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Homocysteine Vs Cholosterol: A Comparison of Pathogenetic Risk Factors

Bruno Riccardi

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Abstract: *The European healthcare landscape of 2025 confirms and worsens the presence of chronic diseases – Non Communicable Chronic diseases (NCDs) – which continue to be the leading cause of illness, disability, and death in most countries. The data emerging from the latest OECD and WHO Europe reports (Health at a Glance 2025) is unequivocal: chronic conditions are no longer a component of the system, but rather its core. The economic sustainability of care, people's quality of life, and governments' ability to respond to increasingly complex and ongoing needs depend on them. In this article we will describe the main chronic degenerative diseases with a focus on the most important and widespread ones, in order to identify the pathogenic factors responsible for their onset and the risk factors to keep under close observation. We will make a comparison between the two main killers for these pathologies, cholesterol and homocysteine and their excess blood values. We will highlight how, while blood cholesterol has become routinely included in cardiovascular disease screening and in established preventive and therapeutic protocols, blood homocysteine has not yet received the necessary attention, as an important, broad-spectrum independent risk factor, for the control of these diseases. Comparing the two metabolic parameters will highlight the urgency of including homocysteine in prevention protocols not only for cardiovascular diseases, but also for many other chronic diseases.*

Keywords: chronic degenerative diseases, risk factors, cardiovascular diseases, hypercholesterolemia, hyperhomocysteinemia, misfolding proteins, prevention and treatment of chronic diseases

INTRODUCTION

Chronic degenerative diseases

Chronic degenerative diseases, also known as non-communicable diseases, currently represent the majority of existing pathologies in advanced societies, both in terms of prevalence and severity of associated clinical conditions. Their outcome is often fatal, and in any case, more or less long-term, always disabling.Population aging is the factor favoring the onset of these diseases, even if their incidence is largely regulated by multiple mechanisms related to their origin.

In fact, this group of diseases recognises environmental, behavioural and genetic factors in its genesis [1].

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Chronic degenerative diseases include the group of non-communicable pathologies, characterised by a long course and a disabling or even lethal outcome [2].They are distinguished from infectious diseases by the way they arise and are transmitted.While infectious diseases are caused by microorganisms, also called Vectors (Viruses, Bacteria, Parasites) and by direct or indirect contagion through the various vectors indicated, they spread rapidly, to the point of affecting entire populations, as in pandemics. They can be disabling and even fatal, or they resolve with recovery. Diseases are not caused by microorganisms, they can have disabling or otherwise negative outcomes for the quality of life and very often be fatal.They have a prolonged course over time and arise due to the concurrence of several causal **factors** , which we define as **predisposing factors** or **risk factors** .

Chronic degenerative diseases are the leading cause of death, mainly in civilized societies, throughout the world. They are a large group of diseases, which includes heart disease, stroke, cancer, diabetes and chronic respiratory diseases, neurological diseases, musculoskeletal and gastrointestinal disorders [3]. Generally, these diseases have a multifactorial origin, which can be genetic or linked to environmental and lifestyle factors. They typically begin in young people but take decades to manifest clinically. Given their lengthy course, they require long-term care, but at the same time offer several prevention options.

At the root of the major chronic diseases are common and modifiable risk factors, such as unhealthy diet, tobacco use, alcohol abuse, and lack of physical activity. This article will examine the epidemiological and preventive aspects of these diseases. Numerous other pathologies (of a hormonal, immune or metabolic nature) become chronic and lead to disability.

The origin of chronic diseases

It is to be found in the alterations and deficiencies of one or more metabolic pathways which, when altered, cause specific physical symptoms and signs. A limitation of modern medicine is that it focuses on the symptoms of chronic disease, neglecting the early pathogenic mechanisms that are its underlying cause. This leads to ineffective treatment interventions. The most common clinical approach today ignores early diagnosis before symptoms appear. Furthermore, the subtle progression of symptoms and the presence of normal blood marker levels do not exclude the development of cardiovascular disease.

Epidemiology of Chronic Degenerative Diseases

Chronic non-communicable diseases (NCDs) include [4]:
cardiovascular diseases, tumors, chronic respiratory diseases, diabetes, autoimmune and neurodegenerative diseases, and represent the **first cause** of morbidity, disability and mortality.

- They begin at a young age but require decades before manifesting clinically;
- The WHO **European Region has the** highest *burden* of these diseases worldwide: cardiovascular diseases and cancer cause almost **three-quarters** of mortality;
- 80 **%** of all cases of heart disease, stroke and type 2 diabetes and a third of cancer cases are preventable

Evolution and Epidemiology of Chronic Diseases Fig.1: [5]

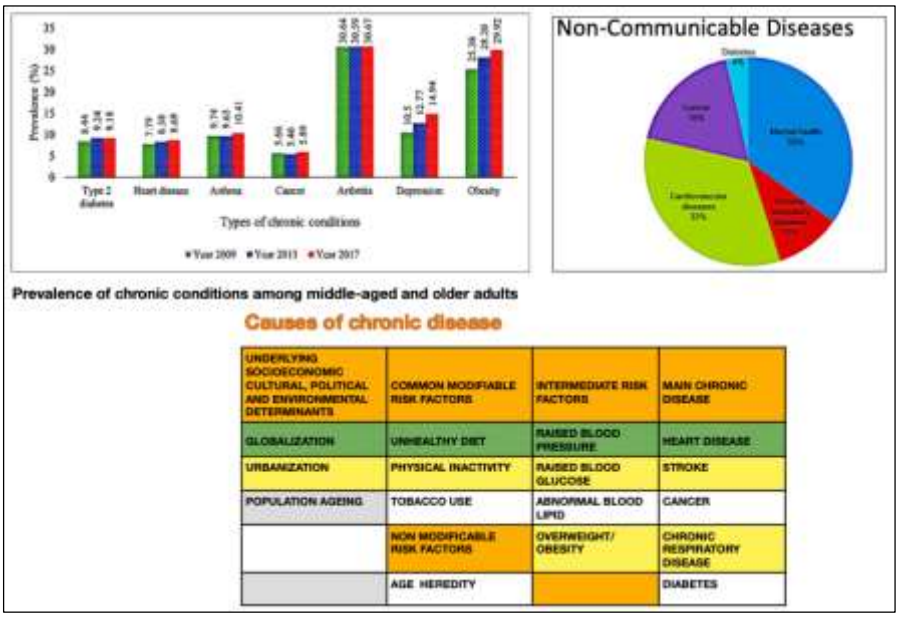

Figure 1- Comparison and Epidemiology of Chronic Degenerative Diseases
From: https://www.physio-pedia.com/Non-Communicable_Diseases

The factors that contribute to the onset and evolution of chronic-degenerative diseases are defined as **Risk Factors, FR,** the most important of which and are represented in Fig.1, [6], [7].

Among the various chronic-degenerative diseases, those of greatest interest for active prevention are cardiovascular and cerebrovascular diseases.
The reason for the greater interest is dictated by their higher incidence, in fact, they occupy the first place among the causes of death, and at the same time because modifiable risk factors can be easily intervened.
We will focus our attention on these in this study.

Cardiovascular diseases

They are the leading cause of death globally, responsible for over **20 million deaths each year** . They account for over 35% of all overall mortality and are estimated to cause more than 6.5 million premature deaths each year.

These are pathologies that recognize multiple pathogenic factors, some modifiable and others non-modifiable.

Among the **modifiable factors** (on which it is possible to implement a preventive intervention) it is worth remembering:

- alterations in lipid metabolism (increase in LDL cholesterol levels and reduction in HDL cholesterol, increase in triglycerides),
- high blood pressure,
- cigarette smoke,

- a sedentary lifestyle,
- obesity or being overweight,
- metabolic syndrome
- diabetes mellitus.

