



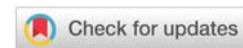
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**\*Corresponding author:** Božidar Kocmur, Faculty of Pharmacy and Biochemistry, Department of Pharmacology, University of Zagreb, Croatia, E-mail: bozidar.kocmur@ri.t-com.hr, bozidarkocmur@gmail.com

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**Review Article**

# Atherosclerosis and lymph // risk factors

**Božidar Kocmur\***

Faculty of Pharmacy and Biochemistry, Department of Pharmacology, University of Zagreb, Croatia

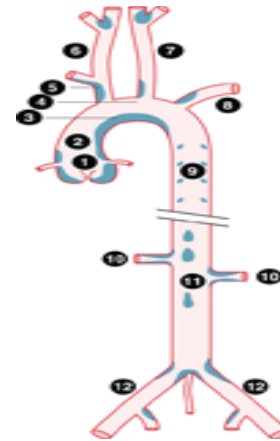
Is there a disease in the human population that has been present since the beginning of the human race, and which has not yet discovered its cause or mechanism of origin? Unfortunately, there is atherosclerosis, a disease that causes the greatest number of unnatural deaths in the world. Atherosclerosis is not the primary disease, as much as the entire life-long degenerative process of thickening and damage to large and medium-sized arteries of the body, related to age. It is characterised by endothelial dysfunction, lipid accumulation, cholesterol, calcium, and several cellular elements. However, when influenced by some of the risk factors, such as excessive food lipid intake (obesity), lack of physical activity, smoking, genetic disorders, family heritage, inflammation and proliferation of arterial endothelium cells in specific sites, preconditions for plaque or atheroma have been created.

Plaque formation results in acute or chronic obstruction of the arterial lumen, impaired blood flow, and reduced oxidation of target tissues or organs. Further development of plaque leads to critical narrowing or complete artery occlusion when there is a high possibility of separation of parts of plaque (atheroma), which usually leads to stroke or heart attack with very often fatal consequences. The consequences of these attacks are the leading cause of sudden and unnatural deaths in the world. Despite the efforts to establish the actual cause and mechanism of this disease, there is still no satisfactory result. The solutions and conclusions presented based on the results of the research so far have not provided an acceptable explanation nor have they indicated the possibility of an imminent solution. Moreover, some, which are constantly insistent on non-critically and which are still present in scientific literature, mislead and direct the interest of young scientists in the wrong direction and to the wrong conclusions. Why?

Because no current explanation or theory gives a complete answer to the key question, namely:

## How do these facts (explanations) relate to the occurrence of atherosclerosis, are we referring to the appearance of plaques, in precisely defined and determined places of the arterial tree?

It has been proven that atherosclerotic changes appear almost excluded at certain places of the aorta, its harbour and segregation sites, the opening of the main arteries of the body [1].



*Atherosclerosis preferentially develops at arterial branches and curvatures. Schematic drawing shows a longitudinal representation of the major arterial vasculature illustrating the observed distribution of atherosclerotic plaques (gray shading) in the vasculature of LDLR<sup>-/-</sup> mice fed a high-fat atherogenic diet.*

1. aortic sinus; 2. ascending aorta; 3. inner curvature of aortic arch; 4. outer curvature of aortic arch; 5. innominate artery; 6. right common carotid artery; 7. left common carotid artery; 8. left subclavian artery; 9. thoracic aorta; 10. renal artery; 11. abdominal aorta; 12. iliac artery

Redrawn from Van der Laan, et al. [1].

The answer to this question is the key that opens the door to a real solution.

In a recently published consensual address to the ESL, from the European Atherosclerosis Society Consensus Panel scientific community, that the LDL is the sole and only real cause of atherosclerosis, the exclusivity demonstrated by such publication, which rejects any possibility of alternative approaches to this problem [2]. Given the importance and role played by this association in the scientific community, effectively discourages efforts towards a possible alternative approach to this problem, disregard for evident, well-known and universally accepted facts indicating the complexity of this problem. The fact is that LDL can and must certainly influence the development and fatal consequences of atherosclerotic changes and that Regulation of their presence in the blood circulation can greatly influence the course of the disease, but there is certainly no room for such exclusion in the stated claim. This is all the more surprising, because they mention many more ambiguities and dilemmas, the empowerment, which they can, or affect, a different view of this issue.

