-density lipoprotein cholesterol, creatinine, urea, electrolyte (NA, K, Cl), calcium, Vitamin-D (25 OH), lactate dehydrogenase, creatine phosphokinase, there are no significant difference (P > 0.05).

Table 16: Biochemical parameters levels in control, MetS and CAD groups.

Biochemical Parameters	Control group	MetS group	CAD group
GLY {g/L}	0.87 ±0.02	1.59 ± 0.17 ***	1.49 ± 0.12***, NS
TG {g/L}	0.77 ±0.05	1.90 ± 0.18 ***	1.36 ± 0.08***,###
TC {g/L}	1.70 ± 0.03	2.07 ± 0.12**	1.73 ± 0.06 NS ,###
HDL-C {g/L}	0.42 ±0.03	0.30 ± 0.01 ***	0.29 ±0.01***,NS
LDL-C {g/L}	1.10 ±0.04	1.25 ± 0.14 NS	1.10 ±0.06 NS ,#
VLDL{g/L}	0.15 ±0.01	0.38 ± 0.03 ***	0.27 ±0.01 *** ,###
Cr {mg/L}	7.31 ±0.24	7.66 ± 0.33 NS	13.09 ± 2.58*,#
UREA {g/L}	0.26 ±0.01	0.29 ± 0.02 NS	0.45 ± 0.04***,###
Sodium {mmol/L}	133.93 ± 0.70	135.44 ± 0.97 NS	134.37 ± 0.79 NS , NS
Potassium {mmol/L}	5.46 ± 0 22	5.09 ± 0.22 NS	4.83 ± 0.20**, NS
Chloride {mmol/L}	102,55 ± 2.32	102.92 ± 2.76 NS	103.19 ± 1.16 NS , NS
ASAT {U/L}	24.64 ± 0.97	30,36 ±1.31 ***	61.05 ± 6.18 ***,###
ALAT {U/L}	21.19 ± 0.89	26.88 ± 1.36 ***	58.70 ± 10.90***,##
ALB {g/L}	44.76 ± 0.28	42.76 ± 0.74 **	35.79 ± 1.10***,###
GGT {U/L}	12.81 ± 0.96	21.49 ± 3.08**	23.13 ± 2.56***, NS
ALP {IU/L}	142.70 ± 10.6	162.45 ± 8.61 *	175.50 ± 11.60**, NS
T. Protein {g/L}	76.48 ± 2.73	71.73 ± 1.59 **	65.57 ± 1.95***,##
Phosphorus {mg/L}	41.02 ± 1.56	34.71 ± 1.30 ***	42.70 ± 2.19 NS ,###
Calcium {mg/L}	94.93 ± 1.00	95.43 ± 1.36 NS	89.93 ± 1.54**,###
AMY{IU/L}	66.05 ± 3.35	54.33 ± 3.29***	49.95 ± 3.26***, NS
Vit-D {ng/mL}	11.43 ± 1.58	10.00± 0.75 NS	8.5 ± 1.05 **, NS
LP {IU/L}	29.27 ± 1.16	25.27 ± 1.40**	25.08 ± 1.98*, NS
LDH {IU/L}	139.36 ± 4.53	151.30 ± 13.6 NS	701.00 ± 103.00***,###
CRP {mg/L}	3.52 ± 0.15	11.11 ± 3.00 **	40.35 ± 8.36***,###
PT {%}	100.00 ± 0.00	95.94 ± 2.52 NS	89.37 ± 3.75**,NS
INR	1.00 ± 0.00	1.00 ± 0.02 NS	1.22 ± 0.13 NS , NS
CPK{IU/L}	108.3 ± 13.4	94.23 ± 9.88 NS	329.30 ± 73.10**,##

(NS) P> 0.05, **(*,#)** P≤0.05, **(**, ##)** P≤0.01, **(***, ###)** P≤0.001. *** (**between patient (CAD, Metabolic syndrome), and control group**). # (**between patient; CAD, and Syndrome Metabolic group**).**

In term of CAD patients as compared to the control groups, the outcomes show that there was a significant increase in GLY, TG, HDL-C, VLDL, UREA, ASAT, ALAT, ALB, GGT, T.Protein ,AMY, LDH , CRP and PT with (P≤0.001), and (P ≤ 0.01) in K , ALP, Ca, VIT-D, LP and CPK and (P ≤ 0.05) in Cr. On the other side there is no significant difference in TC, LDL-C, NA, Cl and PO_4 with (P > 0.05).

For CAD patients as compared to the MetS groups, the outcomes show that there was a significant increase in TG, TC, VLDL, UREA, ASAT, ALB, PO_4, Ca and LDH and CRP with (P≤0.001), and (P ≤

0.01) in ALAT, T.protein and CPK also with ($P \leq 0.05$) in LDL-C and Cr. On the other side there are no significant difference in GLY, HDL-C, electrolyte (NA, K, Cl), GGT, ALP, AMY, Vit-D and LP with ($P > 0.05$).

4.3. Oxidative stress markers

Our outcomes illustrated in graphic columns for all the groups, MDA (Figure 43), SOD (Figure 44), GSH (Figure 45), GPX (Figure 46) and TAC (Figure 47) respectively. Concerning the MetS patients as compared to the control groups, our outcomes show that there was a significant increase in malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GPX) with ($P \leq 0.001$), but there is no significant difference in glutathione (GSH) and total antioxidant capacity (TAC) with ($P > 0.05$).

Regarding the results of CAD patients as compared to the control groups, there is a significant increase in MDA, SOD and GPX with ($P \leq 0.001$), also GSH with ($P \leq 0.01$) and FRAP with ($P \leq 0.05$).

On the other hand, CAD patients as compared to the MetS groups, the outcomes show that there was a significant increase in MDA with ($P \leq 0.001$) also in GSH and TAC with ($P \leq 0.01$) but there is no significant difference in SOD and GPX ($P > 0.05$).

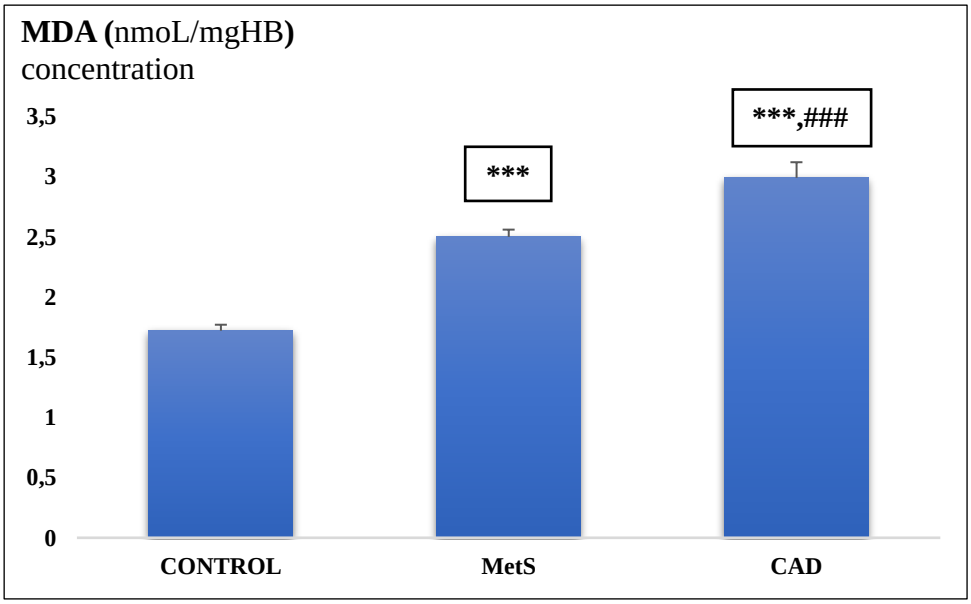

Figure 43: MDA concentration in the control, Mets and CAD groups (N=80).

For all graphic columns of oxidative stress, the following symbols mean

(NS) P> 0.05, **(*,#)** P≤0.05, **(**, ##)** P≤0.01, **(***, ###)** P≤0.001. * **(**between patient (CAD, Metabolic syndrome), and control group**). # (**between patient; CAD, and Syndrome Metabolic group**).**

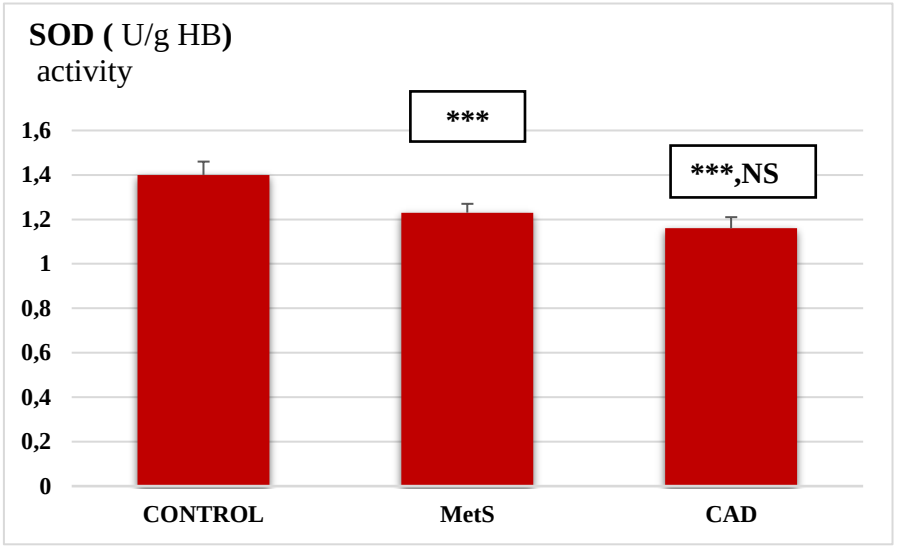

Figure 44: SOD activity in the control, Mets and CAD groups (N=80).

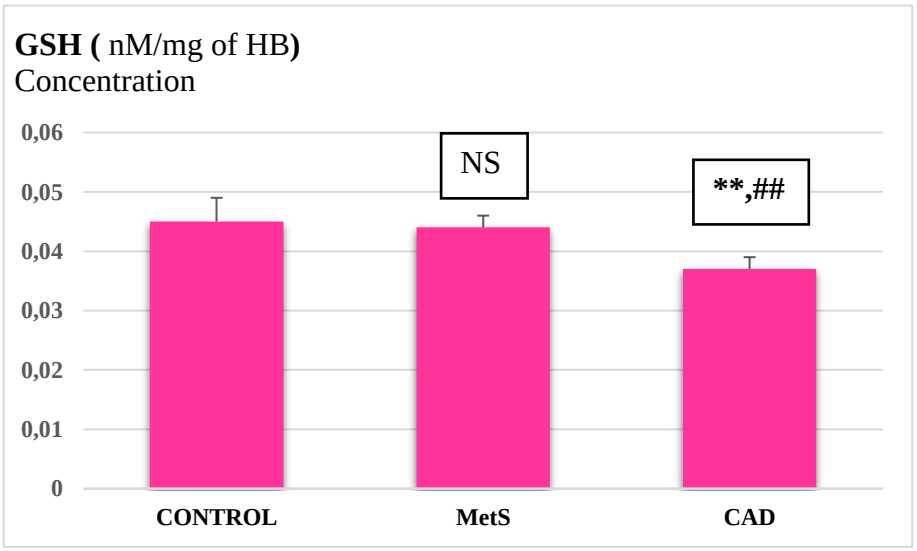

Figure45: GSH concentration in the control, Mets and CAD groups (N=80).

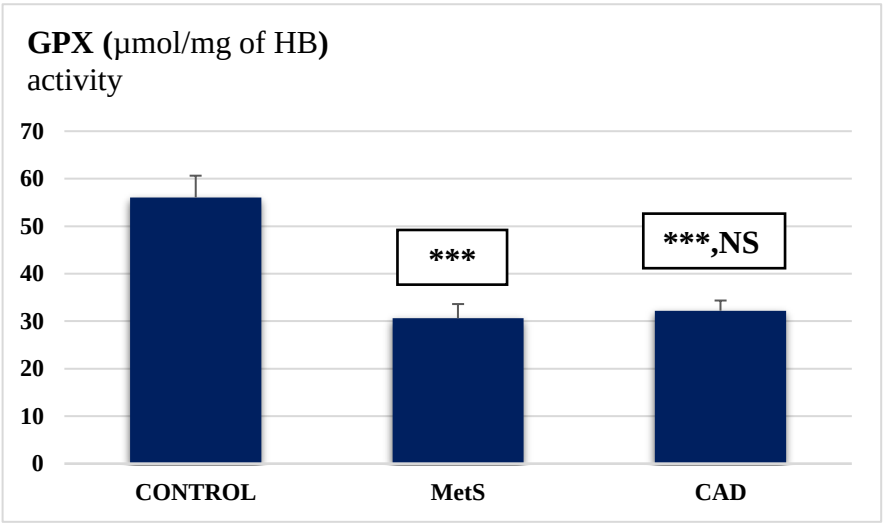

Figure46: GPX activity in the control, Mets and CAD groups (N=80).

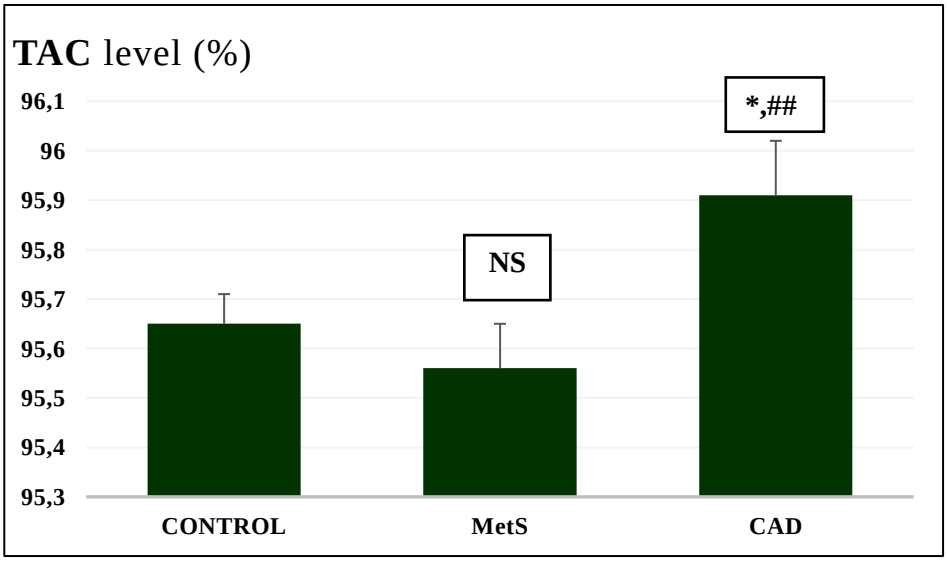

Figure 47: TAC level in the control, Mets and CAD groups.

5. Predictive factors study of biological markers

5.1. Hematological markers

5.1.1. CAD with control group

Our result for both sex women and man, show that WBC, NEUT, MONO, NLR and MLR were a significant predictive factor (P <0.05), with high percentage of specificity (100, 100,100 ,97.6, 100,100%) with AUC (86.5, 88.7,80.7, 90.2,80.8) and important percentage of Sensitivity (35.7, 35.7, 38.1, 23.8,42.9) respectively (Figure 48 and Table 17).

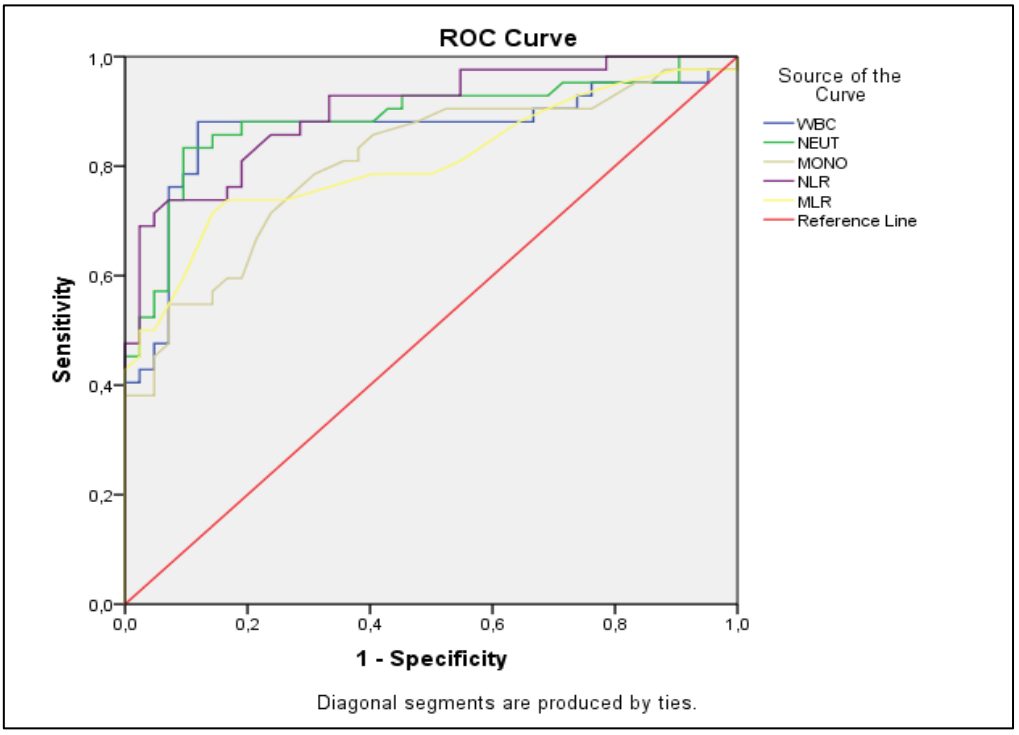

Figure 48: Roc curve of hematological markers in CAD and control group .

Table 17: Sensitivity, specificity and AUV value of some hematological markers in CAD and control group.

Test Result variables	Sensitivity%	specificity%	AUC%	P-Value	CI 95%	
					Lower Bound	Upper Bound
WBC	35.7	100	86.5	**0.000**	0.777	0.953
NEUT	35.7	100	88.7	**0.000**	0.810	0.963
MONO	38.1	97.6	80.7	**0.000**	0.713	0.901
NLR	23.8	100	90.2	**0.000**	0.837	0.966
MLR	42.9	100	80.8	**0.000**	0.711	0.904

5.1.2. CAD with MetS group

Our result for both sex women and man, show that WBC, NEUT, MONO, NLR and MLR blood were a significant predictive factor (P <0.05), with high percentage of Specificity (33.3, 92.9, 92.9, 88.1,95.2, 90.5 %) with AUC (38.6, 75.5 ,80.2, 78.1, 82.8, 78.9) and important percentage of Sensitivity (35.7, 35.7, 38.1, 23.8, 42.9) respectively (Figure 49 and Table 18).