The **non-modifiable factors** are: age and heredity.
Furthermore, the presence of other congenital or acquired heart diseases (valvular insufficiencies or stenosis, alterations in the conduction system responsible for arrhythmias) or other serious pathologies (anemia, lung diseases) can contribute to increasing the severity of ischemic heart disease, sometimes causing its onset even at a young age.
Prevention plays a key role in controlling the onset of chronic degenerative diseases.

A distinction must be made between **Primary Prevention** and **Secondary Prevention.**

Primary prevention aims **to prevent the onset of new cases of the disease,** using the following interventions:

- reduce individual risk (eliminate FRs);
- strengthen the body's defenses;
- remove harmful behaviors (lifestyles, inappropriate diet, sedentary lifestyle);
- induce positive behaviors (promote positive lifestyles):
- interventions on the living and working environment;
- eugenics (genetic counseling, prenatal screening);
- Health interventions (immunoprophylaxis: control, elimination of infectious diseases)

Secondary prevention aims to identify the presence of conditions that promote disease early through population screening.

The method generally adopted for screening consists of periodic clinical chemical examination of blood and urine, to identify the early presence of abnormal values of pathogenic markers.

The tests that are normally required to monitor the incidence of cardiovascular diseases consist solely of the dosage of Cholesterol, in all its variants, Triglycerides, Blood Sugar, and Blood Pressure.

hyperhomocysteinemia (elevated levels of homocysteine in the blood) plays a key role in the pathogenesis of cardiovascular disease, this test is very rarely routinely requested.

In this article, we will compare the two most important risk factors mentioned, cholesterol and homocysteine, to highlight how homocysteine represents a broader pathogenic risk factor than cholesterol, and therefore its measurement can also represent a fundamental preventive resource, which should be adopted routinely.

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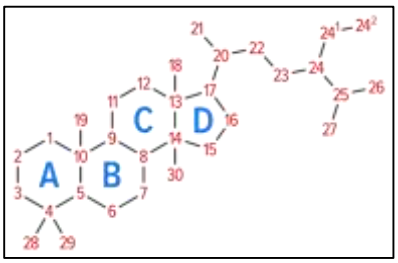
Cholesterol and homocysteine: a comparison of two pathogenic risk factors

Comparison of the two molecular structures and pathogenic properties;

CHOLESTEROL

Cholesterol is an organic **molecule** belonging to the class of lipids, specifically, sterols.
The cholesterol molecule has a structure made up of four rigid rings and is an irreplaceable constituent of animal cell membranes, as well as being a precursor of steroid hormones, vitamin D and bile acids.
It has the following structural formula:



Structure of cholesterol

Cholesterol has a flat molecular structure with a general chemical formula typical of steroids made up of 27 carbon atoms called: ***perhydro-1,2-cyclopentanophenanthrene*** , in which the rings indicated by the letters A, B, C, D are present, and the numbering of the carbon atoms present in the molecule is indicated in the formula [8], [9].

It is an ***amphipathic*** molecule, as it has a hydrophilic, polar end, consisting of the hydroxyl group, and a hydrophobic, non-polar part, represented by the rigid tetracyclic nucleus and the flexible side chain. Because it is insoluble in water, cholesterol can circulate in the blood only in association with plasma lipoproteins.

The concentration of this substance in the blood is called cholesterolemia; cholesterol is contained in plasma lipoproteins, therefore we refer to total plasma cholesterol, or the cholesterol present in **low-density lipoproteins, LDL** , and **high-density lipoproteins, HDL** , or non-HDL cholesterol (which includes the cholesterol transported by all plasma lipoproteins with the exception of HDL).

Properties of cholesterol
In animals, cholesterol is an essential component of numerous cellular structures and functions:

- **In cell membranes** because it is the only lipid species in the organism to have a rigid ring structure, while all other membrane lipids have remarkably flexible carbon structures.

In fact, 85% of free cellular cholesterol is found in the plasma membrane , where >90% of it is inserted into the internal (cytoplasmic) phospholipid layer and 3÷5% into the external one, orienting itself with the -OH group exposed to the surface, in correspondence with the polar heads of the phospholipids Fig. 2 (A).

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Its presence decreases the fluidity of the membrane, a property on which important functions depend, for example: permeability to small water-soluble molecules; activity of membrane receptors and enzymes; mechanical stability; formation of vesicles for the transport of their contents to the various cellular compartments [10], [11], [12].

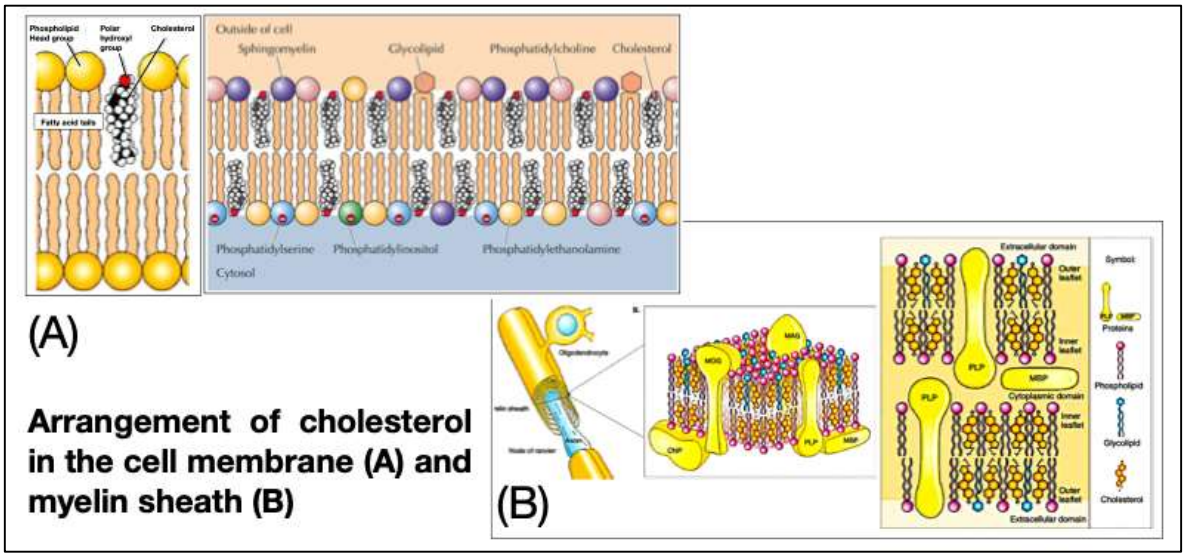

Figure 2- Arrangement of cholesterol in the cell membrane and myelin sheath

- **In the myelin sheath;**
  helps form the myelin sheath of nerves, in which it has an insulating function and allows to accelerate the transmission of nerve impulses Fig. 2 (B).
- **It intervenes in cell division** which leads to cell reproduction.
- **It intervenes in embryonic development** . In fact, there are fetal malformations due to a deficiency in cholesterol formation.
- **It forms bile and bile acids** . In fact, excess cholesterol is eliminated from the body through the formation of bile by the liver.

Precursor of other important molecules

Cholesterol metabolism

Cholesterol synthesis occurs in all cells, but most of it comes from the **liver** (at least 50% of total endogenous synthesis) and **the intestine, in** a smaller part is synthesized by the adrenal cells and the gonads.Free cholesterol, cholesterol esters, and triglycerides are exported from the liver and redistributed to peripheral tissues via **plasma lipoproteins**.

The complex synthesis takes place in the cytoplasm (the last stages are anchored to the smooth endoplasmic reticulum) and occurs in several phases [13],[14],[15]:

T

he entire structure of cholesterol (C27, twenty-seven carbon atoms) derives entirely from **Acetyl - CoA .** The biological cost of synthesizing *a single molecule of cholesterol is very high:*

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The stages of cholesterol synthesis include Fig. 3:

1) **Acetyl-CoA** units to form **mevalonate**, a C6 carboxylic acid intermediate:
2) Mevalonate is converted to isoprene units, activated by pyrophosphate: **Δ3 isopentenylpyrophosphate** ,
3) Union of 6 isoprene units join to give a linear C30 compound: **squalene,**
4) Squalene cyclization: the steroid nucleus and complete cholesterol (C27) are formed.