*„Extensive evidence from epidemiologic, genetic, and clinical intervention studies has indisputably shown that low-Density Lipoprotein (LDL) is causal in this process, as summarized in the first Consensus Statement on this topic. What are the key biological mechanisms, however, that underlie the central role of LDL in the complex pathophysiology of Atherosclerotic Cardiovascular Disease (ASCVD), a chronic and multifaceted lifelong disease process, ultimately culminating in an atherothrombotic event?*

*This second Consensus Statement on LDL causality discusses the established and newly emerging biology of ASCVD at the molecular, cellular, and tissue levels, with emphasis on the integration of the central pathophysiological mechanisms. Key components of this integrative approach include consideration of factors that modulate the atherogenicity of LDL at the arterial wall and downstream effects exerted by LDL particles on the atherogenic process within arterial tissue.*

*Although LDL is unequivocally recognized as the principal driving force in the development of ASCVD and its major clinical sequelae, evidence for the causal role of other apolipoprotein B (apoB)-containing lipoproteins in ASCVD is emerging.*

A particularly intriguing conclusion is that there is no or negligible role of other lipoproteins, chylomicrons are not even mentioned in the process of atherosclerosis. I believe that this is very unfair to many scientists who already showed and proved the significant possible influence of chylomicron on the process of atherosclerosis, although without final confirmation and definite scientific evidence, but still on the trail of a convincing and acceptable solution [3,4].

*„Detailed consideration of the diverse mechanisms by which these lipoproteins, including triglyceride (TG)-rich lipoproteins (TGRL) and their remnants [often referred to as intermediate-density lipoproteins (IDL)] and lipoprotein(a) [Lp(a)], contribute not only to the underlying pathophysiology of ASCVD but also potentially to atherothrombotic events, is however beyond the focus of this appraisal.”*

Of course, the role of risk factors and mechanisms by which they influence the process and later on the process of development cannot be explained in the context of the over-emphasised role of LDL as the key and sole cause of atherosclerosis, because such explanations, among other things, do not provide an integral answer to the key question for understanding this process, namely:

### **How do these facts (explanations) relate to the occurrence of atherosclerosis, are we referring to the appearance of plaques, in precisely defined and determined places of the arterial tree?**

*„The pathophysiological and genetic components of ASCVD are not fully understood. We have incomplete understanding, for example, of factors controlling the intimal penetration and retention of LDL, and the subsequent immuno-inflammatory responses of the arterial wall to the deposition and modification of LDL. Disease progression is also affected by genetic and epigenetic factors influencing the susceptibility of the arterial wall to plaque formation and progression. Recent data indicate that these diverse pathophysiological aspects are key to facilitating superior risk stratification of patients and optimizing intervention to prevent atherosclerosis progression.”*

When citing all factors of risk factors for atherosclerosis, whether accidentally or intentionally, they are omitted, according to all relevant studies and findings, generally accepted by the WHO, probably the most important and most responsible risk factors, i.e., obesity (uncontrolled intake of fatty food), insufficient physical activity and smoking [5]. Studies of the incidence of atherosclerotic diseases in our population show that this problem appears more and more in the young age [6], mainly due to unhealthy diet. The who report and its recommendation to mitigate these consequences also discuss the seriousness of the problem [5]:

- CVDs are the number 1 cause of death globally: more people die annually from CVDs than from any other cause.
- An estimated 17.9 million people died from CVDs in 2016, representing 31% of all global deaths. Of these deaths, 85% are due to heart attack and stroke.
- Over three-quarters of CVD deaths take place in low- and middle-income countries.
- Out of the 17 million premature deaths (under the age of 70) due to noncommunicable diseases in 2015, 82% are in low- and middle-income countries, and 37% are caused by CVDs.
- Most cardiovascular diseases can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol using population-wide strategies.
- People with cardiovascular disease or who are at high cardiovascular risk (due to the presence of one or more risk factors such as hypertension, diabetes, hyperlipidaemia or already established disease) need early detection and management using counselling and medicines, as appropriate.



All listed risk factors in the consensus statement, genetic determinants of arterial wall biology, hypertension, low shear stress, systemic inflammation, smoking, diabetes, are certainly risks, but they have an impact on the development and progression of already occurring inflammatory atherosclerotic changes to the arterial endothelium or are genetically predisposed, and as such are predisposed with fatal consequences.