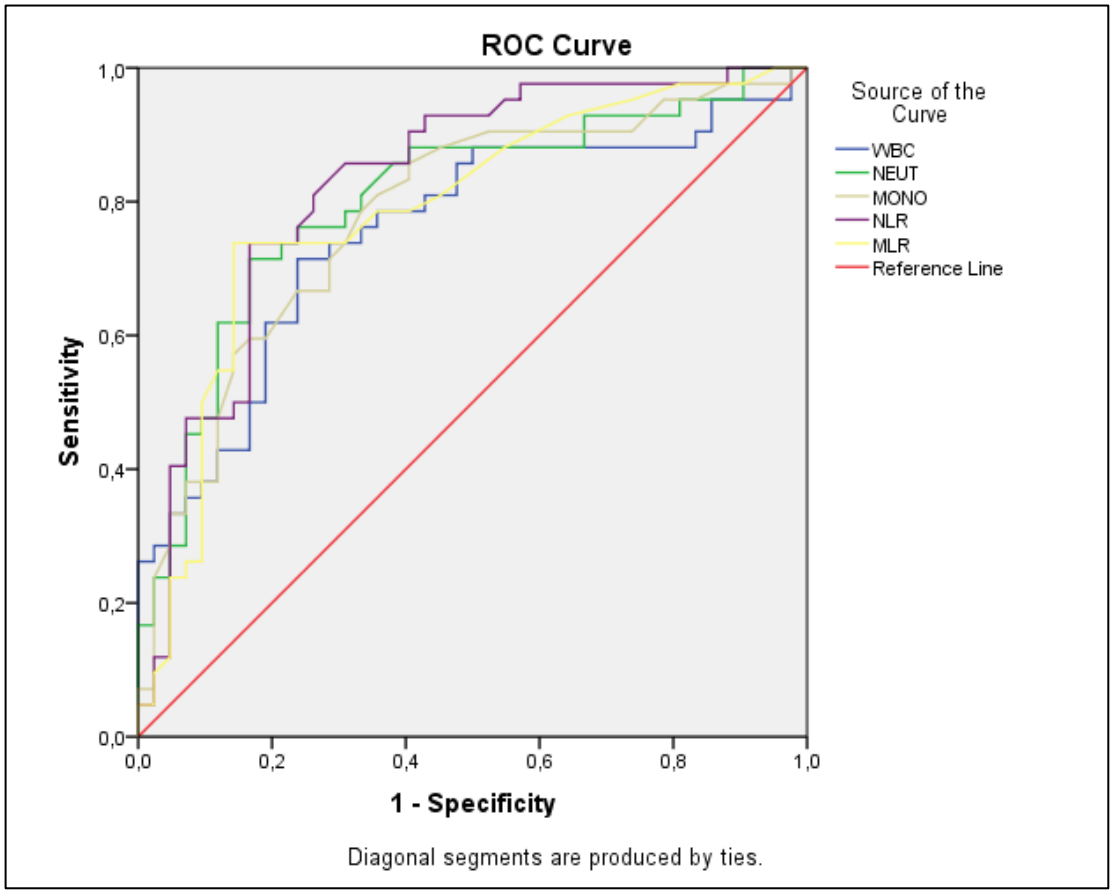

Figure 49: Roc curve of hematological markers in CAD and MetS group.

Table 18: Sensitivity, specificity and AUV value of some hematological markers in CAD and MetS group.

Test Result variables	Sensitivity%	Specificity%	AUC%	P-Value	CI 95%	
					Lower Bound	Upper Bound
WBC	35.7	92.9	75.5	**0.000**	0.649	0.861
NEUT	35.7	92.9	80.2	**0.000**	0.705	0.899
MONO	38.1	88.1	78.1	**0.000**	0.681	0.881
NLR	23.8	95.2	82.8	**0.000**	0.738	0.918
MLR	42.9	90.5	78.9	**0.000**	0.689	0.889

5.1.3. MetS with control group

Our result for both sex women and man, show that, WBC, NEUT, were a significant predictive factor (P <0.05), with high percentage of specificity (88.1, 83.3 %) with AUC (65.4, 65.2) and important percentage of Sensitivity (50, 40.5) respectively (Figure 50 and Table 19).

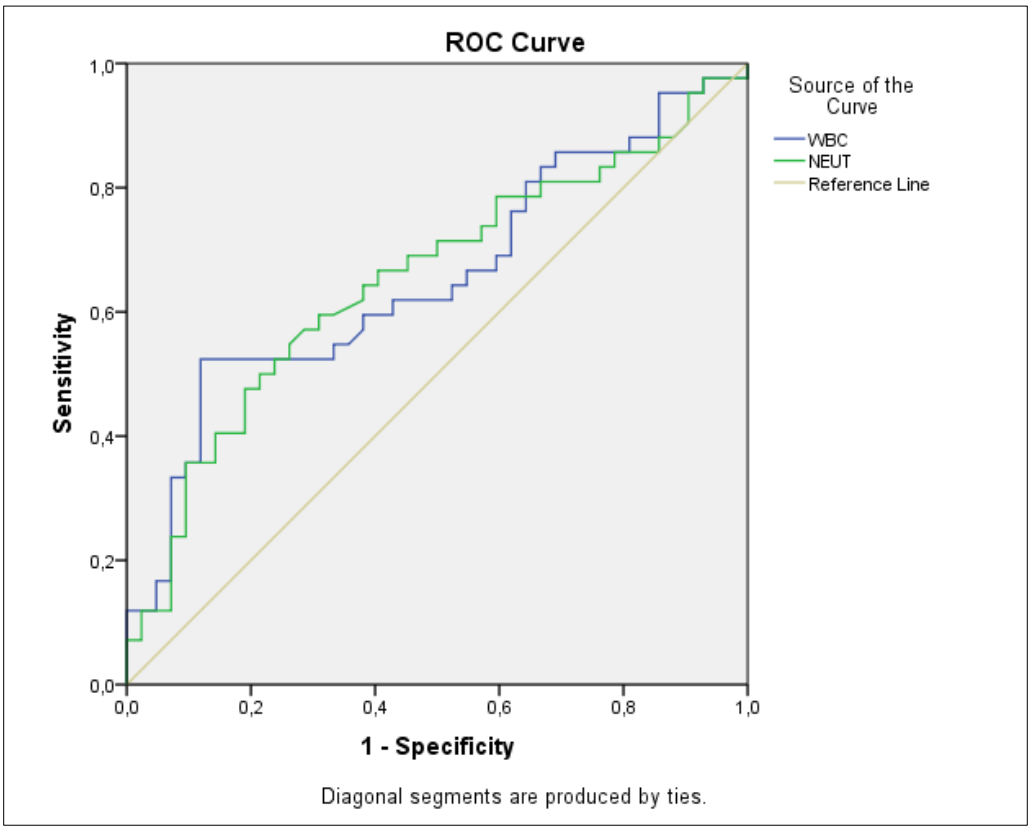

Figure 50: Roc curve of hematological markers in MetS and healthy group.

Table 19: Sensitivity, specificity and AUV value of some hematological markers in MetS and control group.

Test Result variables	Sensitivity%	Specificity%	AUC%	P-Value	CI 95%	
					Lower Bound	Upper Bound
WBC	50	88.1	65.4	**0.015**	0.536	0.773
NEUT	40.5	83.3	65.2	**0.016**	0.534	0.771

5.2. Biochemical markers

5.2.1. CAD with control group

Our result for both sex women and man, show that GLY, TG, VLDL, HDL-C, Cr, UREA, ASAT, ALAT, ALB, PT, AMY, CRP, LDH and CPK serum were a significant predictive factor (P <0.05), with high percentage of specificity (100, 100, 100, 100, 100, 94.1, 100, 100, 1.6, 2.5, 17.6, 100, 100, 100%) with AUC (97.2, 94, 94.1, 25.2, 90, 83.3, 93.8, 89.7, 9.8, 25, 19.3, 96.7, 94.4, 81%) and important percentage of Sensitivity (50, 55.6, 50, 85, 22.2, 33.3, 33.3, 22.2, 55.6, 72.2, 22.2, 22.2, 55.6, 50%)respectively (Figure 51 and Table 20).

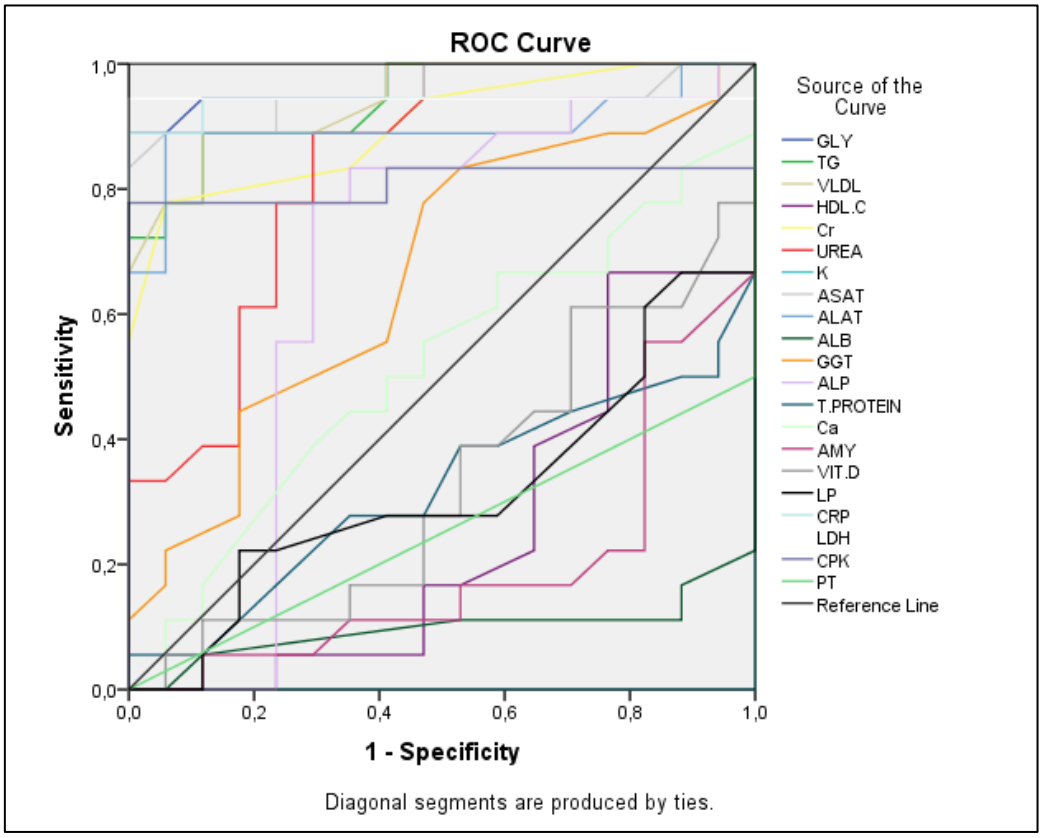

Figure 51: Roc curve of biochemical markers in CAD and control group.

Figure 20: Sensitivity, specificity and AUV value of some biochemical markers in CAD and control group.

Test Result variables	Sensitivity%	Specificity%	AUC%	P-Value	CI 95%	
					Lower Bound	Upper Bound
GLY	50	100	97.2	**0.000**	0.923	1.000
TG	55.6	100	94	**0.000**	0.866	1.000
VLDL	50	100	94.1	**0.000**	0.869	1.000
HDL-C	85	100	25.2	**0.012**	0.089	0.415
Cr	22.2	100	90.0	**0.000**	0.798	1.000
UREA	33.3	94.1	83.3	**0.001**	0.697	0.969
ASAT	33.3	100	93.8	**0.000**	0.843	1.000
ALAT	22.2	100	89.7	**0.000**	0.775	1.000
ALB	55.6	1.6	9.8	**0.000**	0.000	0.218
T.Protein	72.2	11.8	31.9	0.067	0.136	0.501
PT	72.2	2.5	25.0	**0.012**	0.083	0.417
Calcium (Ca)	66.7	23.5	51.3	0.895	0.318	0.708
AMY	22.2	17.6	19.3	**0.002**	0.045	0.341
Vit-D	16.7	52.9	33.2	0.089	0.151	0.512
LP	5.6	88.2	31.9	0.067	0.137	0.500
CRP	22.2	100	96.7	**0.000**	0.911	1.000
LDH	55.6	100	94.4	**0.000**	0.839	1.000
CPK	50	100	81.0	**0.002**	0.637	0.984
Potassium (K)	27.8	58.8	43.3	0.499	0.239	0.627
GGT	11.1	100	66.3	0.099	0.481	0.846
ALP	38.9	76.5	66.2	0.102	0.460	0.864

5.2.2. CAD with MetS group

Our result for both sex women and man, show that, white TG,TC, VLDL, Cr, UREA, ASAT, ALAT, ALB, T.Protein, PO_4, Ca, CRP, LDH and CPK serum were a significant predictive factor ($P < 0.05$), with high percentage of specificity (42.9, 26.2, 42.9, 97.6, 95.2, 100, 100, 9.5, 14.3, 83.3, 31, 95.2, 100, 100%) with AUC (35.8, 36.7, 35.8, 78.4, 78.2, 84.2, 79.5, 15.2, 29.5, 69.9, 32.9, 78.8, 87.5, 69.3%) and important percentage of Sensitivity (44.4, 61.1, 41.7, 25, 36.1, 33.3, 25,52.8, 50, 41.7, 44.4, 27.8, 38.9, 30.6 %) respectively (Figure 52 and Table 21).

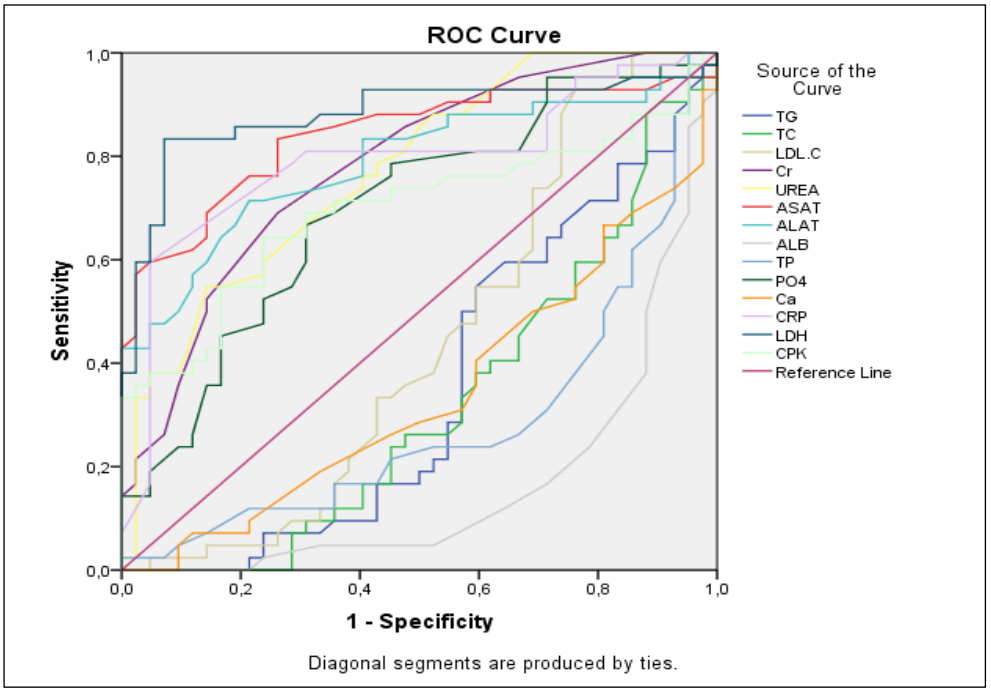

Figure 52: Roc curve of biochemical markers in CAD and MetS group.

Table 21: Sensitivity, specificity and AUV value of some biochemical markers in CAD and MetS group.

Test Result variables	Sensitivity%	Specificity%	AUC%	P-Value	CI 95%	
					Lower Bound	Upper Bound
TG	44.4	42.9	35.8	**0.032**	0.235	0.482
TC	61.1	26.2	36.7	**0.044**	0.244	0.491
LDL-C	52.8	40.5	47.0	0.645	0.338	0.601
VLDL	41.7	42.9	35.8	**0.032**	0.235	0.481
Cr	25.0	97.6	78.4	**0.000**	0.683	0.884
UREA	36.1	95.2	78.2	**0.000**	0.681	0.883
ASAT	33.3	100	84.2	**0.000**	0.744	0.939
ALAT	25.0	100	79.5	**0.000**	0.689	0.901
ALB	52.8	9.5	15.2	**0.000**	0.064	0.240
T.Protein	50	14.3	29.5	**0.002**	0.175	0.415
Phosphorus (PO_4)	41.7	83.3	69.9	**0.003**	0.582	0.817
Calcium (Ca)	44.4	31.0	32.9	**0.010**	0.208	0.415
CRP	27.8	95.2	78.8	**0.000**	0.679	0.897
LDH	38.9	100	87.5	**0.000**	0.784	0.966
CPK	30.6	100	69.3	**0.003**	0.565	0.821

5.2. 3. MetS with control group

Our result for both sex women and man, show that, white GLY,TG ,TC, HDL-C, VLDL, AMY, LP, CRP, ASAT, ALAT, GGT, ALP and PO_4 serum were a significant predictive factor (P <0.05), with high percentage of specificity (100, 100, 100, 47.1, 100, 35.3, 41.2, 100, 91.2, 88.2, 88.2, 79.4, 38.2 %) with AUC (78.4, 90.4, 67.8, 29.4, 90.6, 31.5, 33.6, 88.9, 74.9,73, 68.1, 60.5, 32.7%) and important percentage of Sensitivity (34.2, 44.7, 45.7, 26.3, 42.1, 36.8, 39.5, 23.7, 47.4, 55.3, 26.3, 47.4, 34.2 %) respectively (Figure 53 and Table 22).