Mevalonate is formed from **MHG - coa (hydroxymethylglutaryl Coa),** is the same compound that is also an intermediate in the synthesis of ketone bodies, by the cytoplasmic isoenzyme **HMG-CoAsymyntase** (the ketone body enzyme is the mitochondrial isoform).

HMG- CoA reductase: removes **coenzyme-A** and reduces the terminal carboxyl group to an alcohol, producing mevalonate. The enzyme uses 2 molecules of NADPH.

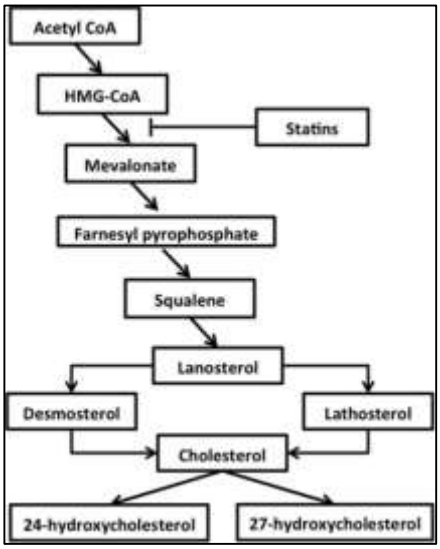

Figure 3- Cholesterol syntesis

HMG- Coa reductase is the key regulatory step in cholesterol synthesis.

Cholesterol produced by the liver is exported in 3 forms: cholesterol esters, bile acids, free cholesterol (little). Cholesterol produced by the adrenal glands and gonads is converted into steroid hormones.Cholesterol compounds and triacylglycerols are insoluble in water and are exported from the liver and transported to tissues by ***plasma lipoproteins, large complexes composed of lipids and proteins*** that transport poorly soluble lipids (cholesterol, and fat-soluble vitamins) in the plasma, interstitial fluids, and lymph, to and from tissues.

Lipoproteins are divided into various classes depending on their density and size. Each class of **lipoproteins** has a specific function, determined by its composition based on the type of lipid transported and identity of apolipoproteins, Table 1

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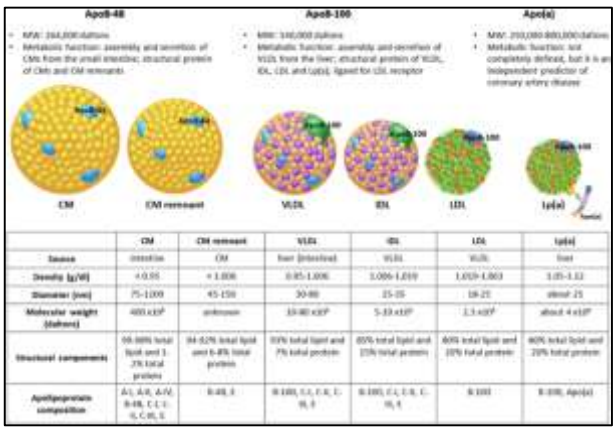

Table 1 - Types of Apolipoproteins - From: https://www.researchgate.net/figure/Characteristics-of-the-different-lipoprotein-classes-and-their-classification-

In pathology , cholesterol contributes to the formation of gallstones and atheromas .
The concentration of this substance in the blood is called cholesterolemia; since ***cholesterol is contained in plasma lipoproteins in the blood*** , its blood level is indicated by total plasma cholesterol, cholesterol bound to **low-density lipoproteins (LDL)** , and cholesterol bound to **high-density lipoproteins (HDL)** , or **non-HDL cholesterol** (which includes cholesterol transported by all plasma lipoproteins with the exception of HDL). Cholesterol values can be normal, low (hypocholesterolemia), or high (hypercholesterolemia), conditions which favor the formation of atherosclerotic plaques.

Formation of atherosclerotic plaques

When the total amount of cholesterol obtained from the diet plus its endogenous synthesis exceeds the amount consumed for metabolic needs, LDL particles accumulate in the blood.
The result is the infiltration of LDL into the intima of the arterial wall, where the LDL is oxidized to LDLox , which activates the recruitment of macrophages, which massively phagocytose it and form ***foam cells*** .

The accumulation and subsequent necrosis of these foam cells forms the lipid core of the plaque (ATHEROMA), inside the blood vessels, [16], Fig.4.

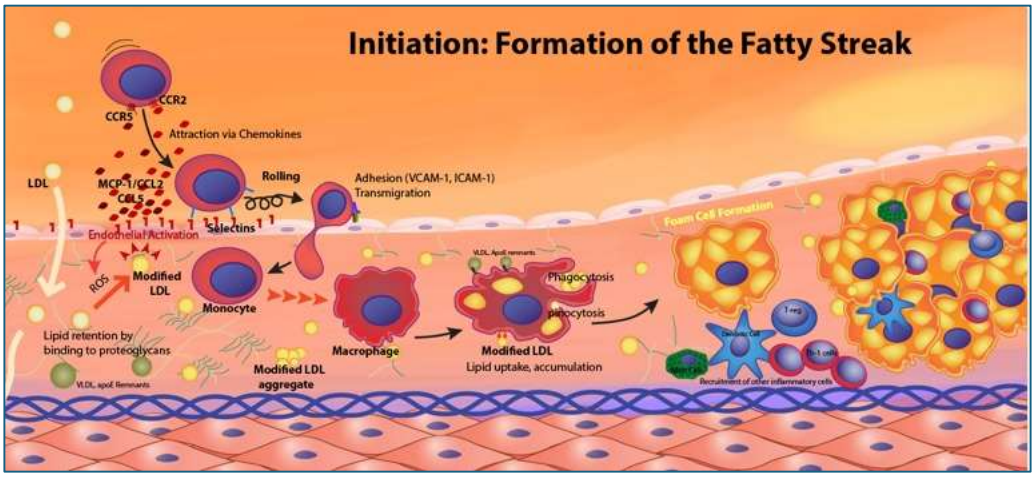

Fig.4- Diagram of atheroma formation and cholesterol recycling
From: National Library of Medicine -The Role of Lipids and Lipoproteins in Atherosclerosis

From the above, atherosclerosis is considered an immune/inflammatory response of the intima to tissue damage. The early stages of the lesion develop beneath the vascular endothelium and are not associated with cell death. They are characterized by an alteration in the endothelium's function, resulting in increased adhesion of circulating monocytes to the vessel walls. The entry of monocytes into the subendothelial space represents the first response to hypercholesterolemia and leads to the formation of ***foam cells (foam cell)*** [17],[18].

Endothelial dysfunction

The endothelium plays a key role in maintaining blood flow and vascular integrity under physiological conditions: it promotes vasodilation, counteracts monocyte adhesion and has antithrombotic and fibrinolytic characteristics. [19],[20].

In some segments of the vascular tree, chronic damage to the endothelium determines an increased accumulation of LDL and a greater adhesion of monocytes on the arterial wall, representing the *primum movens* of the atherosclerotic process. One of the earliest manifestations of endothelial dysfunction is the abnormal vasoconstriction produced by **lysolecithin** , a derivative of LDL peroxidation [21].

Histological classification of atheromatous lesions by the American Heart Association, AHA:

The AHA has developed a practical classification of atherosclerotic lesions based on their histological composition and structure.
The classification follows and describes the evolution of the clinical history of the pathology, and the progression of pathogenic events to identify the most probable causes and the possibilities for therapeutic intervention.