In a monograph, just published, Atherosclerosis. Yet chylomicrons, large [4], as well as Article the mechanism of the Emergence of Atherosclerosis, New Perspectives [3], showed the development of atherosclerosis research, studying all available literature related to these studies, pointing to many wrong assumptions and interpretations that have directed research in the wrong direction. The monograph, using all possible scientific literature, shows the development and development of large chylomicrons under the influence of risk factors to which we are exposed, especially obesity, insufficient physical activity and smoking, which can be presumed, with great certainty, to be the initiators of the process of atherosclerosis, and most importantly, the reasons why atherosclerosis occurs at certain sites of the arterial tree. Results of research indicating the connection of lymphatic system disorders by which chylomicrons are transported to the circulatory system, to the occurrence of atherosclerotic changes [7], further strengthen us in such beliefs.

## Obesity

In the recently published audit review, Regulation of Lymphatic function in Obesity, Katar, et al. [8], explain very detailed and justifiable the effects of obesity on the function and functioning of the lymphatic system, proving that in obesity there is a reduced flow of intestinal lymph, leading to pathological changes on other organ systems.

*“The lymphatic system has many foods, including macromolecules transport, fat absorption, Regulation and Modulation of adaptive immune responses, clearance of inflammatory, and cholesterol Metabolism. Thus, it is evident that lymphatic function can play a key role in the Regulation of a wide array of biologic phenomenon, and that physiologic changes the alter lymphatic function May have found pathology effects. Recent studies had shown that Obesity can markedly impair lymphatic function. Obesity-induced pathology changes in the lymphatic system result, at least in part, of the Accumulation of inflammatory around lymphatic Vessel leadership to impaired lymphatic collecting Vessel pumping capacity, Leaky Initial and collecting lymphatics, Alterations in Lymphatic Endothelial Cell (LEC) gene expression, and degradation of junctional proteins. These changes are important impaired lymphatic function in Obesity May contribute to the Pathology of Obesity in other organ systems in a feed-forward manner by increasing low-grade tissue and the Accumulation of inflammatory inflammation. Sea importantly, recent studies have suggested the interventions that Inhibit inflammatory responses, either pharmacologically or by lifestyle modifications as aerobic exercise and weight loss, improve lymphatic function and Metabolic parameters in handy mice.”*

The author's interest is focused on the accumulation of

cytokines, and the emergence of many inflammatory processes in the lymphoma structure itself and other organs, while our interest is focused on the possible impact of reduced lymph flow on chylomicrons transported by lymphoma into the circulatory system. Since obesity is one of the most important risk factors for the occurrence of atherosclerosis, it remains to be investigated how this change in the lymph system affects possible changes in the structure and behaviour of chylomicrone, which we consider possible causes of atherosclerosis, in certain circumstances.

Excessive fat intake into our organism, primarily resulting in large chylomicrons [9] and then a decisive diet factor, which induces postprandial lipaemia, continued obesity and finally cardiovascular disease. Hayashi, et al. [10] showed that the intake of larger amounts of lipids in the body does not cause an increased number of newly formed chylomicrons in the lymph, as assumed, but that the number of newly formed chylomicrons remains almost the same, but their size increases dramatically, up to 2000 Å, by additional incorporation of incoming lipids. Also, it should be noted that the synthesis of apoB48 remains unchanged and that every, even the largest, chylomicron contains only two molecules of apoB48 proteins, and the question of its stability in the lymph water medium has to be justified. For now, we can only speculate on what can happen when such a large particle, with an  $n^3$ -fold larger mass than normal chylomicron, is thrown out with the heart into the turbulent arterial bloodstream, the arch aorta. In the same paper, the authors asked for the first time in the literature about the possible influence of lymphatic apoB lipoproteins such chylomicrons after entering the lymph flux, obviously in terms of their subsequent incorporation into the structure of such large and unstable particles. We must not disturb the mind that chylomicrons are a large cluster of mostly lipid content and that their existence and stability in the water medium of lymph, and especially blood, is determined by explicit physical laws. Interesting and interesting is the fact that Phillips ML, et al. in 1997. [11], chylomicron particles were found to have only one apoB48 molecule, but they investigated chylomicrons from human serum, not from lymph, so the question of where one apoB48 molecule disappeared can be raised. Generally, increased lipid uptake into circulation and their disposal into fat tissues take place through large chylomicrons. The question of whether such large and unstable chylomicrons present or may pose a certain danger after entering the arterial circulation is highly suspect. However, there are many reasons to believe, due to the exposure so far, that such a danger is highly likely [3,4].