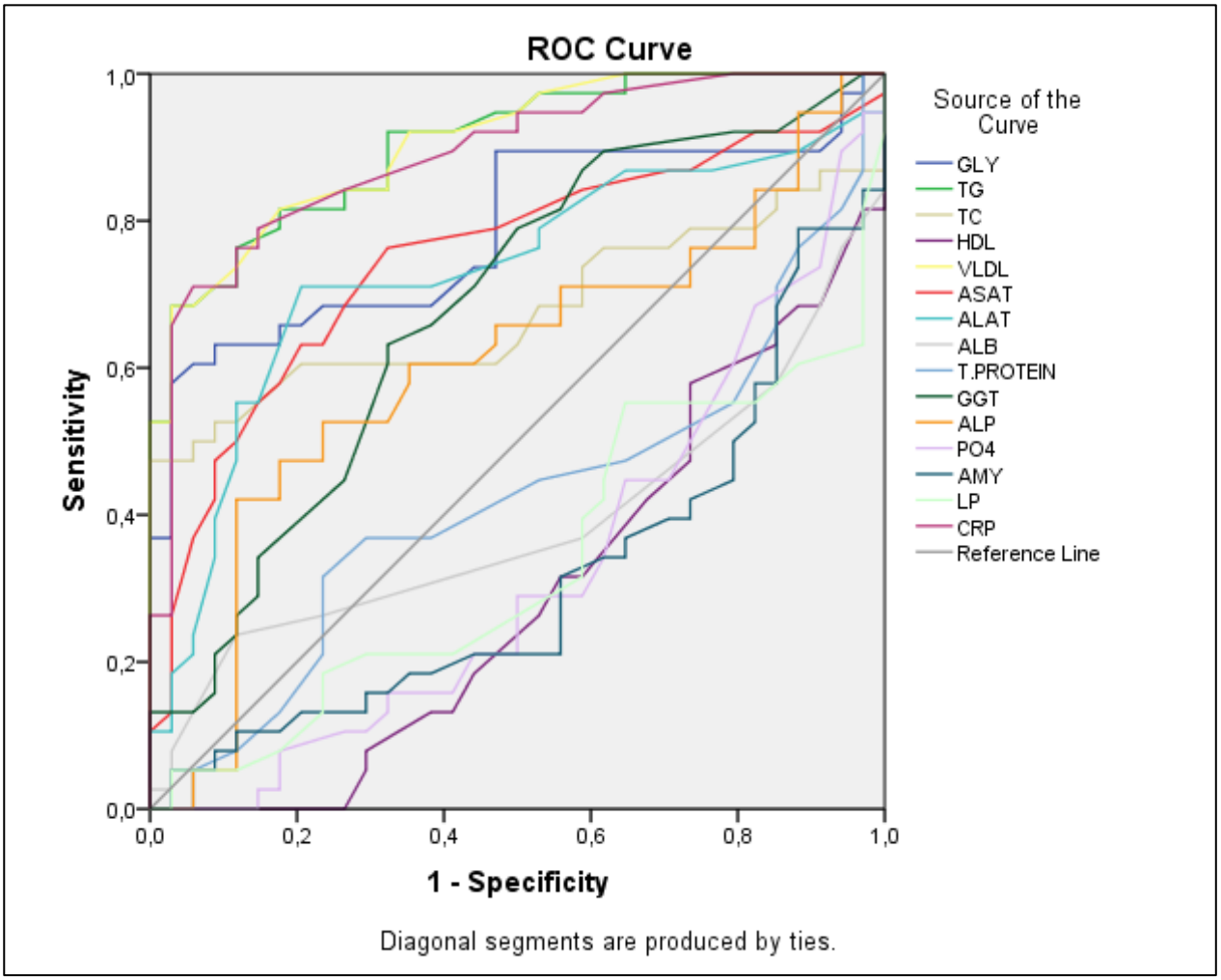

Figure 53: Roc curve of biochemical markers in MetS and control group .

Table 22: Sensitivity, specificity and AUV value of some biochemical markers in MetS and control group .

Test Result variables	Sensitivity%	specificity%	AUC%	P-Value	CI 95%	
					Lower Bound	Upper Bound
GLY	34.2	100	78.4	**0.000**	0.675	0.894
TG	44.7	100	90.4	**0.000**	0.838	0.970
TC	45.7	100	67.8	**0.010**	0.547	0.808
HDL-C	26.3	47.1	29.4	**0.003**	0.175	0.413
VLDL	42.1	100	90.6	**0.000**	0.841	0.971
AMY	36.8	35.3	31.5	**0.007**	0.191	0.439
LP	39.5	41.2	33.6	**0.017**	0.210	0.461
CRP	23.7	100	88.9	**0.000**	0.813	0.964
ASAT	47.4	91.2	74.9	**0.000**	0.634	0.865
ALAT	55.3	88.2	73.0	**0.001**	0.609	0.850
ALB	57.9	14.7	38.7	0.098	0.253	0.520
T.Protein	55.3	20.6	42.0	0.245	0.286	0.554
GGT	26.3	88.2	68.1	**0.008**	0.557	0.805
ALP	47.4	79.4	60.5	**0.126**	0.471	0.739
PO_4	34.2	38.2	32.7	**0.012**	0.202	0.451

5.3. Oxidative stress markers

5.3.1. CAD with control group

Our result for both sex women and man in Table 29 and Figure 54 respectively, show that, MDA, SOD and GPX serum were a significant predictive factor ($P \leq 0.05$), with high percentage of specificity (100, 8.7,21.7%) with AUC (98.7,20.2,18.8%) and important percentage of Sensitivity (28.6,71.4,57.1) respectively.

Table 23: Sensitivity, specificity and AUV value of some oxidative stress markers in CAD and control group.

variables	Sensitivity%	Specificity%	AUC%	P-Value	CI 95%	
					Lower Bound	Upper Bound
MDA	28.6	100	98.7	**0.000**	**0.963**	**1.000**
SOD	71.4	8.7	20.2	**0.001**	**0.069**	**0.335**
GSH	61.9	39.1	46.1	0.655	**0.286**	**0.635**
GPX	57.1	21.7	18.8	**0.000**	**0.054**	**0.323**
TAC	47.6	73.9	65.4	0.080	**0.488**	**0.821**

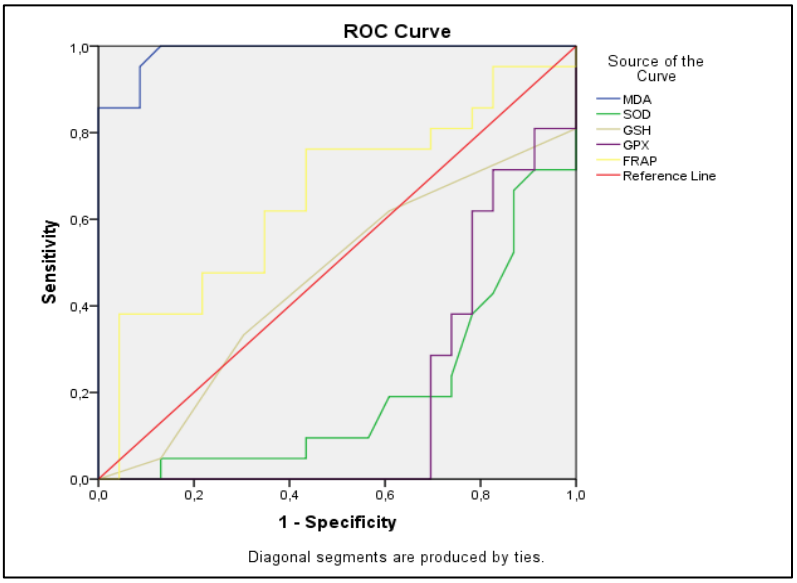

Figure 54: Roc curve of MDA, SOD, GPX, GSH and TAC in CAD and control group.

5.3. 2. CAD with MetS group

Our result for both sex women and man in Table 29 and Figure 55 respectively show that GSH serum were a significant predictive factor ($P \leq 0.05$), with high percentage of specificity (20.8%) with AUC (32) and important percentage of Sensitivity (63.6) respectively.

Table 24: Sensitivity, specificity and AUV value of some oxidative stress markers in CAD and MetS group.

variables	Sensitivity%	specificity%	AUC%	P-Value	CI 95%	
					Lower Bound	Upper Bound
MDA	31.8	87.5	64.8	0.083	0.485	0.810
GSH	63.6	20.8	32	**0.037**	0.159	0.481
TAC	45.5	62.5	65	0.082	0.489	0.810

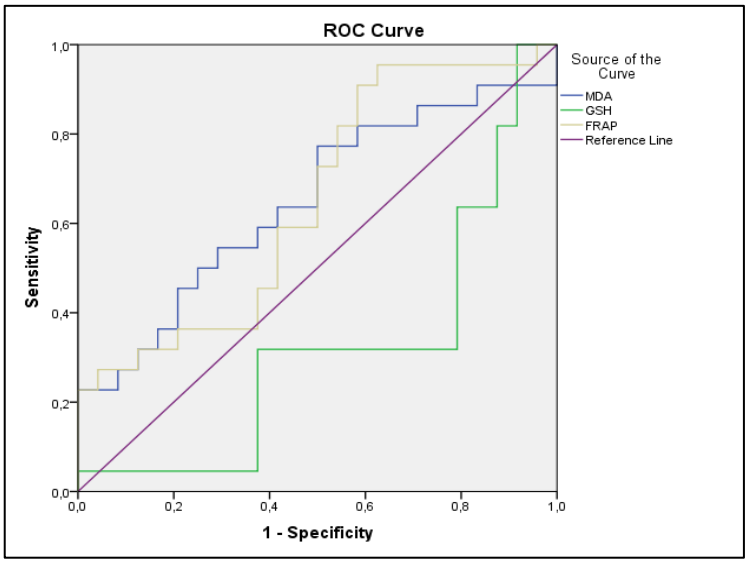

Figure 55: Roc curve of MDA, GSH and TAC in CAD and MetS group (N=80).

5.3. 3. MetS with control group

Our result for both sex women and man in Table 25 and Figure 56, show that, MDA, SOD and GPX serum were a significant predictive factor ($P \leq 0.05$), with high percentage of specificity (100, 17.4, 21.7%) with AUC (98.2, 30.0, 11) and important percentage of Sensitivity (51.9, 48.1, 29.6) respectively.

Table 25: Sensitivity, specificity and AUV value of some oxidative stress markers in MetS and control group (N=80).

Test Result variables	Sensitivity%	specificity%	AUC%	P-Value	CI 95%	
					Lower Bound	Upper Bound
MDA	51.9	100	98.2	**0.000**	0.954	1.000
SOD	48.1	17.4	30.0	**0.015**	0.154	0.445
GPX	29.6	21.7	11	**0.000**	0.023	0.196

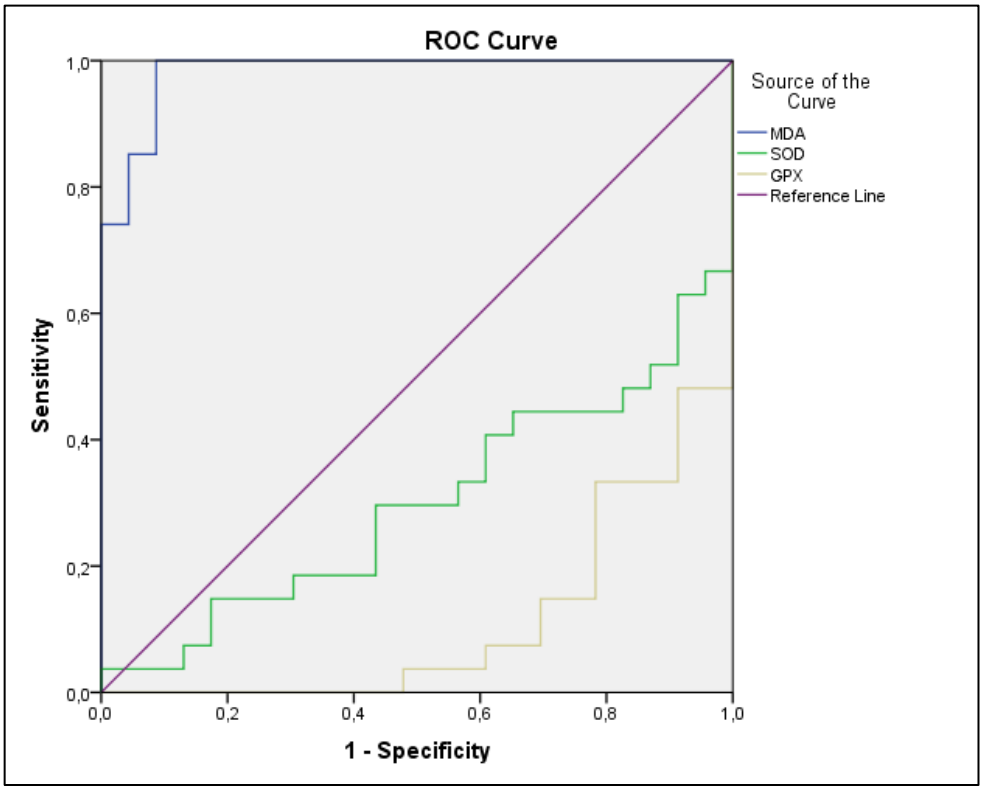

Figure 56: Roc curve of MDA, SOD and GPX in MetS and control group.

6. Correlation between biological markers

6.1. In coronary artery disease group

The correlation results between oxidative stress parameters, hematological parameters, biochemical markers are shown in the Table 26, we are learned a negative correlation with P<0.05 between (serum SOD / CPK), (serum TAC /NEUT), (serum TAC /NLR), (serum TAC /MLR) were shown in (Figures 57,58,59,60) respectively. In contrast there was There was no correlation between the rest of tests with P > 0.05.

Table 26: Correlation between biological markers for CAD patients.

		Serum MDA	Serum SOD	Serum GPX	Serum GSH	Serum TAC
WBC	**P**	0.670	0.411	0.936	0.294	0.052
	R	0.073	-0.180	-0.018	0.262	-0.392
NEUT	**P**	0.523	0.297	0.907	0.262	**0.030**
	R	0.110	-0.227	-0.026	0.279	**-0.435**
MONO	**P**	0.506	0.891	0.102	0.224	0.461
	R	-0.114	-0.030	-0.358	0.301	-0.154
NLR	**P**	0.807	0.439	0.839	0.455	**0.014**
	R	0.042	-0.170	-0.046	0.188	**-0.484**
MLR	**P**	0.771	0.584	0.129	0.217	**0.011**
	R	-0.050	-0.120	-0.334	0.306	**-0.500**
TG	**P**	0.724	0.985	0.980	0.952	0.434
	R	0.061	0.004	-0.005	0.014	0.164
VLDL	**P**	0.722	0.985	0.988	0.958	0.436
	R	0.059	0.004	-0.006	0.014	0.166
Cr	**P**	0.796	0.217	0.213	0.144	0.755
	R	0.045	0.268	-0.276	0.359	-0.066
UREA	**P**	0.668	0.680	0.464	0.369	0.355
	R	0.074	0.091	-0.165	0.225	-0.193
ASAT	**P**	0.283	0.703	0.529	0.749	0.821
	R	0.184	-0.084	-0.142	-0.081	0.048
ALAT	**P**	0.536	0.079	0.392	0.336	0.720
	R	0.107	0.374	-0.192	-0.241	0.075
ALB	**P**	0.976	0.209	0.842	0.732	0.841
	R	-0.005	-0.272	0.045	-0.087	-0.042
T.Protein	**P**	0.951	0.370	0.143	0.231	0.545
	R	0.011	-0.196	-0.323	-0.297	0.127
Ca	**P**	0.470	0.789	0.388	0.581	0.059
	R	0.124	-0.059	-0.193	-0.139	0.383
CRP	**P**	0.459	0.292	0.265	0.398	0.839
	R	-0.127	0.230	-0.249	0.212	-0.043
LDH	**P**	0.278	0.062	0.001	0.584	0.833
	R	-0.186	-0.395	-0.669	-0.138	-0.044
CPK	**P**	0.420	**0.009**	0.167	0.508	0.800
	R	-0.139	**-0.534**	-0.306	-0.167	-0.053

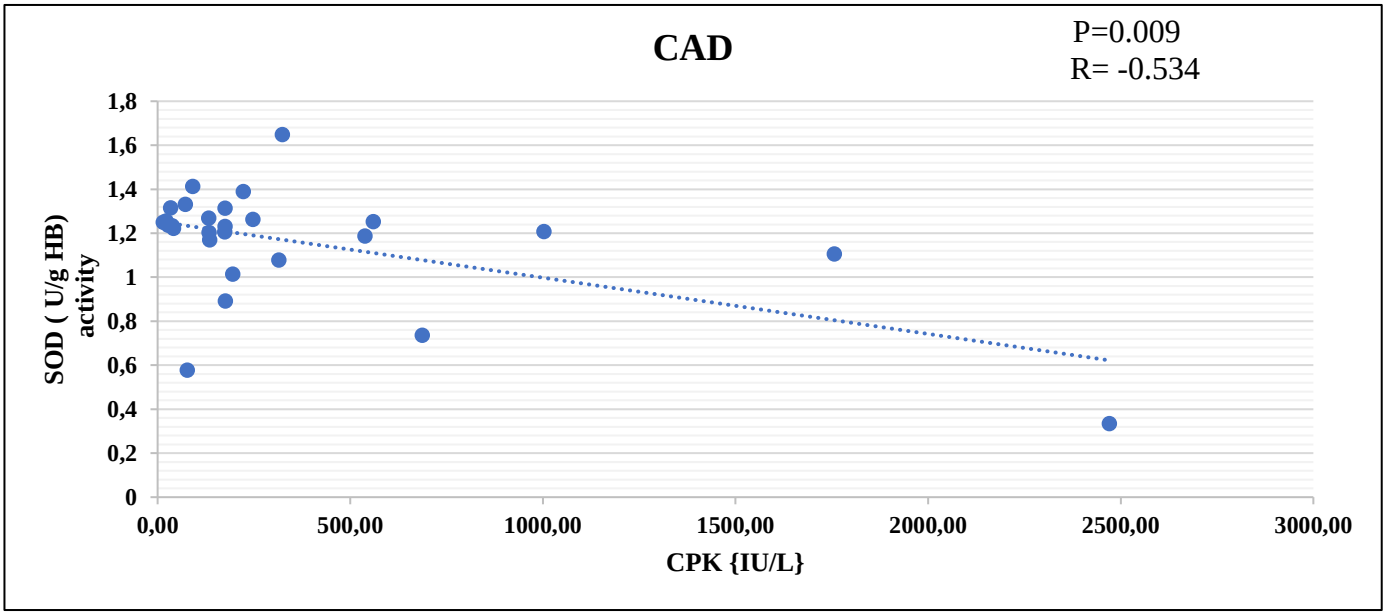

Figure 57: Linear curve of SOD according to CPK in CAD group.