Lesions I-III are silent precursors of advanced lesions (IV-VI) from which clinical events originate. Fig.5

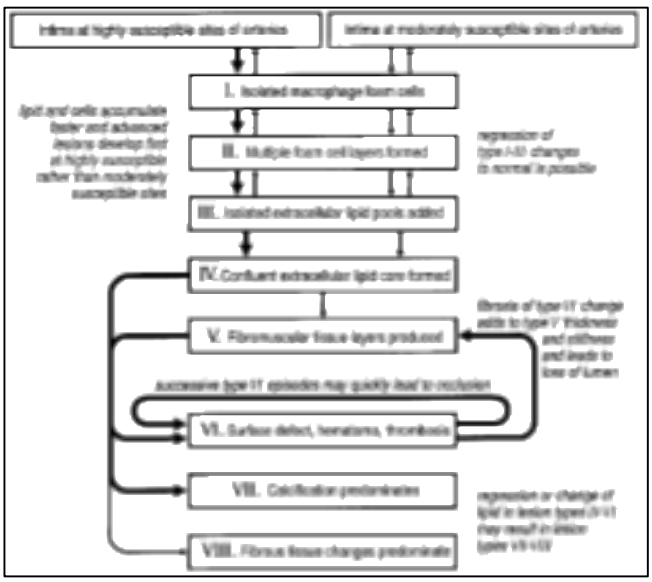

Figure 5- Natural History and Histological Classification of Atherosclerotic Lesion

Considerations on the pathogenetic aspects of cholesterol
All of the above leads us to formulate some general considerations on the biological and pathogenetic aspects of cholesterol, and on the decisive role assigned to it in cardiovascular and cerebrovascular events.
Before becoming harmful, cholesterol performs essential biological functions:

1) Cholesterol is an essential component of cell membranes, and contributes to maintaining their correct and physiological rigidity;
2) It performs essential biological functions and is involved in the synthesis of important substances, page 5;
3) *It assumes a relevant pathogenic role only when it exceeds the homeostatic control levels of lipid metabolism;*
4) *But even in this case, to exert its harmful effects on the endothelium, with endothelial dysfunction, cholesterol does not act alone, but must necessarily bind to plasma lipoproteins with which to activate inflammatory processes.*

Many authors also call into question, as primary pathogenic event, the deleterious effects **of silent inflammation** and **Glycation** , which act as direct pathogenic factors [22],[23].
Glycation : It is a *spontaneous reaction that* ***binds a simple sugar*** *(glucose, fructose or galactose) when it is present in high concentrations in the plasma,* ***to a protein or a lipid.***
A typical example is ***Glycosylated Hemoglobin,*** also called "Glycated" **(Hb1Ac)** , which is associated with Diabetes.

This reaction occurs in the blood where other substances called **AGEs (Advanced Glycation End Products) are present,** which circulate freely and produce irreversible end effects **.**
Typically the association occurs with proteins (Glycation), and leads to the formation of *misfolded Proteins (misfolded proteins) that lose their physiological activity.*

We will encounter this phenomenon when we discuss the effects of homocysteine, which has a broad-spectrum activity in this regard.

At the cardiovascular level, AGEs cause:

- a stiffening of the vessels,
- they inhibit the action of nitric oxide (NO) which allows vasodilation,
- contribute to the oxidation of LDL cholesterol and
- They bind to macrophages, which produce various pro-inflammatory cytokines. Glycation with **fructose** causes twenty times more AGEs than the same reaction with glucose.

Another interesting case of glycation is that of albumin, which occurs when small amounts of the protein pass the renal filtration barrier and leak into the urine.
This initial state of selective renal filtration loss causes ***"Microalbuminuria",*** that is, the presence of traces of albumin in the urine.
It is an important marker for "Endothelial Dysfunction" and can be measured in 24-hour urine.
By definition, we speak of *Microalbuminuria* when albumin concentrations are between 30 and 300 mg in urine over 24 hours.
Furthermore, AGEs accumulated over time are largely responsible for aging, as they negatively affect the collagen structure.

"Silent inflammation, the production of AGEs , and oxidative stress *represent the second major real cause and origin of cardiovascular disease."*
inflammation promoted by **Tnf - α** mediators**, IL-1 and IL-6,** (***Tumor necrosis factor, Interleukin 1 and 6),*** produces a protein called ***"C-Reactive Protein" (CRP)*** in the liver.
High CRP concentration accelerates all processes of atheromatous plaque formation.
Thus, "Endothelial damage resulting in microalbuminuria and increased inflammation leads to elevated CRP, which represents the third major cause and origin of cardiovascular disease. Furthermore, microalbuminuria and CRP are markers of cardiovascular disease risk progression."

From all this, should we conclude that normal levels of total, HDL, and LDL cholesterol indicate the absence of risk for a cardiovascular event?
No, absolutely not. There is no direct correlation between high cholesterol levels and cardiovascular events.
All the cardiovascular risk factors described can be altered without cholesterol levels being altered.
A study published in 2019 and conducted on 347,000 subjects, demonstrated that:
" ***Low LDL Cholesterol Levels*** *are independently and significantly associated with an increased risk of mortality from all diseases, including cardiovascular diseases* ":
(*Ki Chul Sung et al., Low Levels of LDL Cholesterol and Mortality Outcomes in Non-Statin Users – in Journal of Clinical Medicine – 2019*).
Another study published in the British Medical Journal in 2016, concludes that:
" *A reduction in cholesterol does not lead to a reduction in the risk of mortality from all diseases, but a 13.8% reduction in dietary cholesterol increases mortality by 20%."*
(*Ramsen CE et al., Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from the Minnesota Coronary Experiment – 1968-73, British Medical Journal, 2016).*

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Cholesterol: Its Role in Neurodegenerative Diseases

Cholesterol does not cross the Blood- Brain Barrier (BEE).

In the nervous system, cholesterol is an essential component of neuronal cell membranes and is involved in the maturation process of the CNS, in synaptogenesis , in signal transduction processes and in vesicular trafficking.

All cholesterol contained in the brain is synthesised in situ because the Blood Brain Barrier (BEE) does not allow the passage of lipoprotein complexes containing cholesterol from the bloodstream to the brain. 99% of brain cholesterol is contained in a non-esterified form. During embryogenesis and the first years of life, the cells responsible for the synthesis of brain cholesterol are neurons [24],[25]. In adulthood, when the processes of myelination and brain maturation are completed, neurons delegate the synthesis of cholesterol to **astrocytes** and, to a lesser extent, to **oligodendrocytes** .
We have already described the process of cholesterol biosynthesis, we refer you to the relevant paragraph.

Excess cholesterol binds to SREPBs (Sterol regulatory element binding protein), which translocate to the nucleus where they regulate the expression of the HMGCoAR gene .
Synthesized cholesterol is exported from astrocytes via the membrane transporter ATP binding transporter A1 (ABCA1), is loaded onto Apolipoprotein E (ApoE) and the ApoE-cholesterol complex is thus internalized into neurons via the ***low- density*** membrane transporter ***lipoprotein receptors (LDL -R).***

Once inside the neurons, part of the cholesterol is transported to the plasma membranes for the formation of synapses, axons and dendrites and a part is destined for the synthesis of steroid hormones.

Excess cholesterol may be toxic and is therefore esterified and eliminated from the brain in the form of oxysterols and then eliminated by the liver in the form of bile acids.The cholesterol esterification process aims to produce lipophilic metabolites that are removed from tissues more efficiently than unesterified cholesterol.

In humans, plasma concentrations of cholesterol precursors, particularly lanosterol and lathosterol, are considered surrogate markers of the amount of cholesterol synthesized throughout the body. Numerous studies in cellular and animal models demonstrate that altered cholesterol metabolism occurs in neurodegenerative diseases such as Parkinson's disease, multiple sclerosis, Alzheimer's disease, and Huntington's disease.