The WHO warnings explicitly emphasise the role and importance of physical activity in preventing atherosclerosis, as one of the key factors in preventing cardiovascular diseases, which is directly related to obesity as a consequence of harmful lifestyle. How?

## Physical activity

*“The turbulent and non-laminary flow of blood leads to endothelial dysfunction and inhibits the endothelial formation of nitric oxide, which is a potent vasodilator as well as an anti-*

inflammatory molecule. Such blood flow stimulates endothelial cells to form adhesion molecules, which recruit and bind inflammatory cells. The final effect is binding of monocytes and T cells to endothelial, migration of these cells to subendothelial space and initiation and enhancement of local inflammatory response. In subendothelial monocytes are converted into macrophages. Blood lipids, particularly Low Density Lipoproteins (LDL) and Very Low Density Lipoproteins (VLDL) are also bound to endothelial cells and oxidised to the subendothelium. The uptake of oxidized lipid and the conversion of macrophages into foamed cells packed with lipid lead to a typical early atherosclerotic lesion called the fatty stripe" [12].

This quote is from the generally accepted and references professional manual for doctors, MSD (Merck Sharpe & Dome) [10], so it should also mean that this is an official medicine attitude. However, the observation that "turbulent and non-laminary blood flow leads to endothelial dysfunction". "points eyes" and seeks an answer to the question when, how, why, and which answers are missing.

Suppose the turbulent and non-laminary flow of blood, which relates to the aorta harbour area and its detachments, arteries, leads to endothelial dysfunction, which consequently leads to the creation of preconditions for atherosclerosis. Does this mean that increased and indeed more vigorous? More turbulent blood flow through this area, as a consequence of increased physical activity, would have an increased impact on endothelial dysfunction and atherosclerosis?? Physical activity stimulates a faster heart rate and increased blood flow. Consequently, doing sport and any physical activity would be harmful to our body, because it would certainly speed up the creation of preconditions for atherosclerosis.

All previous studies on the influence of physical activity on our health, especially on the health of the cardiovascular system, suggest that sports be dealt with and that physical activity is regular for the preservation of health and the prolongation of life. How is it, therefore, interpret the above conclusion in the published quote and how to accept such decision, by its broader meaning, as a credible confirmation of the real cause the occurrence of atherosclerosis?

When it comes to physical activity, it is almost exclusively thought and implicated in its positive influence on the bloodstream system. The explanation is accepted that exercise helps prevent atherosclerosis in several ways. It keeps arteries healthier and reduces other risk factors for atherosclerosis and blood clots, such as high blood pressure, diabetes, obesity and stress. This is certainly true and justified because the relationship between regular physical activity and heart health and the entire circulatory system has been unambiguously established. Physical activity contributes to increased elasticity of blood vessels, proper heart function, faster exchange of blood components with other organs, general physical condition, etc.

Unfortunately, in cases of significantly reduced or insufficient physical activity, the general health status of the body deteriorates and the condition and worsening functions of many organs, including the blood system, increase the risk of cardiovascular diseases, including atherosclerosis.

## But how do these facts relate to the occurrence of atherosclerosis at certain sites of the bloodstream?

It has been proven that atherosclerotic changes appear almost exclusively in certain places of the aorta, its harbour and places of separation, cracking, major arteries [1].

The fact is that discussions about the importance and impact of physical activity on the health of our body forget, or in this context pay insufficient attention to its impact on **the lymphatic system**. Such forgetfulness is surprising since lymph flow in the lymph system is stimulated and determined almost exclusively by physical activity of the entire body. Lymph collects waste and redundant metabolism products from all body organs and extremities and returns them to blood circulation via the main lymph channel, ductus thoracic. The most essential ingredient of lymph is protein molecules from intercellular space, especially apoprotein, alone, soluble in an aqueous medium, or related to residues of lipoproteins, which are also excreted in the intercellular space after hydrolysis of chylomicron and VLDL in endothelial cells, and which are of different composition from serum lipoproteins, with a significantly higher content of cholesterol and phospholipids [13], from the physiological point of the role of relapse. In doing so, creating a complex with ApoA1, an emerging lipoprotein HDL emerges. ApoA1 is the primary apolipoprotein in HDL, and almost half of the total body ApoA1 is found in interstitial fluid, intracellular or lymphatic [14].