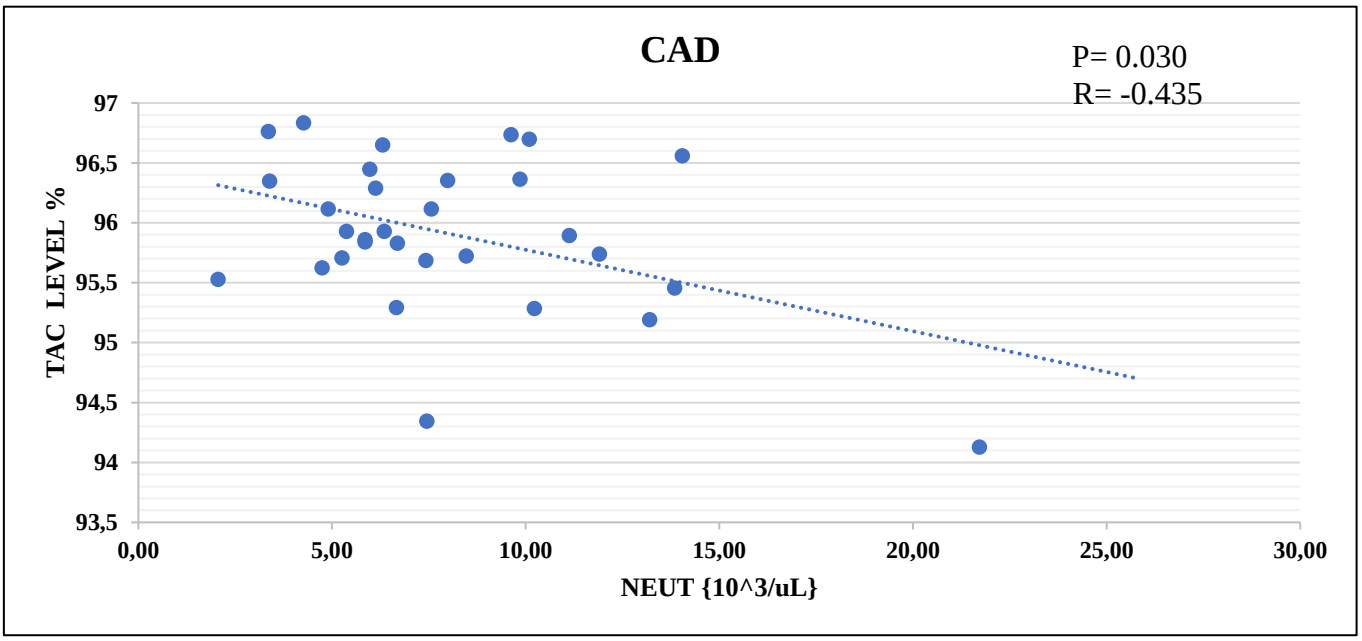

Figure 58: Linear curve of TAC Level (%) according to NEUT in CAD group.

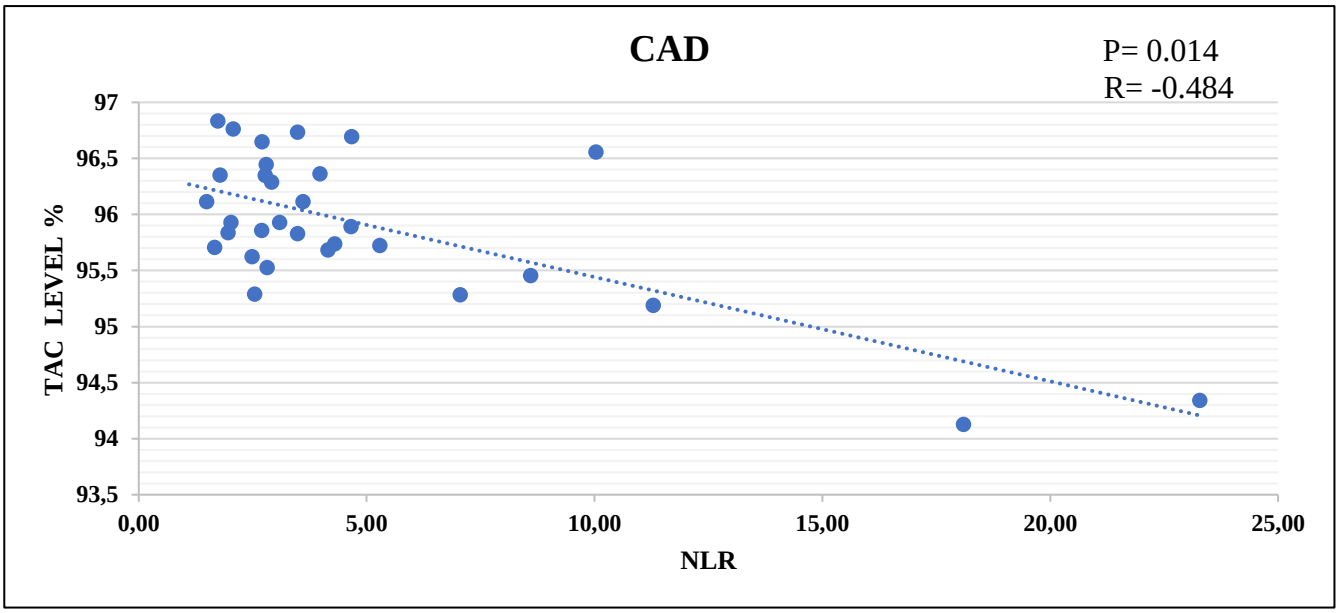

Figure 59: Linear curve of TAC Level (%) according to NLR in CAD group

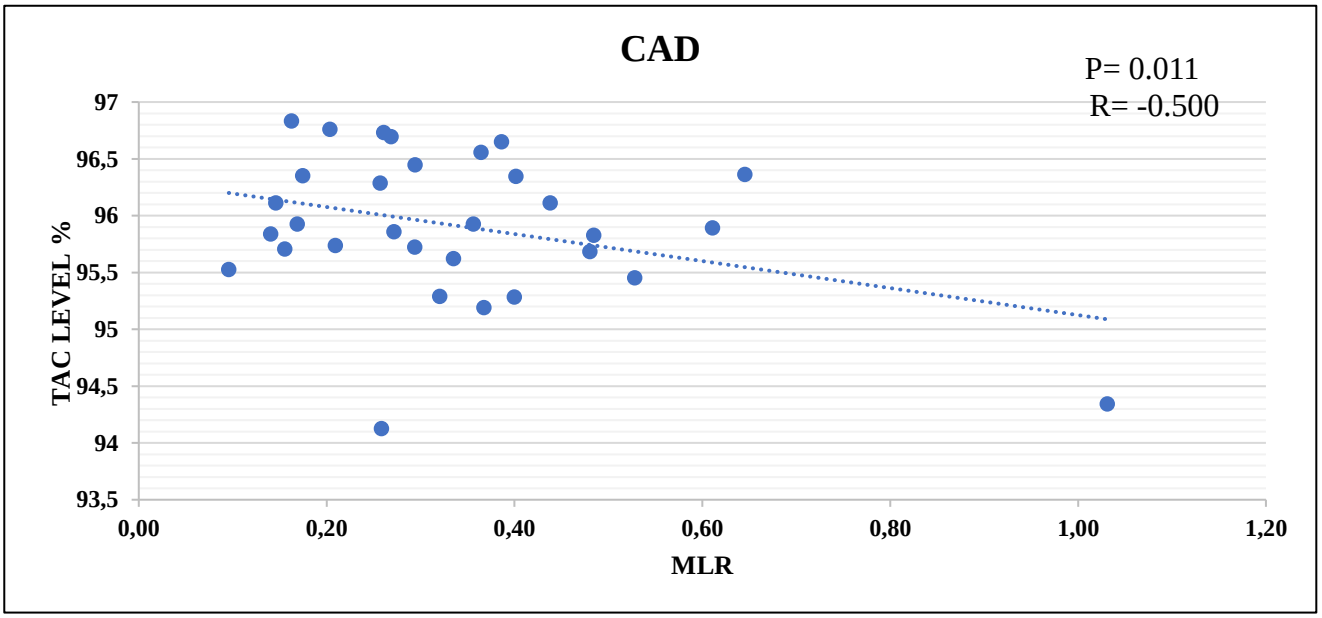

Figure 60: Linear curve of TAC Level (%) according to MLR in CAD group.

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6.2.In metabolic syndrome group

The correlation results between oxidative stress parameters, hematological parameters and biochemical markers are shown in the Table 27, we are learned a positive correlation with P <0.05 between (serum GPX/ CRP). In contrast there was a negative correlation with P <0.05 between (serum GPX / ALB), (serum GPX / T.Protein) and (serum TAC/PO_4) illustrated in (Figure 61,62,63 and 64) respectively. There was no correlation between the rest of tests with P>0.05.

Table 27: Correlation between biological markers for MetS patients.

		Serum MDA	Serum SOD	Serum GPX	Serum GSH	Serum TAC
WBC	**P**	0.549	0.319	0.184	0.178	0.503
	R	0.118	-0.235	0.294	-0.322	-0.114
NEUT	**P**	0.270	0.557	0.111	0.622	0.392
	R	0.216	-0.019	0.349	-0.121	-0.145
TG	**P**	0.515	0.377	0.109	0.158	0.794
	R	0.128	0.101	0.351	0.337	0.044
TC	**P**	0.393	0.277	0.858	0.421	0.761
	R	-0.168	0.256	0.040	-0.196	0.052
VLDL	**P**	0.515	0.377	0.109	0.158	0.795
	R	0.128	0.101	0.351	0.337	0.045
ASAT	**P**	0.244	0.674	0.191	0.820	0.619
	R	-0.228	-0.100	0.290	-0.056	0.085
ALAT	**P**	0.429	0.955	0.190	0.806	0.844
	R	-0.156	0.013	0.290	0.061	-0.033
ALB	**P**	0.158	0.992	**0.042**	0.661	0.598
	R	-0.274	0.002	**-0.438**	-0.108	-0.090
T.Protein	**P**	0.642	0.656	**0.016**	0.860	0.307
	R	-0.092	-0.106	**-0.508**	0.043	-0.172
Phosphorus (PO_4)	**P**	0.360	0.388	0.162	0.772	**0.046**
	R	0.180	-0.204	-0.309	-0.071	**-0.330**
CRP	**P**	0.740	0.639	**0.001**	0.101	0.499
	R	-0.066	0.112	**0.641**	-0.387	-0.115

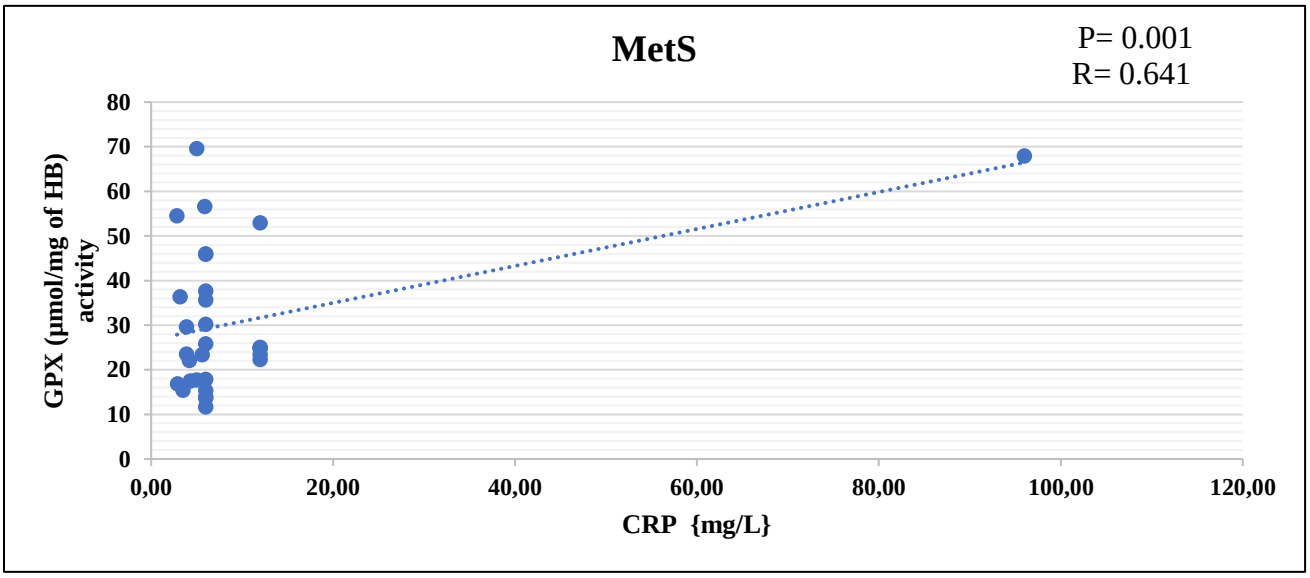

Figure 61: Linear curve of GPX activity according to CRP in MetS group.

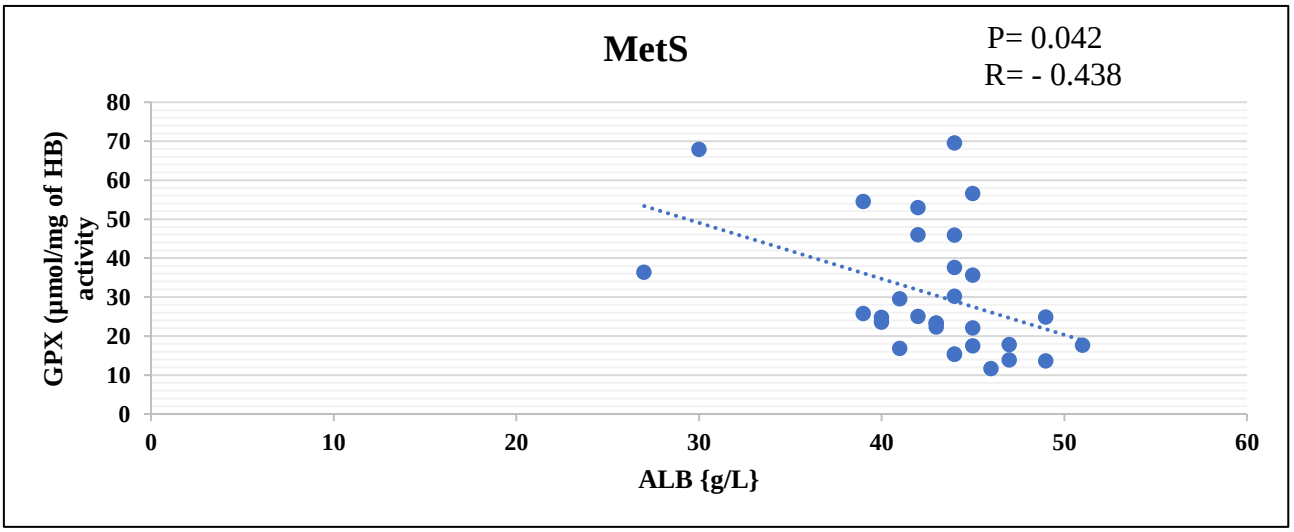

Figure 62: Linear curve of GPX activity according to ALB in MetS group.

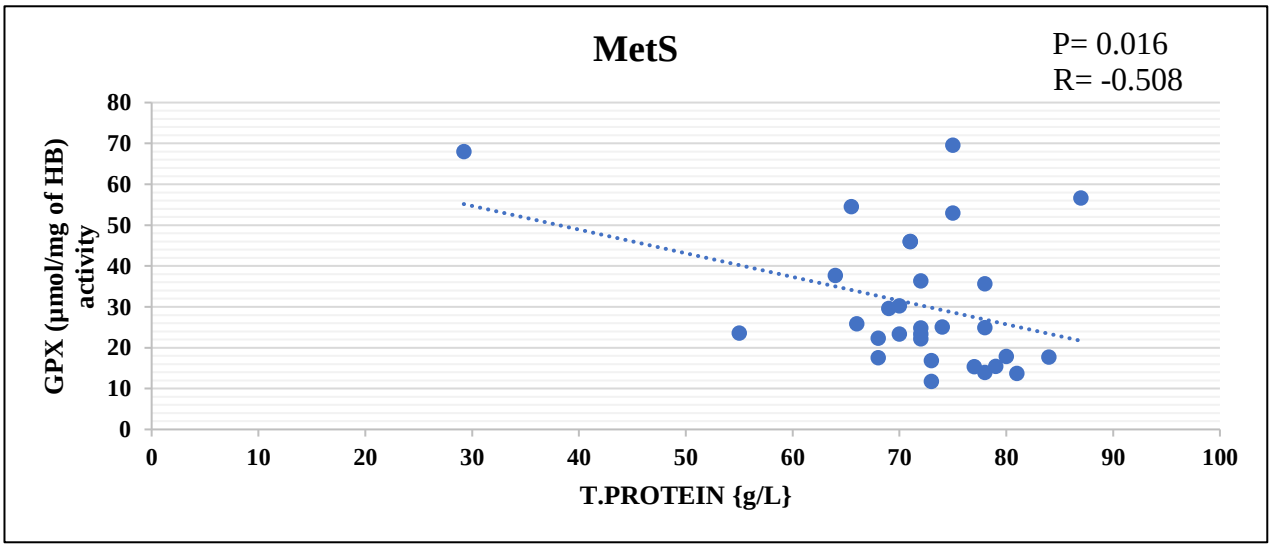

Figure 63: Linear curve of GPX activity according to T.protein in MetS group .

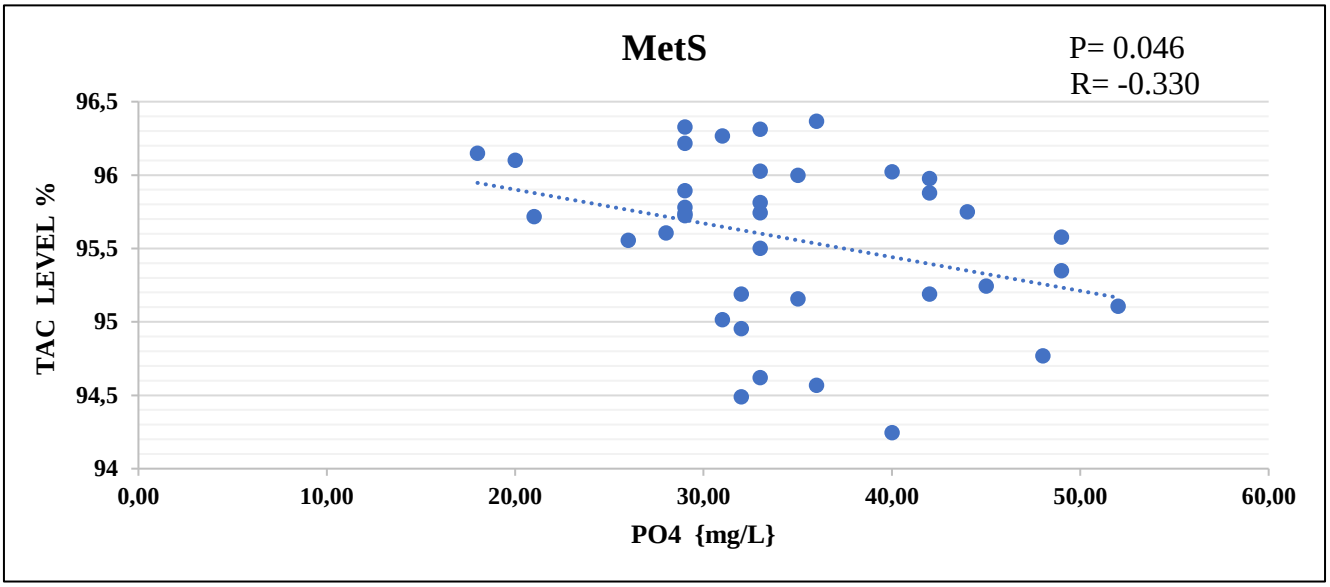

Figure 64: Linear curve of TAC Level (%) according to phosphorus (PO_4) in MetS group.