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive motor, cognitive, and psychiatric disorders. The disease is caused by an abnormal expansion of the CAG triplet in the IT15 gene, which encodes the ***Huntingtin protein (Htt)*** . Htt is implicated in numerous intracellular functions, including vesicle trafficking, signal transmission, and regulation of apoptosis.

Since circulating cholesterol cannot enter the brain, the brain must produce it autonomously, adopting the following system:

• *On-site synthesis* : the brain produces 100% of the cholesterol it needs ex novo, mainly using glial cells (astrocytes and oligodendrocytes) and neurons.
• *High concentration* : Although the brain represents about 2% of body weight, it contains about 20-25% of the body's total cholesterol.
• *Crucial functions* : This cholesterol is vital for the construction and maintenance of myelin sheaths that allow rapid transmission of electrical signals and facilitate synaptic plasticity.
How excess cholesterol is eliminated:
Because cholesterol cannot circulate in the brain through the blood, it needs a way to be eliminated when it is no longer needed. The brain manages this process through brain cells that convert excess cholesterol into specific metabolites such as 24S-hydroxycholesterol (24-OHC).
Only these metabolites can easily cross the blood -brain barrier, enter the systemic circulation, and are processed and eliminated by the liver.

Pathogenic role of the APOE4 gene
This gene alters lipid metabolism in the central nervous system and modifies cholesterol transport and distribution between brain cells.
Since, as we have indicated, mature neurons are unable to synthesize cholesterol autonomously, they depend entirely on astrocytes for its supply via APOE-mediated lipoproteins.
Specific mechanisms that cause brain cholesterol transport dysfunction include:
• ***Defective lipidation*** : Unlike the APOE3 variant, *the APOE4 protein has a lower binding affinity and a reduced ability to assemble lipids. It is less efficient at delivering cholesterol to neurons and removing excess lipids from glial cells.*
• ***Intracellular accumulation*** *:* due to the transport defect, cholesterol does not reach its cellular targets and accumulates inside astrocytes and oligodendrocytes.
• ***Impaired myelination :*** In oligodendrocytes (responsible for myelin formation), APOE4 improperly produces and transports cholesterol. This results in abnormal lipid accumulation within cells and contributes to the thinning of myelin sheaths, compromising brain connectivity and memory.
• ***Neuronal toxicity*** : While glial cells suffer from cholesterol overload, neurons often exhibit a localized deficiency of essential membrane lipids, which compromises synaptic integrity and alters neuronal excitability.

Role of Homocysteine in Neuropathogenesis

Homocysteine is able to cross the ***blood -brain barrier (BEE),*** while cholesterol is unable to do so, therefore, it exerts a direct pathogenic action on neurons.
When its blood levels are high (hyperhomocysteinemia), this amino acid enters the central nervous system where it exerts a strong **neurotoxic action** . Excess homocysteine promotes neuronal damage, oxidative stress and accelerates cognitive deterioration [26],[27].
Homocysteine can cross the blood -brain barrier (BEE), likely via bidirectional cellular transporters. Elevated levels of homocysteine in the blood (hyperhomocysteinemia) actively damage and alter the BBB itself, further exacerbating the leakage of toxic compounds into the brain and impairing cognitive function [28],[29].

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Key interactions with the brain
• *BEE disruption* : High homocysteine levels trigger oxidative stress and degradation of tight junction proteins (such as **claudin-5**), causing microvascular leakage.
• *Excitotoxicity :* Homocysteine acts as an agonist at neuronal NMDA receptors, which can lead to overstimulation and neuronal damage when excess homocysteine enters the central nervous system.
• *Neurological risks* : BEE impairment is closely linked to neurodegenerative conditions such as Alzheimer's disease, stroke and cognitive decline.

Homocysteine (Hcy) Broad-spectrum pathogenic role.
In addition to the relative importance of cholesterol and its metabolites as the fundamental factors responsible for cerebrovascular and cardiovascular pathologies, an additional fundamental role must be assigned to hyperhomocysteinemia , which has been shown to be a broad-spectrum pathogenic factor, and as such responsible for multiple chronic degenerative pathologies [30], [31], [32].

Hyperhomocysteinemia (elevated blood homocysteine levels) is a major asymptomatic risk factor that damages vascular endothelium and promotes oxidative stress. Major diseases and complications increasingly associated with elevated blood homocysteine levels include: [33], [34], [35], [36], [37], [38], [39].

- ***Cardiovascular Diseases* :** Increases the risk of atherosclerosis, myocardial infarction, ischemic heart disease and angina pectoris.
- ***Cerebrovascular Diseases* :** It promotes ischemic stroke and cerebral circulation problems.
- ***Thromboembolic Disorders* :** Increases the tendency of blood to clot, causing deep vein thrombosis and pulmonary embolism.
- ***Neurological and Cognitive Pathologies* :** These are related to cognitive decline, senile dementia and neurodegenerative pathologies such as Alzheimer's and Parkinson's.
- ***Obstetric and Fetal Complications* :** In pregnant women it can cause neural tube defects in the fetus (e.g. spina bifida), spontaneous abortions, preeclampsia and placental abruption.
- ***Bone Pathology* :** It is associated with an increased risk of bone fragility and osteoporotic fractures.

Homocysteinemia levels is mainly caused by nutritional deficiencies (vitamin B12, B6 and folic acid) or genetic predispositions such as the MTHFR gene mutation.

To describe the activity of Homocysteine as an etiological agent of multiple pathologies, we avail ourselves of the fundamental contribution to research in this field of Hieronim Jakubowski , author of the book entitled:

"*Homocysteine in Protein Structure/Function and Human Disease, Chemical Biology of Homocysteine-containing Proteins"* , © Springer-Verlag Wien 2013, and numerous others articles .
The author addresses and describes with in-depth analysis the origin, clinical history and mechanism of action of the substance, in all its declinations, highlighting its multiple pathogenic effects.
Mammals, unlike other organisms, are unable to synthesize their own methionine (Met). In humans and animals, **Methionine (Met)** is an essential amino acid that must be ingested as protein with food, which is then hydrolyzed into individual amino acids. Met is absorbed by the epithelium of the digestive tract and transported in the blood to the cells of various organs. Here, Met is metabolized through two main pathways (Fig. 6):