Since the composition and properties of interstitial fluid differ from tissue to tissue, the resulting HDL lipoproteins are modelled according to physiological and pathophysiological conditions [15]. There is also a significant difference in the composition and function of peripheral lymph and intestinal lymph. Intestinal lymph transmits newly synthesized chylomicrons formed after lipid absorption, while the main lipid component in peripheral lymph is HDL. ApoA1 synthesised in the liver and small intestine is also an integral part of the nascent chylomicron, in combination with phospholipids and cholesterol as a discoidal HDL.

Intestinal lymph, rich in chylomicrons of various sizes, increasing during more prolonged absorption of lipids from the digestive tract, with apoB48 and apoA-1 and apoA-IV in its structure, enter and blends with peripheral lymphoma, rich in apoproteins of all kinds, cholesterol-rich HDL and phospholipids. In such conditions, particularly large, unstable and unfinished chylomicrons likely interact with newly arrived particles and molecules to increase the stability and functionality of their structure. At the same time, the flow rate of interstitial fluid, and thus the amount of newly arrived peripheral lymph, probably influences the faster and necessary process of adding large scents of chylomicron.

Residual large, unstable, structurally unfinished chylomicrons by entering the blood circulation represent a major risk to the endothelial aorta and arteries. The frequent occurrence of such large chylomicrons in particular in persons with reduced or insufficient physical activity leads to an increased possibility of atherosclerotic changes in arteries, in



places and in the way explained in Article the mechanism of the Emergence of Atherosclerosis, New Perspectives [3] and the monograph Atherosclerosis. Yet chylomicrons, large [4].

The Journal of the AMERICAN Medical Association published a very serious and respectable study on the impact of walking on the mortality of a large number of respondents over ten years, largely related to the mortality caused by atherosclerosis [16].

*“The summary outdoor was all-cause mortality. Secondary outcomes were disease (CVD) and cancer mortality.*

The study concluded that; *“based on a representative sample of adults in the USA, a greater number of daily steps are significantly associated with lower mortality than all causes. There was no significant correlation between the intensity of the steps and mortality after adjusting the total steps daily...”*

The optimal daily number of steps 8 000 to 12 000 has been shown, with the mortality of people implementing such a physical activity regimen reduced to half, after ten years of observation, compared to physically inactive people. Which is the reason, the study did not mention.

However, the results presented in this study confirm the settings presented in the chapter on lymph in the abovementioned Article [4], where the potential significance and influence of lymph on the newly formed chylomicrons during their passage through the ductus thoracic is greatly elaborated. In this case, it is an increased or optimal or sufficient flow of peripheral lymph from the lower extremities, as a result of the increased and long-term activity of leg musculature, which is poured into the cisterna chyli and is effectively mixed immediately with intestinal lymphoma rich in scent chylomicrons. As we also emphasized that the peripheral lymph contains numerous constituents (lymph composition) that are probably incorporated into chylomicrons, thus the process of changes in the structure and structure of chylomicrons begins already in the cisterna chyli, and then along the entire route through d. thoracic, especially in the later phase of lipid absorption from the small intestine, when they are growing. Of course, prolonged walking and increased energy consumption lead to increased endogenous lipid consumption. The result is a faster flow of peripheral lymph rich in endogenous lipoprotein degradation products, as a transporter of energy triglycerides into the muscular musculature of the leg, which is poured intensively into the cisterna chyli. In this way, the cisterna chyli and later the d. thoracic reduce the possibility of large chylomicrons, which, by entering the blood system, are probably the greatest risk of atherosclerosis, as explained in this review.

## Smoking

Smoking is justifiably depicted as a very important risk factor in atherosclerosis. The fact is that smoking brings into the organism a large number of very harmful and dangerous substances that can have very dangerous consequences on the endothelium of blood vessels, as well as damage to other

organs. In this sense, damage to the blood vessels may also be an initial factor in the process of atherosclerosis.

## But how do you relate this fact to the occurrence of atherosclerosis in generally specific sites of the bloodstream?

All these toxic and harmful substances enter the body through the lungs, where they are the first to get hurt. Among other things, there are significant changes in mast cell cells, so that after acute exposure to cigarette smoke, the lung mast degranulation occurs. Since degranulation is accompanied by the reduced release of heparin as well as local histamine release, which could affect the smooth muscles of the airways, it is suggested that this may be a mechanism mediating acute bronchoconstriction caused by smoking [17]. Even with more prolonged exposure to passive smoking, a significant decrease in the number of lung mast cells exposed to passive smoking was observed, indicating also intensive mast degranulation contributing to lung damage [18].