7. Wind rose

In our study the wind rose represented the average of different parameters, without correlation between the different groups (Figure 65).

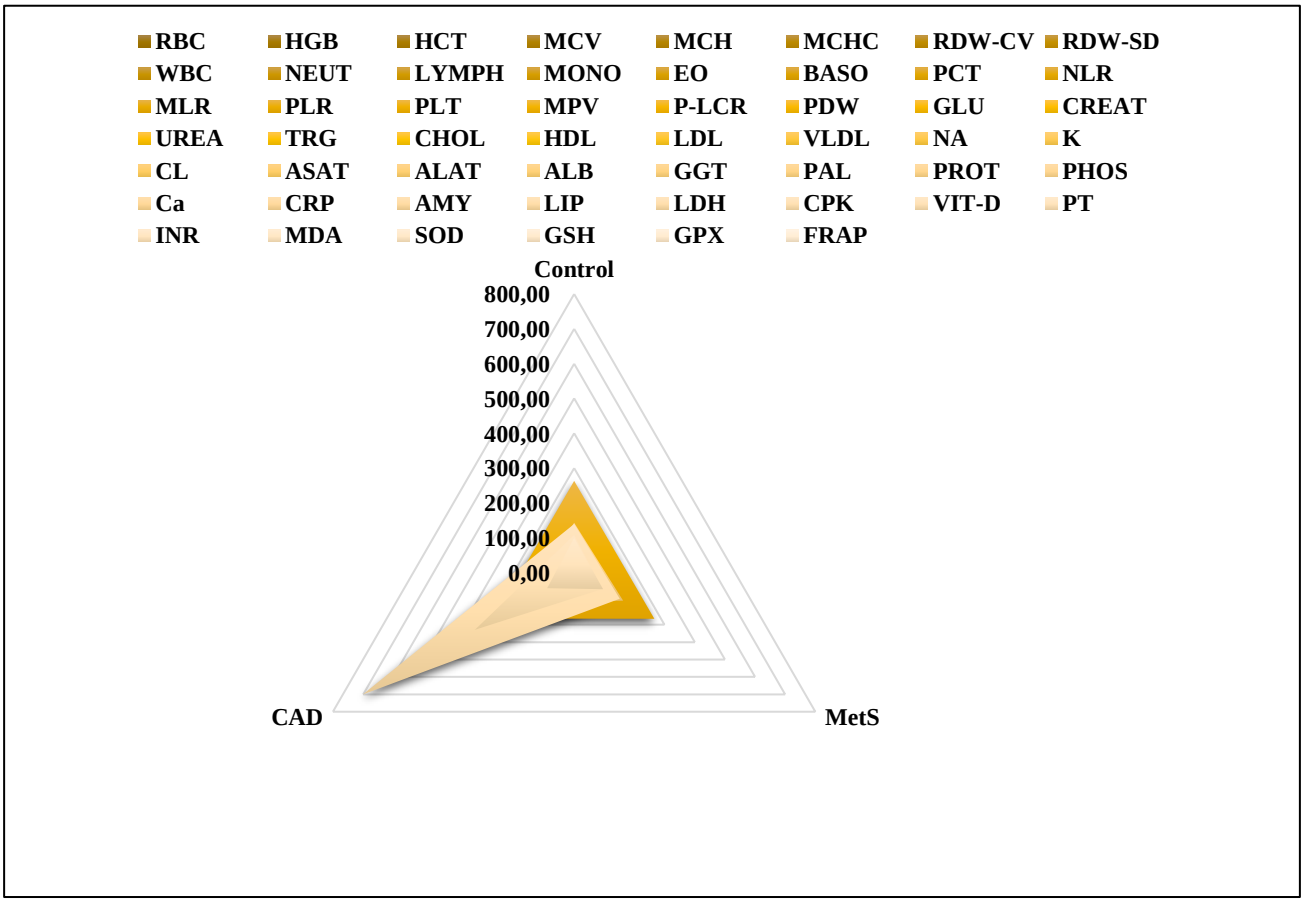

Figure 65: Wind Rose in the control, MetS and CAD groups .

8.HCS (Health Cardiac Software)

We produced, HCS or Health Cardiac Software in December 2023, it is the first medical diagnostic program in Algeria, which allows to doctors to predict coronary artery syndrome through the biological analyses, including biochemical and hematological, also oxidative stress markers.

The users introduce the values into the program and then checks the input data then, if the program accepted the values, the result will be 0 risk score that mean a healthy person, if it refused the result will give the percent risk score for this person which mean if there is a possibility of developing coronary syndrome or metabolic syndrome. It is a predictive software, helps the doctors to make the right decision for the subject, if he needs to be admitted to the hospital or not (Figure 66). In the future, we will try to develop the program as possible thus avoid the sudden death of people.

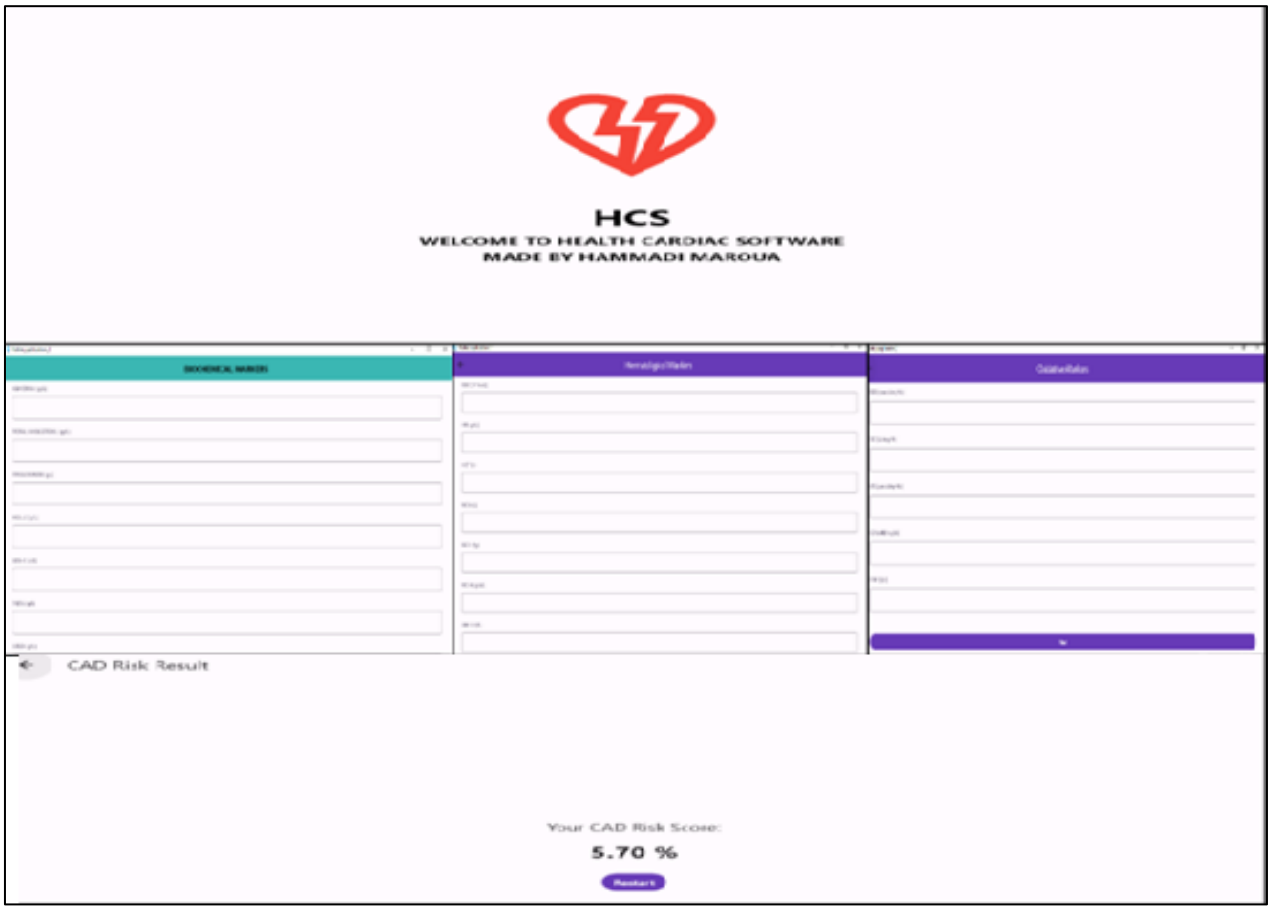

Figure 66: Various pictures taken to show HCS (Health Cardiac Software).

DISCUSSION

IV.Discussion

1.Epidemiological study of CAD in El Oued region

Our research is the first work in El Oued (Algeria) to indicate the prevalence of cardiovascular diseases among El Oued population. We relied on collecting information on hospitals and private medical clinics.

Data on CVD and CAD epidemiology was based on rural and urban area of El Oued, 23422 subjects in different age were randomly involved in our research.

This study is the most extensive hospital-based serial cross-sectional study carried out in El Oued to date, focusing on patients with established CAD.

Although the study has limitations, its findings provide valuable insights into comparing the prevalence of CAD in patients with the general population, comparing risk factors between men and women, analyzing trends of risk factors among CAD patients, and understanding the influence of these risk factors on the age of CAD diagnosis.

The most type prevalence of CVD in our research is hypertension among women and men with 47.69%, 27.01% respectively the findings of our investigation align with the study of Ashley K.K and all, a comprehensive analysis of 33 studies conducted in 15 sub-Saharan African nations revealed that the prevalence of hypertension ranged from 15% to 70% between 1999 and 2013 [291], also the systematic study highlighted the insufficient recognition, management, and regulation of hypertension in this area [292]**.** Also, according to the latest estimates from the World Health Organization (WHO), the number of people with hypertension in Africa is increasing and approaching the higher range of historical data, which is usually around 35-45% of adults. This trend is expected to significantly contribute to the occurrence of cardiovascular disease (CVD) events that could have been prevented. In 2005, a population study conducted in Gabon examined 736 patients aged 40 years and older. The study found that cardiovascular disease (CVD) was mainly caused by high rates of hypertension. Specifically, high blood pressure was found to be a reliable predictor of stroke and peripheral arterial disease (PAD)[293]**.**

Our principal findings of premature CVD events show that the incidence age is between 51 to 60 years old, this secular trend was observed in both males and females, according to study in the United States, cardiovascular disease (CVD) often occurs before the age of 65, resulting in a total of 880,000 hospitalizations and deaths per year. [294] According to a recent analysis, approximately one-third of cardiovascular disease (CVD) events occur in women below the age of 65, while about one-half of CVD events occur in males below the age of 65. Additionally, between a seventh and a quarter of CVD events occur in women below the age of 55, and in men below the age of 55, respectively [295].

Our epidemiological and clinical data have shown a different in several aspects between men and women, there is dominance prevalence of CAD is 16.63% with 9.57% in men and 7.08% in women, similar findings have been reported compatible with our results in a Lebanese cross-sectional study using multistage cluster sample including 1200 subjects ≥ 40 years of age. The prevalence of CAD was 26.8% (17.8% in males, 9.0% in females)[296].Also, were confirmed with Tehranian population (Iran) men revealed a higher prevalence of CHD with 25.1% for men and 23.2% for women in 2016 [297], also the study of Kaveh, H and all, they found Overall, 68% of the patients were men and 32% were women, they diagnosed CAD in men around three years earlier than in women.

Concerning the incidence rate of CAD was growing by years, it is increased by 23.29% from 2010 to 2021, this is with occurrence of GBD (global burden disease) to reach the high prevalence in 2019 with 16,6%, this result is the same with NAME study which show that the incidence of ischemic heart disease (IHD) in NAME increased by 135.1% between 1990 and 2019. Based on the decomposition study, the rise may be attributable to three factors: population growth (76.4%), change in age structure (80.4%), and change in incidence rate (-21.7%). The rise in the number of cases of IHD in all NAME countries, except for Afghanistan and Sudan, can be attributed to population growth and changes in age structure. However, the extent of the increase in incidence rates varied significantly, ranging from a decrease of 80.3% in Turkey to an increase of 65.7% in the United Arab Emirates between 1990 and 2019. [298].

The high prevalence of CAD in 2019 may due to the SARS-Covid 19 infection, as a risk factors for the development of atherosclerosis, as show in the study of (Lukasz, S) lead to various complication such venous thrombosis and pulmonary embolism as a result of a destroying action through alterations in endothelial and coagulation homeostasis may predispose to thrombosis in all arterial beds. The novel coronavirus is similar to most cardiovascular risk factors, disturbs the balance between vascular relaxation and contraction as well as reduces the amount of platelet aggregation inhibitors, coagulation inhibitors and fibrinolysis activators in favor of clotting factors. Venous thrombosis and pulmonary embolism are common complications of COVID-19 as a result of a disordered endothelial homeostasis triggered by either inflammatory cytokines storm or direct infection, causing, for instance, intracellular oxidative stress.[299].[300].

The prevalence of smoking, DM, HTN, dyslipidemia represent respectively 9.63%, 29.01% and 29.08 (SD mean between women and men), 4.24% for the patient with CAD , this result align with the study of M.Brouri and all, which found the incidence of smoking, DM, HTN, dyslipidemia respectively 10%, 29.2% for men and 22.7% for women, 39.5% , also, our results show that the average (SD) age at diagnosis for all years combined was 63.01± 12.41 (1-100 years old), this agree with the study of khaira, B and all, in Setif (Algeria) population, they found the average age of CAD patients 62.7 ± 11 years (20-

91 years) ,maybe as a result of incomplete adjustment for risk factors or a genetically transmitted higher risk factor in men[122].

Regarding the difference prevalence of CAD between rural and urban, we found the higher percent in the urban ; El Oued center with 69,18%, due to the important urbanization , and the life style with food habits of people, which associated with the increase of risk factors also it is may to the several environmental factors, between the city and rural, this opinion agree with European study [301].

2.Study of pathological clinical and socioeconomic risk factors for CAD in El Oued region

Different studies show that the incidence of CAD, refer to the age, genetics and environmental factors, chronic disease associated with life style such as arterial hypertension, diabetes mellitus and dyslipidemia, urbanization and life stress, also work , and the factors of individual and social behavior [301]. may due to life style risk factors, for example smoking is common in men than women [302].

Our research outcomes genetics history and response to therapy this agree with the study of (Manuel, M and all) [303]. Regarding the genetic history (Helena, M and all) says that the Y chromosome has an important role in the heredity of CAD [304].

The results of risk factors study in both CAD compared to both group control and Mets showed that the most risk age of CAD, is over than 60 with (OR= 76.641; P= 0.000) with healthy group, that agree with the study of (Getu, G and all) report 31% (429) of all CVD cases affecting people aged between 51 to 60 years [305][46], with the aging process , the body's system declines, such the cardiovascular system leading to progressive deterioration in the structure and vasculature which lead to atherosclerosis [46]. Marenberg and all show that in monozygotic twins the risk of death from CAD increased 3.8 to 15 times if a sibling died of CAD before age 75 [306]. In addition the study of (Anderson et al., 2013) have shown a large international case-control study reported a rise in the risk of MI if one parent had MI (OR=1.67), or one parent had MI before age 50 (OR=2.36), or both parents had MI (OR=2.90) and if both parent had MI before age 50 (OR=6.56) [307]

Also most of Metabolic Syndrome and CAD patient represent a significant numbers of low education , this make a risk factor in health awareness and this agree with the study of (Gunhild, B and all), who confirmed the importance of health literacy to avoid different risk factors such as smoking, alcohol, unhealthy food contribute to CAD [308].

Additionally , there are a strong association between the obesity, hypertension, diabetes mellitus and stroke as high-risk factors for CAD with (OR= 4.495; P= 0.000, OR= 154.846; P= 0.000, OR= 116.217 P= 0.009, OR= 9.791) in CAD compared to healthy subjects, this according to the study of a multitude of risk variables were identified in epidemiological surveys. In 2016, the Global Burden of Disease (GBD)

study identified the most prevalent risk factors in the Middle East and North Africa (MENA) region. These risk factors were ranked in terms of their impact, with high blood pressure being the most significant, followed by obesity, diabetes, and smoking [309]. Aldo another studies indicated that most of the individuals with a significant family history of heart disease/stroke/hypertension were more likely to develop CVD themselves. [310]. The obesity makes health problems contribute to cardiovascular disease, due to the accumulation of fat in the abdominal visceral and an excess of fat in the abdominal tissues that activate the different metabolic such as increase in the level of LDL, lead to atherosclerosis [154] The Framingham study and INTERHEART show that around 30% of overweight responsible of CAD mortality [311].

Concerning the rheumatism, smoking, they present a significant risk factors for CAD with (P= 0.000, OR= 3.296; P= 0.001, OR= 23.222; P= 0.000) respectively in CAD compared to healthy, that agree with the study of (Jacqueline K and all) which confirmed the rheumatism is a pathological inflammatory associated with a large complication of CVD like atherosclerosis; vasculitis; cardiac valve failure; endo, myo, and pericarditis; and heart failure [312], a cohort studies involving 20 million people appear that 70 % of smokers with CAD more mortality than non-smokers with CAD [154],also another studies show that the smoking induce oxidative stress process lead to activation of cascade inflammatory process, which link with to coronary atherosclerosis[313] also intense cigarette smoking will in general increment myocardial O^2 consumption by increasing heart rate and blood pressure associated with blood flow in the coronary arteries in normal subjects compared with CAD patients there is no increase or actual decrease in coronary blood flow [314].