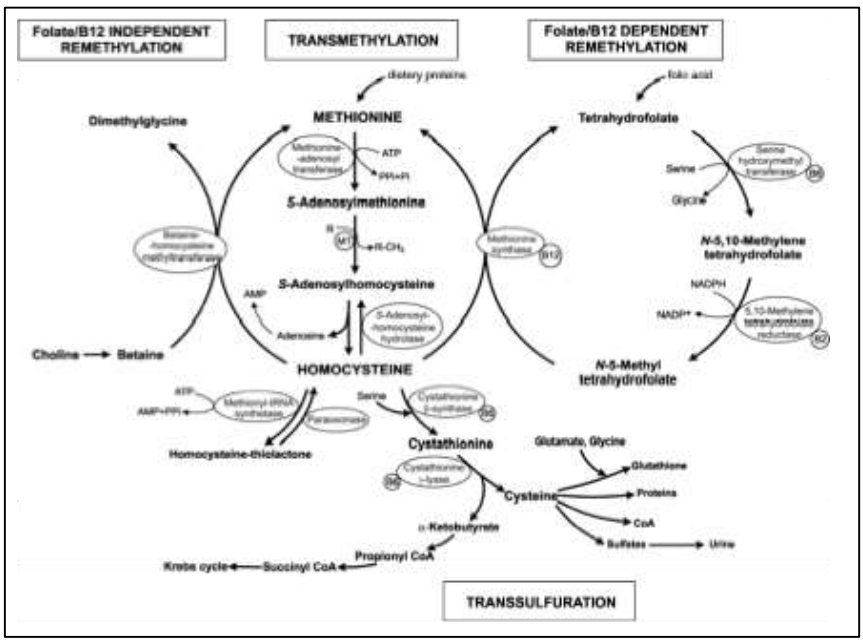


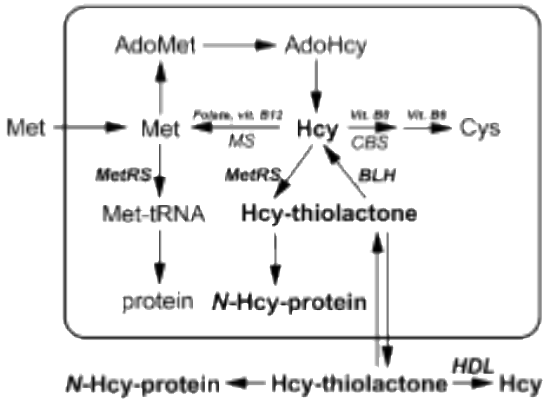
Figure 6- homocysteine metabolism

(1) as a building block for the synthesis of new proteins in the ribosomal biosynthetic apparatus and (2) as a precursor of ***S-adenosylmethionine (AdoMet),*** a universal methyl group donor for biological methylations.In metabolic processes (1) and (2), Methionine is activated by ATP, although in a specific manner for each pathway. It is the utilization pathway of Met . (2) which ultimately leads to **Methionine** . As a result of the transfer of its methyl group to an acceptor, **AdoMet** is converted to **S- adenosylhomocysteine (AdoHcy)** .

Reversible enzymatic hydrolysis of AdoHcy is the only known source of Hcy in the human or animal body. Under normal circumstances, most, but not all, **of the homocysteine (Hcy) formed in** transmethylation reactions is remethylated to methionine or converted to cysteine in transsulfuration reactions. Hcy is also metabolized to the cyclic thioester Hcy **-thiolactone** [40].

The Hcy -thiolactone metabolic pathway becomes predominant when remethylation or transsulfuration reactions are impaired by genetic alterations of enzymes involved in Hcy metabolism , such as cystathionine β- synthase (CBS) , methionine synthase (MS) or methylenetetrahydrofolate reductase (MTHFR), or by an insufficient intake of folate, vitamin B12 or vitamin B6 [41] (Fig. 6).

Hcy -thiolactone is formed by **methionyl-tRNA synthetase (MetRS)** in an error-correction reaction in protein biosynthesis, ***when Hcy is mistakenly selected for methionine.***



Homocysteine (Hcy) and N- homocysteinylated proteins

Homocysteine, as we have said, is a sulfur-containing amino acid, chemically it is a **γ– *thio* –α– *aminobutyric acid*** ($C_4H_9 NO_2 S$), which is formed, as an intermediate product, in the enzymatic transformation of methionine ($C_5 H_{11} NO_2 S$) into cysteine ($C_3 H_7 NO_2 S$), through the removal of methyl groups: the prefix homo- (derives from the Greek *ὁμο* -) indicates similarity between two compounds.

The conversion of homocysteine to methionine (a process called remethylation) or its conversion to cysteine (transsulfuration) represent the main metabolic pathways capable of maintaining its intracellular levels within a narrow range; its release into the bloodstream allows us to measure its plasma concentrations, which represent an index of the tissue homocysteine status .
Homocysteine levels in the blood must be kept under strict control in order to prevent the numerous pathogenic effects reported in the literature and schematically indicated in Fig.7.

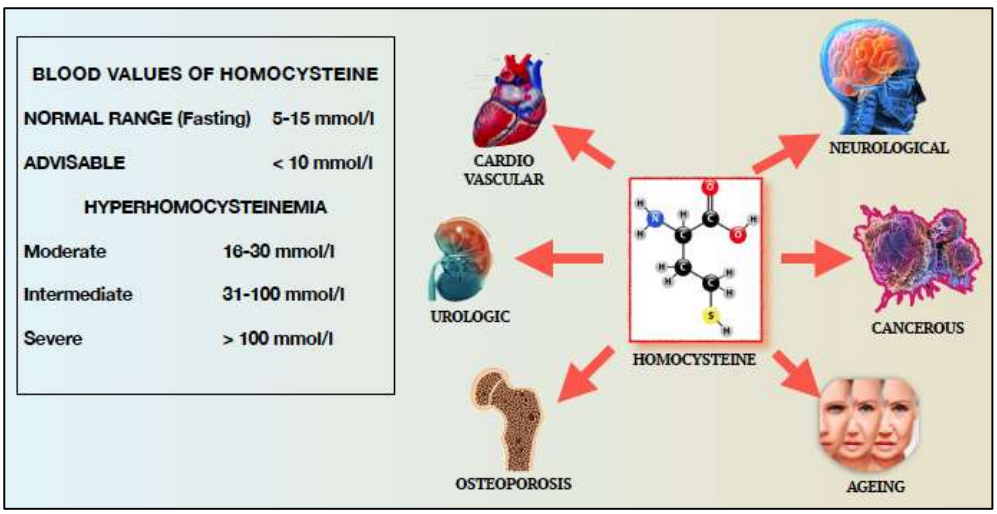


Figure 7 – Blood values of homocysteine and pathologies resulting from Hyperomocysteinemia

Homocysteine, present in high concentrations in the blood, facilitates the binding of the substance to lysine residues present in proteins, or is selected in place of methionine by methioninyl-tRNA synthetase during protein synthesis [42], [43].

This process results in the formation of **homocysteine- thiolactone** in the human body.
It is a chemically reactive **thioester metabolite** that modifies protein lysine residues in a process called **N- homocysteinylation** .

This change causes protein damage/aggregation, a hallmark of many diseases.
homocysteinylated proteins lose their normal function, are cytotoxic, promote immune, inflammatory, thrombotic, and atherogenic processes, and have been linked to cardiovascular disease, Alzheimer's disease, diabetes, kidney disease, neural tube defects, and male infertility.

For this reason, hyperhomocysteinemia is considered a primary risk factor for cardiovascular and other pathogenic events.

The primary pathogenic effects induced by hyperhomocysteinemia are found on the endothelium.
The endothelium is the functional unit of the cardiovascular system , and is made up of epithelial cells that line the inside of all blood vessels.

The normal endothelium functions as a semipermeable cell layer and acts as a sensor and transmitter of signals in the circulating environment. Endothelial cells are important for maintaining the homeostatic balance of vessels by producing factors that regulate intracellular signaling, vascular tone, coagulation, neutrophil recruitment, lipid transport, hormone trafficking, and the proliferative cellular response, among others.

The pathogenic effect of homocysteine- thiolactone is expressed through the alteration of the proteins composing the endothelial scaffolding which produces the breaking of the bonds between the endothelial cells and consequent alteration of the homeostatic functions Fig.8.