Unlike heparin found exclusively in lung mastocytes, heparan sulphate is found as proteoglycan on the surface of endothelial cells of arteries and capillaries of tissues, containing LPL. It is used as a connection site for LPL with chylomicron [19]. Recent studies of mast cells (proteoglycans) in the vascular endothelium indicate their importance in the process of atherosclerosis and disease development [20].

By entering chylomicron into the circulatory system, the first organs through which they pass are the lungs (the heart is metabolically inactive), after which chylomicrons enter the arterial circulation and into all other organs and tissues in the body. Back in 1976. we found that through the passage of chylomicron, obtained from the cisterna chyli, through the lungs, it became a much better substrate for LPL [21]. Therefore, we concluded that the lungs play an important role in the metabolic chylomicron, assuming that the process of “heparinization” takes place in them, i.e. the binding of heparin or heparin sulphate of proteoglycans from mast cells in the capillaries of lungs to the apoE, which ends the process of maturation of chylomicron, and after which they are ready to enter the arterial bloodstream and capable of binding and hydrolysis from LPL to the surface. This conclusion applies to chylomicrons, conditionally, of normal size, which occurs during the absorption of lipid in a standard, balanced diet. Does this also apply to chylomicrons multiple the average resulting from abundant and long-lasting lipid absorption, along with other physiological factors (physical activity, smoking), remains to be established?

The role of mast cells in the process of atherosclerosis is also emphasized by Conglin L, et al. [22].

*„Prior studies have established an essential role of mast cells in allergic asthma and atherosclerosis. Mast cell deficiency or inactivation protects mice from allergen-induced airway hyper-responsiveness and diet-induced atherosclerosis, suggesting that mast cells share pathologic activities in both diseases. Allergic asthma and atherosclerosis are inflammatory diseases that contain similar sets of elevated numbers of inflammatory cells in addition*



to mast cells in the airway and arterial walls, such as macrophages, monocytes, T cells, eosinophils, and smooth muscle cells. Emerging evidence from experimental models and human studies points to a potential interaction between the two seemingly unrelated diseases. Patients or mice with allergic asthma have a high risk of developing atherosclerosis or vice versa, despite the fact that asthma is a Th<sub>2</sub>-oriented disease, whereas Th<sub>1</sub> immunity promotes atherosclerosis. In addition to the preferred Th<sub>1</sub>/Th<sub>2</sub> responses that may differentiate the two diseases, mast cells and many other inflammatory cells also contribute to their pathogenesis by much more than just T cell immunity.“

However, in these studies, the authors were not associated with the possibility that chylomicrons could also be those particles affected by the possible effect of mastocyte dysfunction, although as early as 1999 Nog O. et al. [23], showed that heparin proteoglycan from the mastocytes of the lungs represents a physiological macromolecule capable of activating cellular and humoral contact (cell adhesion) in allergic reactions and consequently could have the same role by binding of chylomicrons to LPL endothelial cells of arteries and capillaries.

We emphasized the possible importance of lungs in the metabolism of chylomicron, so that lung mastocyte in normal circumstances probably participate in the process of the final formation of chylomicron before entering the bloodstream. Especially due to the very wide range of capillary nets, which enabled close contact of chylomicron with capillary endothelium and possible acceptance and installation of released heparin or heparin sulphate proteoglycan. All these facts indicate that smoking must play a very important role in the process of atherosclerosis in the circumstances when mast degranulation occurs in the lung tissue, and thus disruption in the synthesis of heparin and heparin proteoglycans with possible and probable effects on chylomicron particles of all sizes.

## Conclusion

It can be concluded that risk factors mentioned and highlighted in all WHO reports presenting a risk for the occurrence and development of atherosclerosis, but not due to the impact on the behaviour and pathogenic activity of endogenous lipoproteins, but primarily on exogenous lipoproteins, chylomicrons, as exclusive lipid transporters from the digestive tract into the blood circulation. We must not disturb the mind that chylomicrons are non-cellular particles whose primary function is to bind to the surface of arteries and capillaries to deliver their contents to organs for use. Disturbances in this process are a possible cause of inflammatory processes on the arterial endothelium and a continued occurrence of atherosclerosis.

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