For kidney dysfunction , we found it represent a risk factors for CAD with (OR= 4.831; P= 0.008) in the group of CAD compared to control, that demonstrated that the kidney diseases contribute to the progress of the atheroma plaque formation, this finding is compatible with Autopsy investigations [315] have shown that individuals with chronic kidney disease (CKD) had more advanced atherosclerotic plaques and a larger occurrence of calcified atherosclerotic lesions compared to those without CKD. However, there seems to be only minimal calcification in the coronary arteries of CKD patients [316].Additional research has shown a higher level of inflammation in the coronary plaques of individuals with chronic kidney disease (CKD) compared to those without kidney problems (non-renal control cases) [317].

Studies conducted on the general population using pathological and radiographic methods have indicated that there is calcification present in the Coronaries can be classified as either "micro" or "macro" . Microcalcification predominantly occurs in younger people are more susceptible to developing inflammation and plaque instability, which can contribute to the development of acute coronary

syndromes (ACS). On the other hand, macro-calcifications typically develop in elderly individuals who have more stable coronary artery disease (CAD) and multiple blockages in their blood vessels. The alteration of lipoproteins (such as the carbamylation of low-density lipoprotein and the dysfunction of high-density lipoprotein) in chronic kidney disease (CKD) is likely to play a role in the faster advancement of coronary artery disease (CAD). Risk factors for calcification include inflammation, aging, mechanical factors (such as shear stress and elastin fatigue), and the potential buildup of microbiome-related metabolites like trimethylamine N-oxide [318].

About the chest pain it represents a diagnostic for CAD, it is a big risk factors with (OR= 42.667; P= 0.000), our investigation is compatible with other studies which report that the Chest pain is a significant symptom of coronary artery disease, among various other symptoms.[319]

However, when it comes to cardiac chest discomfort, commonly known as angina, doctors prioritize the elimination of coronary artery disease (CAD) and other life-threatening illnesses.

Evidently, it must be acknowledged that not all people having chest pain inevitably suffer from coronary artery disease. A further study conducted by Verdon et al confirmed the claim, revealing a prevalence of 2.7% for chest pain within a group of 24,620 individuals from Switzerland. Out of all the patients, only 12% were diagnosed with coronary artery disease.[319]

Our finding also show that the gallbladder dysfunction represents a high-risk factor for CAD, with (OR= 12.236; P= 0.002) in CAD compared to control group, this explain that coronary artery disease (CAD) and gallstone disease have several shared risk factors, this is compatible with other studies which found the gallstone disorders including metabolic syndrome (MetS) and diabetes mellitus (DM) [320]and non-alcoholic fatty liver disease (NAFLD) with CAD [321] . The liver is the primary organ responsible for regulating cholesterol metabolism and maintaining optimal levels of cholesterol in both the bloodstream and bile [322] .Patients with Metabolic Syndrome (MetS), Diabetes Mellitus (DM), and fatty liver have compromised pathways that result in either dyslipidemia or supersaturation of biliary cholesterol [323].In order to minimize the potential impact of selection bias, we ensured that patients in both our CAD-positive and -negative groups were paired based on three characteristics that were not evenly distributed: age, gender, and MetS. By employing this method, we discovered that gallstone disease itself was linked to coronary artery disease (CAD). Additionally, we discovered that CAD and gallstone disease have multiple shared risk factors, including elevated total cholesterol and decreased HDL cholesterol levels. They have a connection with CAD even after controlling for age, gender, and MetS. The simultaneous occurrence of the two disorders could be attributed to the metabolic pathway of cholesterol in the gut-liver axis [323].

Elevated fasting glucose levels or the presence of diabetes mellitus might impact the metabolism of cholesterol and lipoproteins, leading to impaired gallbladder contractility [324].

Concerning the depression and stress, and its pathophysiology relation, it disposed as risk factor for the development of CAD process with (OR= 2.630; P=0.001) in the group of CAD compared to control, which is corresponds with multiple studies have suggested that depression can have both behavioral and direct pathophysiological impacts on coronary artery disease (CAD).

Depression is linked to a lack of following recommended changes to reduce risk in various medical problems, such as smoking cessation, poor patient compliance, including not controlling blood sugar levels well in diabetic patients, and not taking prescription medication as directed. Furthermore, there have been proposed direct pathophysiologic mechanisms that connect depression to coronary artery disease (CAD). [325]

The presence of abnormal platelet function, specifically enhanced platelet reactivity, elevated levels of platelet factor, increased platelet reactivity to serotonin, and reduced platelet reactivity to adenosine diphosphate, has been thoroughly examined. Furthermore, unlike the administration of the antidepressant did not counteract the elevated levels of platelet factors which are indicators of platelet activation, in patients with depression and coronary artery disease (CAD). [326]

There is a hypothesis that suggests hypercortisolemia and increased levels of corticotropin-releasing factor are equally important factors in the development of depression associated with CAD.[327]

Also the salt intake was posed as a risk factors for CAD pathophysiology , although there is no direct relation with the process of atherosclerosis but it enter in the increase of HTN which represents a high risk factors for CAD process, the intake of salt represent a significant difference with (OR=2.509 ; P=0.008), in the group of CAD compared to control, our finding is compatible with the studies of Christopher R and all, which show that While the use of salt has been associated with physiological factors, such as blood pressure, there is currently no direct epidemiological data that links dietary salt intake to cardiovascular mortality and morbidity. Indeed, one study that has faced significant criticism has shown that following a low-sodium diet is linked to an increase in cardiovascular morbidity and death [325]

A significant drawback of the National Health and Nutritional Interview Study was its reliance on a solitary 24-hour recollection for assessing salt consumption, without any rigorous independent evaluations of sodium intake. The findings indicated a weak negative association between salt intake and

cardiovascular and all-cause mortalities. However, there was a positive correlation between mortality and sodium intake per joule ingested. [328]

In contrast, the exercise practice and the age less than 40 y, represent a protective factor for CAD and MetS in the group of MetS compared to control with (OR=0.422; P=0.033, OR=0.061; P=0.000) respectively, our outcomes are similar with other researchers who found that the positive impacts of physical activity are also evident in the secretion of myokines, which are cytokines, interleukins like IL-6, and other peptides that are generated by muscle fibers. They engage in protecting against diseases associated with inflammation, such as atherosclerosis. Exercise training can also lead to the reduction of inflammation through the modification of intracellular signaling pathways controlled by nitric oxide (NO) and oxygen free radicals. The augmentation of NO and oxygen free radicals during exercise has a crucial role in stimulating the activation of anti-inflammatory defensive systems. Oxygen free radicals display both advantageous and harmful effects. When the body is unable to progressively recycle extra free radicals or when its natural defenses are weakened, the buildup of free radicals leads to a condition known as "oxidative stress". Research has demonstrated that regular exercise enhances the ability of cells to effectively eliminate high levels of reactive oxygen species. This benefit applies to both adults and older adults, who possess antioxidant activity comparable to young individuals leading sedentary lives. Engaging in physical activity can be advantageous for older adults as it helps safeguard against oxidative damage and mitigate age-related ailments [329].

Metabolic syndrome (MetS) is linked to insulin resistance and can lead to obesity. Studies show that a 2-year intervention involving dietary changes and physical activity can decrease leptin levels and increase adiponectin levels. Reduced physical activity is highly correlated with obesity. Effective approaches for reducing body fat include altering dietary habits and increasing energy expenditure through physical exercise. Visceral fat contributes to systemic inflammation, resulting in insulin resistance, type II diabetes, and atherosclerosis. Exercise enhances the capacity of skeletal muscle to utilize fats instead of glycogen, leading to reduced lipid levels in the bloodstream. Exercise also enhances the functioning of lipoprotein lipase (LPL), responsible for breaking down chylomicrons and VLDL. Studies have found significant variations in lipid markers between those with sedentary lifestyles and those who engage in regular exercise. Increased screen time can adversely affect the lipid profile, specifically HDL levels, regardless of age, gender, education, profession type, income, physical activity, dietary variables, and smoking.[330]

Also, the age less than 40 y, only the population with smoking is exposed to CAD, this is similar to the study of Mohammad P. M and all who show that the majority of young patients with CAD are male, and the primary risk factors for CAD in young adults are dyslipidemia, smoking, and overweight/obesity.

Moreover, the risk of vascular disease and myocardial infarction was more common among patients under the age of 45. [331]

Despite similar distributions of risk factors between genders, there were significant disparities in the correlations between risk factors and CAD, with several correlations observed in men but not in women. This implies that there are probable risk factors and disease pathways that are exclusive to females and are not commonly included or utilized in cardiovascular risk assessments. Gestational diabetes, estrogen status (time since menopause, hormone replacement medication usage), and pregnancy-related hypertension are being recognized as potential gender-specific risk factors for coronary artery disease (CAD) in women. These factors could be incorporated into risk assessments for CAD in women [332].

Furthermore, the levels of sex hormones, such as estrogens and testosterone, might impact an individual's vulnerability to developing common risk factors like hypercholesterolemia. These hormone levels can also influence the biological impact of these risk factors on the development of coronary artery disease (CAD).[333]

We observed the increase of risk factors lead to dramatically increase in CAD, with a high percent this may due to the rise in the occurrence of risk factors in our population is primarily attributed to the process of urbanization and globalization, which encompasses various factors, particularly diets high in carbohydrates, red meat, sugar, and sweetened drinks, and low consumption of fruits and vegetables.

Additionally, lifestyle changes such as physical inactivity and smoking contribute to this trend. This shift results in an increase in obesity, exacerbating levels of metabolic disorder, which in turn increases the risk of cardiovascular disease. In addition, it has been noted that individuals with poor socioeconomic level experience an exacerbation of specific risk factors and cardiovascular [334].

3.Study of biological parameters for CAD in El Oued region

The coronary arteries syndromes represent a continuum of myocardial ischemia ranging from angina, which indicates reversible tissue injury, through frank MI with extensive tissue necrosis. Various factors of suffering by the coronary arteries disease such as the combination of hypertension, high blood cholesterol, smoking and diabetes leads to the formation of atherosclerotic plaques [335] [336].

Results show that the immune inflammatory markers have a significant increase in CAD patients compared to healthy and MetS group, this result agree with the study of M. Madjid and all , it demonstrated that the leukocytes play a key role in pathophysiology of CAD; it effects on the instability of atherosclerotic plaques. During the first phase leukocytes permeate endothelial cells and become activated when reaching the tunica intima. They cause micro vascularity to form there, consequently increasing the risk of plaque rupture[337], [338] also with many studies have demonstrated a relation

between leukocytosis and a higher risk of cardiovascular death [339][340]**.** As shown inflammation is a known mechanism in several pathological situations , the leukocytosis considered as indicator of systemic inflammatory it was agree with previous studies [341]**.** About the WBC subtype, our study revealed the increase of monocytes with high specificity 88.1% and sensitivity with 38.1% in the CAD compared to MetS due to its nature which is involved in both innate and adaptive immunity ,it can adhere to the arterial wall, differentiate into macrophages, and initiate the release of pro-inflammatory cytokines, matrix metalloproteinases, as well as reactive oxidative species which play an role in the initiation and formation of Atherosclerotic plaque rupture this agree with the study of Fayad ZA *et al* [342][343] also we observed the decrease of LYMPH in the CAD compared to MetS and healthy subject may due to the immune system activation in the acute phase of coronary artery disease increased lymphocyte apoptosis in atherosclerotic lesions, which led to the destabilization of plaque causing atherosclerosis [344]. Nunez et al. conducted an investigation on 1030 patients and found that a low lymphocyte count was linked to a higher risk of myocardial infarction or death. Elevated monocyte levels and decreased lymphocyte levels have been established as separate risk factors for cardiovascular illnesses. [345].

The monocyte-to-lymphocyte ratio (MLR), which is determined by comparing the number of monocytes to lymphocytes, in term to determinate with logistic analysis in the group of CAD with MetS represent (OR= 78.9; P= 0.000), However, there is currently no research on the association between MLR and the severity of coronary lesions.

But it according to other studies which based on our understanding, there is a connection between MLR and the severity of coronary lesions in CAD. A total of 543 patients were included in our retrospective investigation, with a multivariable logistic regression (MLR) odds ratio (OR) of 3.94 and a 95% confidence interval (CI) ranging from 1.20 to 12.95. Additionally, our investigation revealed that the amount of circulating MLR was a reliable indicator of the severity of coronary lesions (OR: 2.05, 95%CI: 1.15 – 3.66), demonstrating superior predictive ability. [345]

Significative changes in neutrophils count with (8.04 ± 0.73 in CAD and 4.35 ± 0.33 with $P \leq 0.000$), with elevation count, The strong association between elevated neutrophil levels and acute cardiovascular events is widely recognized due to the detection of neutrophil infiltration at the site of plaque rupture in both animal models and human postmortem cases. [346].

On the other hand the study of Jintong J confirmed that NLR as neutrophil to lymphocyte ratio, is a better marker associated with plaque rupture than a single white blood cell count [345][346] our outcomes propose that an NLR > 1.5 considered as a predictive factors of inflammation and in the risk of plaque rupture CAD patients compared to MetS group with a sensitivity of 23.8% and specificity of

95.2% , also we demonstrated that it was an independence markers in the severity and prevalence of CAD this agree with the study of Verdoia and all [347].

Also we found a significative increase in GLY, TG and VLDL in CAD compared to healthy group with high specificity (100,100,100%) and sensitivity (34.2, 44.7, 42.1 %) according to (Miao Wang), who show that the high blood glucose and hyper-insulinemia (insulin resistance), lead to the atherosclerotic cardiovascular disease [87], because the diabetes characterized by the increase of cholesterol and decrease of HDL level, high levels of very low-density lipoprotein (VLDL) cholesterol and high levels of total VLDL [154].

For the renal factors, we observed a significant increase in the urea and creatinine in the serum of CAD patients as compared to the MetS**,** with ($P<0.05$) and high specificity 95.2%, 97.6% and sensitivity 36.1 %, 25.0% respectively, this significant increase relate with the severity of CAD, various risk factors involved in the relationship between the serum creatinine and the risk of CAD, primarily the muscle is the principal source of creatinine also insulin's target organ Therefore, it is suggested that serum creatinine levels could be a useful indicator for both CAD and diabetes[348]. Concerning the 25-hydroxy vitamin D [25(OH)D], the is a significant decrease in CAD patients compared to healthy subjects with ($P\leq0.01$) , the vitamin-D-deficient patients, contributed to alteration in the cholesterol transport, leading to an increase in circulating cholesterol levels, which cause the atherosclerosis development [349][350]**.**

Concerning the biochemical parameters, the serum levels of CRP were significantly higher in subjects with CAD lesions than in MetS patients with $P \leq 0.001$, specificity 95.2% and sensitivity 27.8%. however there is no association between CRP and the severity of the coronary heart disease, these observation are in accordance with previous study of Rifai et al which included 100 men with 1-, 2-, and 3-vessel disease documented by coronary angiography (cases) and 100 controls, they found significantly higher CRP levels in cases than in controls [351][352] one hypothesis suggested by researchers may agree with our outcomes that is The biochemical markers of inflammation reflect the diffuse atherosclerotic process in the vascular system rather than the degree of localized obstruction from atherosclerotic plaques [353].

We indicate that there is a significative increase in phosphorus in CAD compared to MetS group with $P \leq 0.001$, this study shows that an increase in serum phosphorus levels is linked to various other biochemical cardiovascular risk factors, including high levels of serum cholesterol, high levels of triglycerides, and elevated fasting blood sugar levels. Hence, our data offer a new insight that the level of serum phosphorus could potentially serve as a predictor for cardiovascular disease and exacerbate diabetes and its associated complications, [354] as we observed a low concentration of Vit-D in CAD compared to healthy and patients With (8.5 ± 1.05 in CAD, 10.00 ± 0.75 in MetS and 11.43 ± 1.58 in healthy subjects), the mechanism behind this association remains unclear, but several correlates have been

attributed. High phosphorus levels inhibit vitamin-D synthesis, which is linked to cardiac contraction and increased coronary calcification.[355].

The Framingham Study found an association between higher levels of serum phosphorus and increased cardiovascular disease (CVD) risk. This association is linked to vascular endothelial dysfunctions in thoracic arterial rings and direct incubation of endothelial cell culture with phosphorous. Hyperphosphatemia with impaired kidney function induces vascular smooth muscle cells to change into chondrocytes or osteoblasts, causing deterioration of cardiovascular systems and increased morbidity and mortality. Hyperphosphatemia also increases circulating parathyroid hormone levels, which is proinflammatory and produces interleukin 629, which is associated with increased CVD risk [356], [357].

Concerning CPK marker, we found a significant difference in CAD group compared Mets group with specificity 100 %, sensitivity 30.6%; CI : 0.565-0.821 with $P \leq 0.001$, we indicate that CPK alone was poor diagnostic marker for MI but is an important marker for calculated the percentage of CK-MB which indicate the lyse of myocardial cells , our finding according to study of Mohammed K and all [358].

The ROC curve analysis show the increase levels in liver enzymes including ASAT and ALAT also lactate dehydrogenase (LDH) in CAD compared to MetS group with high specificity (100, 100, 100%) and sensitivity (33.3, 25, 38.9) respectively, may lead to the increase of dyslipidemia, which according to another studies which demonstrated liver dysfunction [350]. The presence of elevated total serum LDH levels may be attributed to the involvement of cardiac LDH isoenzymes. During myocardial ischemia, there is a progressive increase in LDH levels in the blood, resulting in a change in the LDH-1/LDH-2 ratio. Normally, this ratio is less than 1, but it can exceed 1, especially after intense physical activity. This occurrence was noticed in 15 individuals diagnosed with coronary artery disease (CAD) who had total serum LDH levels that fell within the highest fifth percentile of the normal range determined by the laboratory[359]. Additional studies on patients with coronary artery disease (CAD) conducted 48 hours after ergometry, as well as on 8 healthy off-season collegiate basketball players, likewise demonstrated a notable alteration in cardiac LDH isoenzymes within the acceptable range. The study discovered that the correlation between total serum LDH levels and CAD remained significant, even after accounting for physical activity and ergometry fitness levels. This indicates that additional LDH isoenzymes, specifically the main myocardial LDH isoenzymes, have a role in the typical elevation of total serum LDH within the normal range.[360]

Our investigation found low concentration of albumin (ALB) and calcium (Ca) compared to healthy and MetS groups with Mean SD (35.79 ± 1.10 , 89.93 ± 1.54), our findings is with consistent respectively other studies which show that the albumin insufficiently produced by the liver during

inflammation, also other studies Low levels of albumin have been found to be associated with an elevated risk of cardiovascular mortality and morbidity because studies of Kuller and all propose that low serum ALB may indicate injury to the arteries and progression of atherosclerosis process [350] also low serum Ca contributed to clusters of early heart attack in contrast the supplemental calcium with normal amount of vitamin D is hypo-cholesterolaemic and reduces total lipid disposition in the aorta [361], [362].