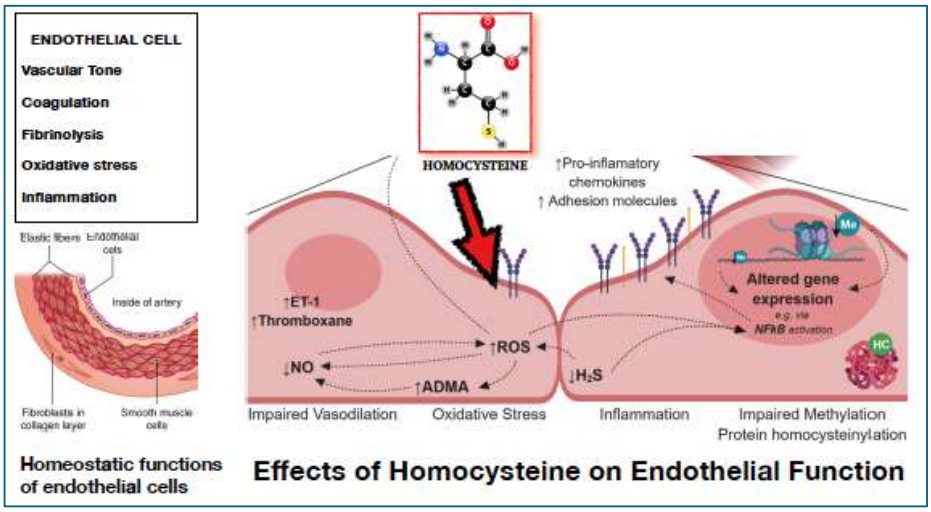


Figure 8- Schematic of the pathogenic activity of Homocysteine

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Molecular mechanism and biological effects of N- homocysteinylation

Protein N- homocysteinylation is a pathological post-translational modification in which homocysteine (through its metabolite, homocysteine thiolactone) covalently binds to lysine residues in proteins. This process damages cells, inactivates enzymes, and promotes disease development.
The mechanism of toxicity is due to:

- ***Misincorporation*:** The enzyme **methionyl-tRNA synthetase (MetRS)** can accidentally select homocysteine over methionine during protein translation, converting it to a reactive thioester called ***homocysteine thiolactone*** (HTL).
- ***Covalent bonding (N- homocysteinylation):*** HTL reacts non-enzymatically with free ε-amino groups of lysine residues in native proteins.
- ***Protein misfolding*** : This unwanted modification alters the native structure of the protein. It adds a free thiol group , which increases the protein's susceptibility to oxidation and aggregation [44], Fig.9.

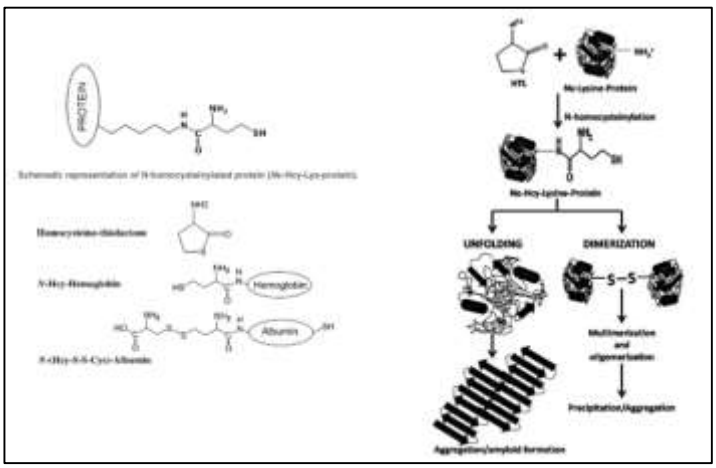

Figure 9 - From: Protein N- homocysteinylation : From cellular toxicity to neurodegeneration, Biochimica et Biophysica Acta (BBA), Volume 1850, Issue 11 , November 2015, Pages 2239-2245

Homocysteine also interferes with the synthesis of lipoproteins that form the systems and structures of the cell membrane and myelin, producing misfolding and malfunction.

Pathological consequences

N- homocysteinylation causes proteins to lose their normal function, developing toxic properties and altering their function. This phenomenon is strongly implicated in:
Cardiovascular disease : Changes in structural proteins and enzymes in blood vessels promote atherosclerosis, thrombosis, and inflammation.
Neurodegenerative diseases : Homocysteinylated proteins are *pro- amyloidogenic* and contribute to the formation of toxic protein aggregates, commonly seen in Alzheimer's disease.

Collagen Diseases and Osteoporosis :

Kidney diseases:
Maternal-fetal diseases:
Tumor Diseases:

Clinical context
Under normal conditions, homocysteine is metabolized into harmless byproducts by enzymes that depend on vitamins such as **folic acid, vitamin B6, and vitamin B12** . However, in hyperhomocysteinemia (abnormally elevated blood homocysteine levels), HTL production and the resulting N- homocysteinylation of proteins increase significantly.

Prevention and treatment strategy for chronic degenerative diseases

The prevention and treatment measures for chronic degenerative diseases involve two different intervention phases, separated in the temporal description of the events to be adopted, but coinciding and simultaneous in the operational phase, in order to make them effective.
The two interventions are

(1) The PREVENTION PHASE:
which requires common measures for all chronic-degenerative diseases, with targeted restrictive intervention on modifiable risk factors:

- **The Diet:** Must eliminate the quantity and quality of atherogenic foods, which promote the accumulation of fats and an increase in blood pressure (saturated fats, red meat, simple sugars, high sodium concentrations, alcohol) and promote the intake of foods that contribute to the control of lipids, blood sugar and blood pressure (polyunsaturated fats, vegetables, fruit, white meat);
- **Smoke;**
- **Sedentary lifestyle;**
- **Overweight and obesity.**

(2) The SCREENING:
Periodic blood chemistry tests for the early identification of altered physiological marker values.

In the presence of altered values of pathogenic markers and risk factors, the following is intervened:

The Corrective Treatment
Corrective treatment must be adopted at the same time as preventive measures, and includes differentiated interventions for:
Hypercholesterolemia-Atherosclerosis , administration of **Statins** and supplements effective in controlling cholesterolemia, **Fermented Red Rice** (Monacolin K);

Hyperhomocysteinemia , Administration of Folic Acid, Vitamin B6 and Vitamin B12.

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DISCUSSION AND CONCLUSIONS

General comparison between the two markers: **Cholesterol** and **Homocysteine,** Table II
They are two fundamental biochemical indicators, but they assess cardiovascular risk in very different ways.

- **Cholesterol:** It represents the material that accumulates inside the blood vessels (the cause of plaque deposits, Atheroma).
- **Homocysteine:** Damages the inner lining of blood vessels (the endothelium), making them rough and predisposing to inflammation, promoting the adhesion of cholesterol itself.

The two factors act synergistically: an excess of homocysteine accelerates vascular damage by facilitating the oxidizing action of LDL cholesterol.

Main differences compared

Characteristic	LDL cholesterol	Homocysteine
Nature	Lipid (fat) carried in the blood.	Sulfur-containing amino acid derived from proteins.
Damage mechanism	It accumulates in the arterial walls forming atherosclerotic plaque.	It irritates and corrodes the internal walls of the vessels, increasing the formation of clots (thrombi).
Optimal Values	< 100 mg/ dL (for at-risk subjects).	Between 5 and 10 µmol /L.
Main causes	Diet high in saturated fat, genetics, overweight.	Deficiency of B vitamins (folic acid, B12, B6), genetics (MTHFR mutation), smoking.
Speed of action	It works slowly over the years.	It can promote adverse events much more quickly.
Management / Prevention	Lifestyle, low-fat diet and any drug therapy (e.g. statins).	Targeted supplementation with B vitamins and a diet rich in leafy vegetables.

Table II

Measuring both values—along with other markers of systemic inflammation such as C-reactive protein (CRP)—provides a much more accurate assessment of vascular health than monitoring cholesterol alone.

Chronic degenerative diseases constitute a large group of diseases related to age and, in a decisive way, to incorrect eating habits and lifestyle. They represent the main causes of death in industrially advanced countries, and have a significant impact on national health spending. Researching and

identifying the risk factors that contribute to their pathogenesis allows for the adoption of effective preventive measures to prevent their onset or halt their progression.

The development of epidemiology has been an effective tool for identifying modifiable risk factors (hypertension, smoking, a sedentary lifestyle, poor eating habits, etc.), leading to the implementation of preventive measures. While the non-modifiable risk factors: age and heredity, remain unaffected. The need to address modifiable risk factors as effectively as possible is increasingly pressing.

Historically, the potential risk of suffering from heart and cerebrovascular accidents has been assessed with cholesterol and triglyceride tests, which have become a routine part of periodic diagnostic tests. We have highlighted that there is no strict cause-effect relationship between hypercholesterolemia and cardiovascular diseases, which are often multifactorial events whose cause eludes us.