4.Study of oxidative stress markers for CAD in El Oued region

Our study examined variations in the concentrations of enzymatic antioxidants (SOD, GSH, GPX) and TAC (anon-enzymatic antioxidant) between individuals with coronary artery disease (CAD) and individuals without any health issues. We also identified MDA as a mediator of inflammation. Our findings did not show any statistically significant variations in GPX activities, TAC, and MDA. However, previous studies have reported significant differences in these parameters among patients with cardiovascular diseases. [363][359].

We revealed the differences in the levels of oxidant and antioxidant markers between CAD, MetS patients and healthy persons. in CAD patients, the oxidant marker is significantly increased in MDA between CAD and healthy subjects with high specificity (100%) and sensitivity (28.6%) with $P \leq 0.001$, this is with accordance with other study [364][365]. Significant increase in MDA levels a lipid peroxidation product, and decrease in total antioxidant capacity indicate elevated oxidative stress in CVD patients. McMurray et al. [366]

However the enzymatic non-enzymatic antioxidants respectively , the super oxide dismutase (SOD) and GSH play an important role in the reducing tissue damage due to the formation of free radicals, this outcomes the same with the results of Ghosh and al[367][368].On our study we observed a decreased level of GSH with specificity 20.8% and sensitivity 63.6% in CAD group compared to MetS and control groups ,it explain to the increased oxidation or GSH consumption by electrophilic substances such as lipoperoxidation aldehydes may be the cause of GSH depletion .Furthermore, it has been noted that hyperlipidemia, which is itself linked to elevated cholesterol levels, results in erythrocytes with decreased GSH concentration[369]. Oxygen-free radicals are generated particularly in the early stage of myocardial infarction and GSH is involved in the reduction of hydrogen peroxide radicals, resulting in a decrease in GSH levels during that period [370].

For GPX and SOD were significatively decrease activity in CAD compared to control group with $P \leq 0.001$, specificity (21.7, 8.7%) and sensitivity (57.1, 71.4%) this is accordance with the study of Serdar and all [371]. The decrease in SOD activity seems to result from the effect of increased oxygen-

derived free radicals. Thus, lower O^- concentrations induce the SOD activity while higher O^- concentrations inhibit it. [372], [373].

According to our findings, Senthil et al. and Pandey et al. have demonstrated a decline in superoxide dismutase (SOD) activities in red blood cells and platelets among individuals with myocardial infarction. The reduction in SOD activity can be attributed to an increase in oxygen-derived free radicals. Therefore, lower levels of O_2- enhance the activity of SOD, whereas greater levels of O_2- hinder it. [374].

The results of linear regression analysis, with an increase in the severity of CAD, ta negative correlation between SOD and CPK, with P= 0.009 and R= -0.139, this explain the increase activity of SOD in CAD to reduce the concentration of CPK which demonstrated at the damage cardiac cell during the infraction myocardial, our result are consistent with other studies [375].

Also, there were a negative correlation between TAC, and inflammatory markers (NEUT, NLR and MLR) with (P= 0.030; R= -0.435, P= 0.014; R=-0.484, P= 0.011; R= -500) respectively, this explains the role of antioxidant marker to reduce the inflammation process, it helps to predict risk of CVD evets.

In metabolic syndrome group, there are a negative correlation between GPX / albumin and total protein, and TAC with phosphorus, in contrast there is a positive correlation between GPX/ CRP, these finding is similar with the studies which demonstrate that the significance of antioxidant capacity in preventing cardiovascular disease is based on the concept that the oxidation of LDL cholesterol in the walls of blood vessels is a step in the development of atherosclerosis. Our data indicated that the blood total antioxidant status (TAS) levels in patients with coronary artery disease (CAD) were significantly lower compared to those of the control subjects.[376].

Previous clinical research has previously reported using the TAS approach to examine the correlation between antioxidant capacity and CAD. [377]Semra and her colleagues found no discernible disparity in total antioxidant status (TAS) levels between patients with coronary artery disease (CAD) and individuals in the control group [378] .Additionally, Yegin and colleagues discovered a decline in the activity of GSH-Px in red blood cells that corresponded with the severity of coronary artery disease (CAD), which aligns with our findings [360].

CONCLUSION

&

RECOMMENDATIONS

Conclusion & Recommendations

This work examines the distribution of CAD patients to improve facilities and implement effective treatment measures to control the disease and thus help to reduce mortality in the society associated with this disease.

This study appears continuous increases of the coronary artery diseases rate prevalence. The prevalence in El Oued shows a significant rate, especially with the chronic disease and the bad routine of life, these results require sounding the alarm in order to develop a strategy to limit the spread of this disease and prevent it.

On the other hand, it was found that heredity, heart diseases, stroke, HTA, diabetes, cardiac surgery, metabolic syndrome, rheumatism, chest pain, the age range between 40-60 and < 60 years old are major risk factors for CAD. Knowing these factors is important in order to determine methods of prevention and avoiding falling ill with the disease. Also, knowing the prevention factors facilitates mitigating the spread of the disease.

In the CAD patients, we observed an important change in the leukocyte lineage parameters which indicate the immunological system disturbance are among the complication factors of metabolic syndrome.

For the CAD patients, results show that there was a change in urea and albumin, creatinine, total protein, calcium and CRP parameters. These results indicate the role of the biochemical markers in the diagnostic of the CAD among the MetS patients and in the renal complications of these diseases.

The study found a change in oxidative stress markers levels among CAD and MS patients. This confirms the essential role of oxidative stress in the occurrence of diseases and identifying its complications, which requires taking into account antioxidants in any treatment protocol for either disease.

The indices NLR, MLR, ALB, CRP and MDA had independent positive predictive values for those with high-risk of CAD. NLR and MLR are sensitive and cardiac-specific clinical markers that are valuable for diagnosing myocardial infarction (MI) and for assessing the level of risk. NLR and MLR are novel hematological markers that indicate platelet reactivity and early myocardial necrosis and plaque disruption all show potential for improving patient risk assessment, that help the clinicians to intervene to avoid adverse outcomes.

We assessed the frequency of the primary cardiometabolic risk variables in a representative sample of El Oued population in Algeria. The prevalence of the components of metabolic syndrome is expected to

increase significantly in Algeria, which will have significant implications for national healthcare costs. Sex-specific disparities indicate that metabolic syndrome is linked to a range of factors in both males and females. A potential benefit could arise from redefining waist circumference and HDL-cholesterol levels for certain ethnic groups through extensive longitudinal investigations. The findings of our study indicate that effective strategies to avoid metabolic syndrome in adults should incorporate both physical activity promotion and the promotion of a healthy diet.

In relation to medical practice, it is important to strengthen the screening process for patients who are at a high risk of cardiovascular diseases. This is particularly crucial for males, since they tend to utilize medical care less frequently than women, as seen by the significant number of cases where hypertension remains untreated.

Modulating the phenotype of monocytes has emerged as a targeted therapeutic approach for preventing and treating cardiovascular disorders.

We suggest that the development of antioxidant treatments is a promising approach for treating ROS disease. Antioxidant therapy, including the administration of polyphenols, flavonoids, antioxidant supplements, and other nutritional substances, in conjunction with moderate aerobic activity, has the potential to counteract the harm caused by oxidative stress. Therefore, understanding the specific oxidative pathway of a particular antioxidant linked to reactive oxygen species (ROS) might facilitate the detection of disease indicators and the formulation of preventive and curative treatment strategies.

Increase the awareness of people about their life style in foods and habits such as in physical activities especially the decrease of walking process and replaced by cars.

Also, various post mortem studies and death certificates revealed that 62-85% of patients who died out of hospital have past family history of CAD for that we recommended the obligation of autopsy for the corpse to determine the causes of sudden death, and to member of families of the died person on the importance of doing medical exams to the heart, for the early diagnostic to protect the people life.

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ANNEX

بطاقة استبيان Appendix 01. (Arabic version)

العمر:..... المهنة:..... الحالة الاجتماعية:.....

الوزن:..... الطول:..... فصيلة الدم:.....

مكان السكن :..... المستوى التعليمي:.....

مؤشر كتلة الجسم:..... قياس ضغط الدم:.....

الرقم	السؤال	نعم	لا	ملاحظات
	العوامل السريرية			
01	هل يوجد في عائلتك شخص مصاب بمتلازمة الشريان التاجي ؟			
02	هل تعاني من احد الأمراض المزمنة ؟			
03	هل تعاني من أي خلل في الكلى ؟			
04	هل تعاني من أي خلل في الكبد ؟			
05	هل قمت باستئصال اللوزتين؟			
06	هل تعاني من أي خلل في المرارة ؟			
07	هل انت مصاب بمرض معدي؟			
08	هل انت مصاب بفقر الدم؟			
09	هل أجريت عملية جراحية من قبل؟			
10	هل تعاني من أي نوع اخر من امراض القلب؟			
10	هل تعرضت من قبل لجلطة دماغية؟			
12	هل أجريت عملية جراحية على مستوى القلب؟			
13	هل لديك ضغط الدم؟			
14	هل انت مصاب بداء السكري؟			
15	هل تعاني من الالتهابات على مستوى جسمك؟			
16	هل انت مصاب بمرض الروماتيزم ؟			
17	هل تشعر بآلام على مستوى الصدر او القلب حين تبذل مجهودا؟			
18	هل تعاني من أي مشاكل في التنفس؟			
19	هل سبق وان توفي أحد من افراد عائلتك بسكتة قلبية؟			
	العوامل الاجتماعية والاقتصادية			
01	هل انت مدخن حديث او قديم؟ أو لديك أحد من افراد العائلة يدخن؟			
02	كم تدخن مرة في اليوم؟ وماهي عدد سنوات التدخين؟			
03	هل تتعاطى الكحول؟			
04	هل تعاني من الاكتئاب والتوتر المستمر؟			
05	هل تعرضت لنوبات عصبية من قبل؟			
06	هل تمارس الرياضة بانتظام؟			
07	هل عانيت من سمنة مفرطة من قبل؟			
08	هل تستهلك الحليب ومشتقاته بكثرة؟			
09	هل تستعمل الأعشاب كأدوية بديلة؟			
10	هل تتناول الحلويات بكثرة؟			
11	هل تستهلك الملح بكثرة في طعامك؟			
12	هل تستهلك الخبز بكثرة؟			
13	هل تتناول المعجنات بكثرة؟			
14	هل تتناول اللحوم الحمراء بكثرة؟			
15	هل تستهلك الأدوية بكثرة؟			
16	هل تستهلك المعلبات الغذائية بكثرة؟			
17	هل لديك دهون كثيرة على مستوى البطن؟			

Appendix 02. Questionnaire Card (English version)

Age:……. Function :…… Marital status :…….....

Weight:……. Height :…… Blood type:…….....

Address:…….……. Educational level:…….……

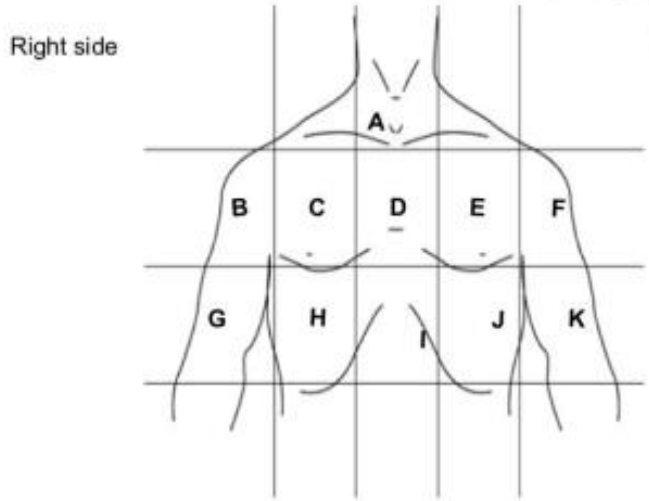
BMI:…….……. Tension measurment:…….……

N^{br}	Questions	YES	NO	Observations
	Clinical factors			
01	Does your family have someone with coronary artery syndrome?			
02	Do you suffer from a chronic disease?			
03	Do you suffer from any kidney disorder?			
04	Do you suffer from any liver disorder?			
05	Did you have your tonsils removed?			
06	Do you suffer from any gallbladder disorder?			
07	Do you have a contagious disease?			
08	Do you have anemia?			
09	Have you had surgery before?			
10	Do you suffer from any other type of heart disease?			
11	Have you ever had a stroke?			
12	Have you had heart surgery?			
13	Do you have HTN ?			
14	Do you have diabetes mellitus?			
15	Do you suffer from inflammation throughout your body?			
16	Do you suffer from rheumatism?			
17	Do you feel pain in the chest or heart when you exert yourself?			
18	Do you have any breathing problems?			
19	Have any of your family members ever died of sudden death?			
	Socioeconomic factors			
01	Are you a modern or old smoker? Or do you have a family who smokes?			
02	How many times a day do you smoke? And how many years of smoking?			
03	Do you drink alcohol?			
04	Do you suffer from depression and constant stress?			
05	Have you ever had nervous attacks?			
06	Do you exercise regularly?			
07	Have you suffered from excessive obesity before?			
08	Do you consume milk and its derivatives a lot?			
09	Do you use herbs as alternative medicines?			
10	Do you eat a lot of sweets?			
11	Do you consume a lot of salt in your food?			
12	Do you consume a lot of bread?			
13	Do you eat a lot of pastries?			
14	Do you eat a lot of red meat?			
15	Do you consume medications frequently?			
16	Do you consume a lot of canned food?			
17	Do you have a lot of belly fat?			

Appendix 03. WHO Rose Angina questionnaire (Arabic version).

1- هل عانيت من ألم أو اعتلال (عدم ارتياح) بمنطقة الصدر؟
*نعم *لا

2- في أي جزء مما يظهرة الشكل؟ أشر إلى المكان المحدد...



3- هل يحدث (الألم أو الاعتلال) أثناء السير صعوداً أو المشي على عجل؟؟
*نعم *لا

4- هل يحدث عند السير مستوياً بالمعدل المألوف (الطبيعي)؟
*نعم *لا

5- ماذا تفعل عند حدوثه بينما أنت تمشي؟
- تتوقف
- تهدي السير
- تواصل بنفس المنهج
- غير ملائم/ مطابق

6- هل يتلاشى الألم أو الاعتلال في الصدر عند التوقف؟
*نعم * لا

7- كم من الوقت يستغرق الأمر لكي يتلاشى الألم؟

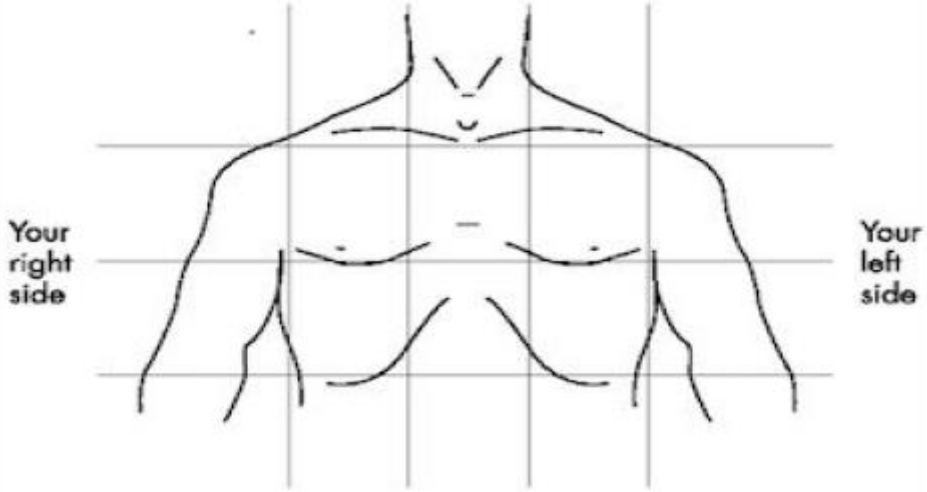
*أقل من 10 دقائق *أكثر من 10 دقائق

Appendix 04. WHO Rose Angina questionnaire (English version).

1 Do you ever have any pain or discomfort in your chest?

Yes/No

2 Where do you get this pain or discomfort?
Please mark **X** on the appropriate places



3 When you walk at an ordinary pace on the level does this produce the pain?

Yes/No/Unable

4 When you walk uphill or hurry does this produce the pain?

Yes/No/Unable

5 When you get any pain or discomfort in your chest on walking, what do you do?

Stop Slow down Continue at same pace Not applicable

6 Does the pain or discomfort in your chest go away if you stand still?

Yes/No

7 How long does it take to go away?

10 minutes or less
more than 10 minutes

Research article

A study on the prevalence and risk factors of coronary artery disease in patients with metabolic syndrome infected and not infected with COVID 19 from El- Oued (Algeria) region

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Corresponding author: **Samir Derouiche.** Email: dersamebio@gmail.com **ABSTRACT**

Introduction and Aim: Coronary artery disease (CAD) is a pathological process described by atherosclerosis plaque in the epicardial arteries. CAD is a chronic process that begins during adolescence and slowly progresses through life. Several traditional risk factors genetics and environmental, involve in the development of atherosclerosis process. This study was aimed to investigate the prevalence of CAD and its associated risk factors among the El Oued (Algeria) population.

Materials and Methods: An epidemiological study was carried out on 23422 patients who suffered from cardiovascular diseases. The study of risk factors analysis was focused on 300 voluntary individuals, their origins from different El-Oued areas, and the CAD and metabolic syndrome patients selected from public and private health interests. All the information was obtained by a questionnaire. The risk of socio-clinical factors has been estimated by Binary Logistic regression was carried out between CVD and its associated risk factors. $P < 0.05$ from two-sided statistical tests was regarded as statistically significant.

Results: Through the results presented in our study, we found that the clinical factors such as hypertension (OR=154.846, and; P =0.000), the group aged> 60 (OR=154.84, and; P =0.000 and chest pain (OR=42.667, and; P =0.000), present significant risk factors with CAD patients compared to healthy people (control), respectively, in contrast we show that the most dangerous Socioeconomic factors alcohol consumption and stress respectively for (OR=13.500= and; P =0.001), and obesity (OR=4.495= and; P =0.000), but we estimate that sport is important protective factors for the disease with OR=52.6, P 0.500) in the CAD patients compared to metabolic syndrome patients.

Conclusion: The increasing prevalence of risk factors for coronary artery disease among the population has raised concerns for public health, which creates a health threat, especially with inadequate promotion and awareness programs.

Keywords: CAD; CVD; risk factors; protective factors; El-Oued.

INTRODUCTION

As we know that the burden of cardiovascular disease (CVD) presents unhealthy problems worldwide due to the increase of mortality and morbidity, especially in the developing countries. Africa includes more than 1 billion people; it represents high rates in the burden of CVD, that makes the CVD related to 38% of deaths over all the non-communicable deaths (1). In North Africa, Algeria is one of the countries suffering from the increase of sudden death, because of CVD, particularly the heart ischemic disease (IHD) (2). In Algeria in 2012 the death percentage was estimated at approximately 41% of cardiovascular, 7% diabetes, which includes obesity (22.4% women and 9.6% men) (3). According to the United Nations reports of the NCDs in 2011, the WHO is working to reduce the premature disease caused by CVDs by 25% by 2025 (4). Among the CVD, which represent the most percent, lead to sudden death is ischemic heart disease, which is a threat of prevalence of CVDs (5). Ischemic heart disease is known as coronary artery disease (CAD) or coronary heart diseases (CHD), it is a pathological process described by atherosclerosis plaque in the epicardial arteries, where it obstructs the passage of the blood through the arteries, the disease can be stable or unstable in any time due to the presence of acute atherothrombotic, the progress nature of CAD results different clinical presentation, either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS) (6). CAD is a chronic process that begins during adolescence and slowly progresses through life (7). Several traditional risk factors genetics and environmental, involve in the development of atherosclerosis process, such as family history of premature CAD, cigarette smoking, diabetes mellitus, hypertension, Metabolic Syndrome , a sedentary lifestyle, advanced age, gender and obesity (5). These risk factors may complex or induce the inflammatory process which include in the progress of

atherosclerosis plaque (8). The incidence of CAD prevalence is associated with pattern of risk factors, according to the INTERHEART study which include 52 countries, it demonstrates that nine risk factors represent 90% initiate the myocardial infarction, these risk factors have a similar effects in both men and women, in different geographic regions, These nine risk factors include cigarette smoking, abnormal blood lipid levels, hypertension, diabetes, abdominal obesity, a lack of physical activity, low daily fruit and vegetable consumption, alcohol over consumption, and the psychosocial index (9). The increase of risk factors rate due to the modification in life style, such the fast urbanisation by years, The TAHINA (Epidemiological Transition and Health Impact In North Africa) project is currently investigating the burden of non-communicable disease in Tunisia and Algeria, and recent data demonstrate a high prevalence of hypertension (30% and 24%, respectively) and obesity (27% and 21%, respectively)
(10). Our study research aims to the determination of clinical and social risk factors for coronary artery disease, to take the necessary prevention tools, to protect people's life from heart attack disease, which lead to myocardial infarction, and contribute to sudden death.

MATERIALS AND METHODS

Epidemiological study

Wilaya of El-Oued is in southeast Algeria, it covers an area estimated 54 573 km² and has a 28 commune, and 12 districts. The total population of Wilaya was estimated around 702,021 inhabitants, a density more than 12 inhabitants per km^2. El-Oued has a socioeconomic development in Algeria especially in the agricultural domain; in this study the El-Oued population over 20 years old was estimated at 99.29%.

Data source

The data records of all patients' illness with coronary artery disease (CAD) were collected and diagnosed from internal diseases services of Ben Amor Djilani Hospital, and from Heart's clinic of Dr. Salhi in El Oued. We obtained information, such as age, gender, living address, and the antecedent disease of CAD patients in different areas of El Oued. The retrospective study included 23422 patients and was conducted over a period of 11 years from October 2010 until December 2021.

Data analysis

The descriptive data, of coronary artery disease's patients which included various demographic variables such as age, gender etc., were encoded and classified to obtain the frequency prevalence of CAD in the El-Oued area. The different El-Oued areas were categorised according to the 12 districts by locations, Center (El-Oued) north (Guemar, Reguiba, Djamaa, Mghair), south (Bayadha, Robah), west (Mih Wensa), and east (Debila, Hassi Khalifa, Taleb Larbi, Magren).

Study of risk factors

Our study is a transversal epidemiologic, destined for the determination of coronary artery disease's risk factors, clinical such as metabolic syndrome, hypertension, diabetes, genetics history, and socioeconomics like life style; physical activities, foods. In our article we present the Algerians who live in El Oued (it is Wilaya located in the south east of Algeria), patients and controls in different medicals centre of El Oued district, the site implanted in various area of El Oued, civilised and rural, the rural areas is located far of the civilised centre (around 30 and 50 Km from the centre city of El Oued), we estimated the controls levels of risk factors such as diabetes, metabolic syndrome, hypertension, for the patients diagnosed.

Study population

The study focused on 300 voluntary people, divided to 3 groups, healthy people (n=100) with average age 35.50±10.22 years old, CAD patients (n=100) with average age 63.01± 10.22 years old and metabolic syndrome patients (n=100) with average age 57.32±14.80 years old, all the voluntary people live in different El Oued areas.

The variables demographics information was included such as age, gender, index mass, social case, job, educational level, and blood group; all were collected by the questionnaire by direct discussion with the voluntary people. In the questionnaire we relied on various variables, clinical and socioeconomics, which can be risk factors, contributed to the progress of the disease, such as HTA, genetics history, diabetes, and consumption of fried foods, meat consumption, and abdominal obesity.

Inclusion and exclusion criteria

The criteria of the patient selection focused on the cardiologist and endocrinologist diagnosis, they confirmed that all the patients suffered of heart ischemic and chronic disease from a long time and there were who had a heart surgery or complication contribute to CAD, control people who had healthy, all of them were included. Other kinds of disease were excluded.

Statistical analysis

The obtained results of different groups are present as frequency per population or as the mean standard deviation (SD). We use the Chi-square test to extract the risk and protective factors of coronary artery disease. Relative risks and Odds ratios were calculated by Cochran's and Mantel Haenszel statistics using SPSS 25. Odds ratios >1 and $P<0.05$ indicate a significant risk factor. $OR<1$ and $P<0.05$ indicate a significant protective factor.

RESULTS

Epidemiological study

The study covers 3936 cases with CADs. Table 1 shows the frequency's prevalence of CADs among women and men based on age, gender, year wise, region wise, associated chronic disease such as HTA, diabetes, dyslipidemia, stroke, insufficiency renal, asthma, heart failure and dysthyroidia and lifestyle such obesity and smoking from October 2010 to December 2021.

Table1: Demographics of CAD patients in this study

Variable	No. of cases	Frequency (%)
Age groups		
≤ 40	281	7.13
41–50	478	12.14
51–60	885	22.48
61–70	1019	25.91
> 70	1273	32.34
Gender		
Male	2265	58
Female	1671	42
Years		
2010-2011	150	3.81
2012-2013	351	9
2014-2015	651	16.50
2016-2017	834	21.16
2018-2019	1077	27.36
2020-2021	873	22.17
Region		
Centre	2723	69.18
Northern	349	8.86
Eastern	476	12.09
Western	77	1.97
Southern	311	7.9
CAD associated Diseases		
Diabetes		
HTA	1652	42
Stroke	2288	58.13
Dyslipidaemia	164	4.16
Insufficiency	237	6.02
Renal	42	1.06
Asthma	67	1.70
Heart failure	251	6.37
Dysthyroidia	23	0.58
Smoking	379	9.62
Obesity	315	8

The eleven years appear continuous increases of the coronary artery diseases rate prevalence. The prevalence in El Oued, over the period 2010-2017 shows a significant rate, especially with the chronic disease and the bad routine of life.

Study of CAD risk factors

Population characterisation

The description of population demographics is shown in Table 2. This study included 300 volunteers with each group containing 100 people (50 women and 50 men). The results showed a significant homogeneity for both metabolic syndrome and coronary artery disease patients, while there is a significant difference concerning age, job (worker, unworked, retired) and educational level between the coronary artery disease patients and control groups. The blood types are similar approximately in the distribution of percent for the three groups studied.

Study of socioeconomic and clinical factors

The Tables 3 and 4 present significant risk factors for clinic pathological factors; we estimate from odds ratio (OR) values that CAD heredity, heart diseases, stroke, HTA, diabetes, cardiac surgery, metabolic syndrome, rheumatism, chest pain, the age range between >40 and < 60 years old were a risk factors leading to CAD, with p-value >0.05. Also the odds ratio (OR) values for socioeconomic factors in table (3,4) show that smoke, alcohol consumption, depression and stress, epileptic crisis, obesity, with p- value >0.05, which demonstrated that the wrong routine followed in life influence negatively on the human health, which present a high risk rate lead to atherosclerosis with p-value >0.05, also the tables showed the sport practise as protective factors to CAD.

DISCUSSION

Our research outcomes showed the age prevalence among women and men, was 63 years old, with average age 63.018±1.632 years old (1-100 years old), which agrees with the study of Khaira *et al.*, in Setif (Algeria) population, they found the average age of CAD patients 62.7 ± 11 years (20-91 years) (11). Our epidemiological and clinical data shows differences among men and women in several aspects. There is dominance prevalence in men with 58% than women with 42%, these outcomes were confirmed with the study of Kaveh *et al.*, they found overall, 68% of the patients were men and 32% were some may due to lifestyle risk factors, for example smoking is common in men than women (12) genetics history and response to therapy this agree with the study of Manuel *et al.*, (13).

Regarding the difference prevalence of CAD between rural and urban, we found higher percent in the urban; El Oued centre with 69.18%, due to the important urbanisation, and the lifestyle with food habits of people, which associated with the increase of risk factors also it is may to the several environmental factors, between the city and rural, this opinion agree with Framingham study (14).

Table 2: Description of study population of control, MS Patients and CAD patients' group (n=300)

Variable		**Control**	**MS Patients**	**CAD Patients**
Age (years)		10.22±35.5	57.32±14.8	63.01±12.41
Length		38.96±38.99	40.05±39.79	38.83±37.39
Weight (kg)		74.33±19.26	76.46±18.32	74.02±12.24
Body mass index (BMI) (kg/m^2)		35.23±32.54	36.6±33.18	35.29±31.19
Job %	Worker	79	37	24
	Unworked	18	47	51
	Retired	3	16	25
Educational level %	Illiterate	3	35	50
	Primary	3	20	16
	Medium–Secondary	50	30	33
	High School	44	15	1
Address (living)	Inside El Oued	61	61	46
	Outside El Oued	39	39	54
Blood types %	O	50	59	54
	A	30	25	23
	B	17	11	19
	AB	3	5	4
SARS-COV-19 %	exposed	60,3%	59.2	40.8
	Not exposed	43,4%	44.4	55.6

Table 3: Comparison of the clinical factors of coronary artery disease patients and control group

N	**Risk factor**	**Control (%)**	**CAD patients (%)**	**OR**	**CI 95%**	***P-value***
1	CAD Heredity Positive Negative	 50.9 49.7	 49.1 50.3	0.952	0.515-1.759	0.500
2	Heart disease Positive Negative	 12,5 51,6	 87,5 48,4	7,452	0,900-61,729	**0,032**
3	Stroke Positive Negative	 10 52,1	 90 47,9	9,791	1,217-78,806	**0,009**
4	Hypertension Positive Negative	 1,6 71,7	 98,4 28,3	154,84	20,739-1156,136	**0,000**
5	Cardio surgery Positive Negative	 4,8 44,7	 95,2 55,3	16,162	2,123-123,039	**0,000**
6	Diabetes Positive Negative	 1,8 68,3	 98,2 31,7	116,21	15,592-866,248	**0,000**
7	Metabolic syndrome Positive Negative	 2,5 61,9	 97,5 38,1	63,295	8,477-472,583	**0,000**
8	Rheumatism Positive Negative	 5 55	 95 45	23.222	3.047-177.207	**0.000**
9	Chest pain Positive Negative	 5.9 72.7	 94.1 27.3	42.667	14.485-125.68	**0.000**
10	Age >40 years Positive Negative	 95,8 24,2	 4,2 75,8	0,014	0,004-0,047	**0,000**
11	Age < 60 years Positive Negative	 1,6 71,7	 98,4 28,3	154,84	20,739-1156,13	**0,000**

*OR > 1 and P < 0.05 indicate a risk factor. *OR < 1 and P < 0.05 indicate a protective factor

Table 4: Comparison of the clinical factors of coronary artery disease patients (CAD) and patients with metabolic syndrome (MS)

N	Risk factors	MS Patients (%)	CAD Patient (%)	OR	CI 95%	*P-value*
1	CAD Heredity					
	Positive	49.1	50.9	1.051	0.565-1.956	0.500
	Negative	50.3	49.7			
2	Heart disease					
	Positive	61.1	38.9	0.609	0.226-1.641	0.230
	Negative	48.9	51.1			
3	Stroke					
	Positive	47.1	52.9	1.137	0.420-3.078	0.500
	Negative	50.3	49.7			
4	Hypertension					
	Positive	50	50	1.000	0.566-1.765	0.558
	Negative	50	50			
5	Cardio surgery					
	Positive	13	87	8,083	2,318-28,187	**0.000**
	Negative	54,8	45,2			
6	Diabetes					
	Positive	51.4	48.6	0.886	0507-1.547	0.388
	Negative	48.3	51.7			
7	Metabolic syndrome					
	Positive	71.9	28.1	3.564	2.731-4.651	**0.000**
	Negative	0	100			
8	Rheumatism					
	Positive	54.8	45.2	0.785	0.397-1.555	0.301
	Negative	48.7	51.3			
9	Chest pain					
	Positive	28.1	71.9	5.333	2.899-9.812	**0.000**
	Negative	67.6	32.4			
10	AGE> 40 years					
	Positive Negative	80	20	0.227	0.062-0.830	**0.014**
		47.6	52.4			
11	AGE < 60 years					
	Positive	43	57	0.958	0.546-1.680	0.497
	Negative	42.9	58.1			

*OR > 1 and P < 0.05 indicate a risk factor. *OR < 1 and P < 0.05 indicate a protective factor

Regarding the prevalence of coronary artery disease by years, we observed a significant increase from 2010 to 2015 by 8.24%, but 2019 was the most year which registered the most high percent of prevalence with 16.6%, different studies show that the incidence of CAD, refer to the age, genetics and environmental factors, chronic disease associated with lifestyle such as arterial hypertension, diabetes mellitus and dyslipidemia, urbanisation and life stress, also work , and the factors of individual and social behaviour (15).

The results of risk factors study showed that the most risk age of CAD, is over than 50, that agree with the study of Getu *et al.,* report 31% (429) of all CVD cases affecting people aged between 51 to 60 years (16), with the ageing process, the body's system declines, such the cardiovascular system leading to progressive deterioration in the structure and vasculature which lead to atherosclerosis (7). Also most of metabolic syndrome and CAD patient represent a significant numbers of absence of awareness health, this make a risk factor in health awareness and this agree with the study of Gunhild *et al.,* who confirmed the importance of health literacy to avoid different risk factors such as smoking, alcohol, unhealthy food contribute to CAD (17).

We report that covid19 infection represent a threat for CAD, as show in the study of Lukasz lead to various complication such venous thrombosis and pulmonary embolism as a result of a disordered endothelial homeostasis triggered by either inflammatory cytokines storm or direct infection, causing, for instance, intracellular oxidative stress, that helps the development of atherosclerosis plaque (18). Also it is shown in the study of Jhumki *et al*., confirming that the family history leads to the development of disease (19). Post mortem studies and death certificates revealed that 62-85% of patients who died out of hospital have past family history of CAD (13).

Marenberg *et al*., show that in monozygotic twins the risk of death from CAD increased 3.8 to 15 times if a sibling died of CAD before age 75 (20). In addition, the study of Anderson *et al.,* have shown a large international case-control study reported a rise in the risk of MI if one parent had MI (OR=1.67), or one parent had MI before age 50 (OR=2.36), or both

parents had MI (OR=2.90) and if both parent had MI before age 50 (OR=6.56) (21). Also there are a strong association between the obesity, hypertension, diabetes and metabolic syndrome with CAD, this agree to the study of Wang, who show that the high blood glucose and hyper-insulinemia (insulin resistance), lead to the atherosclerotic cardiovascular disease (22), because the diabetes characterised by the increase of cholesterol and decrease of HDL level, high levels of very low-density lipoprotein (VLDL) cholesterol and high levels of total VLDL, the metabolic syndrome was defined as hypercholesterolemia or hypertriglyceridemia or both, with high low-density lipoprotein (LDL) and low high-density lipoprotein (HDL), also it is a raised in apo B to apo A-1 ratio. Also obesity makes health problems contribute to cardiovascular disease, due to the accumulation of fat in the abdominal visceral and an excess of fat in the abdominal tissues that activate the different metabolic structures such as increase in the level of LDL, leading to atherosclerosis (23).

Concerning the rheumatism, smoking, they present a significant risk factors for CAD, that agree with the study of Jacqueline *et al*., which confirmed the rheumatism is a pathological inflammatory associated with a large complication of CVD like atherosclerosis; vasculitis; cardiac valve failure; endo, myo, and pericarditis; and heart failure, a cohort studies involving 20 million people appear that 70 % of smokers with CAD more mortality than non-smokers with CAD (24),also another studies show that the smoking induce oxidative stress process lead to activation of cascade inflammatory process, which link with to coronary atherosclerosis (25) also intense cigarette smoking will in general increment myocardial O_2 consumption by increasing heart rate and blood pressure associated with blood flow in the coronary arteries in normal subjects compared with CAD patients there is no increase or actual decrease in coronary blood flow (26).

We found that physical activities protect factors with p value=0.500. They decrease obesity and get rid of abdominal obesity, also reduce insulin resistance, and also provide benefits for children and youth to facilitate maintenance of a healthy body weight (10). The physical activities is polypill due to its numerous beneficial effects on cardiovascular risk factors and cardiovascular system physiology, it was recommended for the coronary artery patients for because it increased survival among men and women with CAD, even among those with a doctors regimen, previously sedentary patients will need support to work up to 30-60 min most days, resistance exercises maintain muscle mass, strength, and function and, with aerobic activity, have benefits regarding insulin sensitivity and control of lipids (27).

CONCLUSION

This study examines the distribution of CAD patients to improve facilities and implement effective treatment measures to control the disease and thus help to reduce mortality in the society associated with this disease. On the other hand, it was found that heredity, heart diseases, stroke, HTA, diabetes, cardiac surgery, metabolic syndrome, rheumatism, chest pain, the age range between 40-60 and < 60 years old are major risk factors for CAD.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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