At the same time, we are beginning to realize that the fundamental marker homocysteine is increasingly being implicated as a recognized independent and broad-spectrum risk factor for multiple chronic degenerative diseases.With this article, we would like to appeal to authorities and healthcare professionals to include this marker in routine periodic preventive tests. The adoption of this marker will represent a great opportunity and an effective tool in the fight against chronic degenerative diseases and in reducing healthcare costs.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

REFERENCES

[1] World Health Organization, Noncommunicable Diseases, progress monitor 2022;
[2] OECD, Health at. A Glance 2025 ; OECD Indicators, https://data-explorer.oecd.org/s/306
[3] ISTAT, La salute in Italia, 2026
[4] François G. Schellevis; Epidemiology of multiple chronic conditions: an international perspective, Journal of Comorbidity 2013;3:36–40
[5] About Chronic Diseases, National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)
[6] Krisela Steyn and Albertino Damasceno. Lifestyle and Related Risk Factors for Chronic Diseases 2006, National Library of Medicine
[7] Australian Government, Risk factors to health; Web report | Last updated: 07 Aug 2017
[8] Daxin Cui et al; Cholesterol metabolism: molecular mechanisms, biological functions, diseases, and therapeutic targets, *Molecular Biomedicine (2025) 6:72*
[9] Cagen, Lauren M, Cholesterol, EBSCO 2023
[10] Karel Paukner et al ; Cholesterol in the Cell Membrane—An Emerging Player in Atherogenesis , *Int. J. Mol. Sci.* **2022**, *23*, 533
[11] Muhammad Ahmed; The Role of Cholesterol in Membrane Fluidity and Stability, J Membr Sci Technol, Vol.14 Iss.4 No:1000408

[12] Julie Grouleff, The influence of cholesterol on membrane protein structure, function, and dynamics studied by molecular dynamics simulations, Biochimica et Biophysica Acta 1848 (2015) 1783–1795
[13] Jiarui Guo et al; Cholesterol metabolism: physiological regulation and diseases, MedComm. 2024;5:e476.
[14] D.R. Arnold, P.O. Kwiterovich Jr; CHOLESTEROL | Absorption, Function, and Metabolism, ScienceDirect, 2003
[15] Diana Cardoso , Esperanza Perucha ; Cholesterol metabolism: a new molecular switch to control inflammation, *Clin Sci (Lond)* (2021) 135 (11): 1389–1408.
[16] Michal Kowara and Agnieszka Cudnoch-Jedrzejewska; Pathophysiology of Atherosclerotic Plaque DevelopmentContemporary Experience and New Directions in Research, Int. J. Mol. Sci. 2021, 22, 3513.
[17] William Insull, Jr.; The Pathology of Atherosclerosis: Plaque Development and Plaque Responses to Medical Treatment, The American Journal of Medicine (2009) 122, S3–S14
[18] Peter Libby et al; Atherosclerosis, Nature reviews disease primers, 16 August 2019
[19] Hadi AR Hadi et al; Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome, Vascular Health and Risk Management 2005:1(3) 183–198
[20] Eugenio Carulli et al ; Addressing Endothelial Dysfunction in Heart Failure: The Role of Endothelial Progenitor Cells and New Treatment Horizons, Cardiac Failure Review 2025;11:e21
[21] Piero O. Bonetti et al; Endothelial Dysfunction A Marker of Atherosclerotic Risk, *Arterioscler Thromb Vasc Biol*. 2003;23:168-175.
[22] Ana Belén Uceda et al: An overview on glycation: molecular mechanisms, impact on proteins, pathogenesis, and inhibition, Biophysical Reviews (2024) 16:189–218
[23] Meghan S. Martin et al; The chemical language of protein glycation, *Nature Chemical Biology* volume 21, pages324–336 (2025)
[24] Ingemar Bjo¨rkhem, Steve Meaney ; Brain Cholesterol: Long Secret Life Behind a Barrier , *Arterioscler Thromb Vasc Biol*. 2004;24:806-815.
[25] Ilinca Savulescu-Fiedler et al; The Cross-Talk Between the Peripheral and Brain Cholesterol Metabolisms, *Curr. Issues Mol. Biol.* **2025**, *47*, 115
[26] Rima Obeid, Wolfgang Herrmann; Mechanisms of homocysteine neurotoxicity in neurodegenerative diseases with special reference to dementia, FEBS Letters 580 (2006) 2994–3005
[27] Mao-Yang Zhou, Homocysteine Drives Hippocampal Blood–Brain Barrier Disruption and Cognitive Decline Under Chronic Stress via DNA Hypomethylation of Cav1.2 , *Brain Sci.* **2026**, *16*, 491
[28] Olaf Stanger et al; Homocysteine, folate and Vitamine B12 in Neuropsychiatric disease, Expert Rev, 9 (9) 2009
[29] Antonio Siniscalchi; *Hyperhomocysteinemia in the neurological diseases, Recenti Progressi in Medicina, 95, 7-8, 2004*
[30] Coen van Guldener; Why is homocysteine elevated in renal failure and what can be expected from homocysteine-lowering? Nephrol Dial Transplant (2006) 21: 1161–1166
[31] Hieronim Jakubowski; Homocysteine in protein structure/function and human disease: Chemical biology of homocysteine-containing proteins, Book 2014 :

[32] Henrieta Škovierová et al; The Molecular and Cellular Effect of Homocysteine Metabolism Imbalance on Human Health, *Int. J. Mol. Sci.* **2016**, *17*, 1733;
[33] Deqiang Yuan, et al; Mechanism of homocysteine-mediated endothelial injury and its consequences for atherosclerosis *Front. Cardiovasc. Med.* 9:1109445.
[34] Holly E. Holmes et al; Elevated homocysteine is associated with increased rates of epigenetic aging in a population with mild cognitive impairment, *Aging Cell.* 2024;23:e14255.
[35] Hussam Alkaissi , Samy I. McFarlane; Hyperhomocysteinemia and Accelerated Aging: The Pathogenic Role of Increased Homocysteine in Atherosclerosis, Osteoporosis, and Neurodegeneration, Cureus 15(7): e42259.
[36] B.T. Zhu; On the mechanism of homocysteine pathophysiology and pathogenesis: a unifying hypothesis, Histol Histopathol (2002) 17: 1283-1291
[37] Hieronim Jakubowski, Pathophysiological Consequences of Homocysteine Excess, American Society for Nutrition. 2006
[38] Re ́gis Levasseur; Bone tissue and hyperhomocysteinemia, Joint Bone Spine 76 (2009) 234e240
[39] Avinash Kumar et al.; The metabolism and significance of homocysteine in nutrition and health, Nutrition & Metabolism (2017) 14:78
[40] Kritika Kumari et al.; Functionally active cross-linked protein oligomers formed by homocysteine thiolactone, Scientific Reports (2023) 13:5620
[41] Hieronim Jakubowski; Homocysteine in Protein Structure/Function and Human Disease, Chemical Biology of Homocysteine-containing Proteins, Springer 2013
[42] Alla V. Glushchenko, Donald W. Jacobsen; Molecular Targeting of Proteins by L-Homocysteine: Mechanistic Implications for Vascular Disease, *Antioxid Redox Signal*. 2007 November; 9(11): 1883–1898
[42] Nadejda Capatina et al.; Elevated homocysteine activates unfolded protein responses and causes aberrant trophoblast differentiation and mouse blastocyst development, *Physiological Reports*. 2022;10: e15467.
[43] Iftikhar J. Kullo et al.; Novel Genomic Loci Influencing Plasma Homocysteine Levels, *Stroke*. 2006;37:1703-1709.
[44] Bruno Riccardi, The Language of Proteins, And Protein Structure. Journal of Medical and Clinical Case Reports 2(4) , 22 August 2025