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Short Communication

The Mechanism of the Emergence of Atherosclerosis, New Perspectives

BO IDAR KOCMUR*

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

Abstract

In all the previous research conducted on chylomicrons and their metabolidsm, the potential influence onto the formation and development of atherosclerotic and other changes in the body, the chylomicrons obtained by means of the cannuling of the ductus thoracicus are used exlusively in its abdominal part, immediately from or next to the cisterna chyli. So obtained chylomicrons present essentially a mixture of the particles of various sizes, chemical composition and superficial distribution of the lipid, cholesterol and protein phase, so that their averaged effects are always measured. Chylomicrons obtained from the serum, which are certainly not native chylomicrons, but their remnants, given the proved speed of their decomposition within the circulation. Another extremely important fact has not been researched yet, related to the cannuling of the ductus thoracicus, during which the mixing of chylomicrons with the lymph inflow is permanently disabled, as well as the inflow of chylomicrons and a large part of the lymph into the circulation. Thus, an organism is brought into the state of starvation, which probably leads to changes in the plasma lipoprotein metabolism. Such a situation may also have a retroactive effect on the generation and composition of the newly formed chylomicrons in the small intestine.This fact indicates significant shortcomings in the research of chylomicrons, in defining their potential role and impact on the generation of cardiovascular diseases, since the impact of the lymph and the lymphatic circulation has not been researched. The passage of chylomicrons through the lungs, and the potential impact of mastocytes on their final structure and composition at the moment of their entering the circulatory system has not been researched either. The passage of chylomicrons through ductus thoracicus and lungs can be considered a grey zone, an area which has not been researched yet, and which is to be thoroughly researched.

Special attention is to be paid to the generation and role of large chylomicron particles, which I believe are the primary cause of the formation of atherosclerotic, and I hope there will be a research conducted in the future to confirm this.

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***Corresponding author**

BO IDAR KOCMUR, Faculty of Pharmacy and Biochemistry, Department of Pharmacology, University of Zagreb, Croatia,
Email: bozidar.kocmur@ri.t-com.hr

Discussion

The atherosclerotic plaque, as a consequence of atherosclerotic process inside large and medium-sized arteries, including coronary, carotid and cerebral arteries, the aorta and its branches, as well as large-sized of upper and lower extremities, consists mostly of lipids, the intracellular and extracellular cholesterol and phospholipids, inflammatory cells (macrophages, T-cells), smooth muscle cells, connective tissue (such as collagen, glycosaminoglycans, elastic fiber), thrombins and potassium deposits [1].

All the stages of atherosclerosis, from the initial growth to complications caused by te plaque, are considered to be an inflammatory response to injury. It is believed that the endothelial blood vessel injury plays a primary role in the emergence of atherosclerosis [2].

Atherosclerosis is characterized by a tendency to affect certain branches of the arterial tree, mostly at the branch point of arterial blood vessels [3].

So far, this can be explained by the fact that the turbulent and non-laminar blood flow causes endothelial dysfunctionand inhibits the production of endothelial nitric oxide, which is a potent vasodilator, as well as an anti-inflammatory molecule. Such blood flow stimulates endothelial cells to produce adhesion molecules which regulate and bind the inflammatory cells [1]. Since the exact mechanisms of such processes are unknown, the true relationship between the level of triglycerides in the plasma with the emergence of cardiovascular (atherosclerotic) diseases has not been proven yet, and there is no general agreement yet about to the type of lipoprotein participating in such processes. The fact remains that the emergence of atherosclerosis is still unknown [4]. Still though, there are ever more research papers indicating the possibility that the penetration of chylomicrons, accompanied by apoB proteins, into the blood circulation, may cause inflammatory processes on the blood vessel endothelium, which points to the importance and role of chylomicrons in the development of atherosclerosis [5].

In all the research papers on lipoproteins, the obtained results refer to lipoprotein groups (classes and subclasses) which, in fact, are a mixture of particles differing in size, chemical composition and surface distribution of the lipid, cholesterol and protein stage, so that their averaged effects are always measured [6]. This applies particularly on the chylomicron lipoprotein group, with the particle size ranging from 800 A to even 3600 A, depending on the duration of the absorption

of lipides through digestion [7] which, after they get into the arterial circulation find themselves in the specific conditions of the turbulent and dynamic blood flow at the beginning of the arterial blood flow.

The fact is that, in the conditions of different hypercholesterol anemias with familial combined hyperlipidemias, resulting in life expectancy being reduced significantly due to the emergence of atherosclerosis, the attention has been focused on cholesterol as the main factor in the process of the generation of the disease. This is what population studies have usually been confirming. LDL is a particle with the largest cholesterol content. In comparison with chylomicron, the LDL particle contains up to 100 times more cholesterol, as well as statins, the enzyme which inhibits the synthesis of cholesterol and reduces the level of LDL cholesterol, as well as the emergence of atherosclerosis. This has focused greater attentio onto LDL particles as the main factor contributing to the emergence of atherosclerosis, while chylomicrons have been unduly pushed into the background.

Chylomicrons contain proportionally substantially less cholesterol, but with respect to their size and the speed of their clearance from the circulation which is measured by minutes, while for LDL particles it lasts up to 4 days, the possibility of transferring the cholesterol is signficant and it resembles the LDL particles [1]. Karpe et al. [8] have shown that there is a correlation between apo B48, which is the compulsory structural apoprotein of chylomicrons, and the atherosclerosis of carotid arteries even in normotriglyceridemic and hypertriglyceridemic respondents. The argument that chylomicron particles cannot be considered atherogenic since due to their size they could not enter the subendothelial arterial space is no longer valid, because apo B48 have been found in atherosclerotic plaques in the studies on people and animals [9,10]. The discovery of this in people has been confirmed in other studies as well [11].

The mechanism which is used by macrophages for the clearing of the remnant chylomicron particles has been extensively researched. The chylomicron remnant competes with LDL for the intake through LDL receptors [12], but the apo B48 specific chylomicron receptor [13,14]. Elsegood at al. [15] have described a43K, the macrophage-chylomicron remnant binding protein as another candidate for the macrophage sterol recognition, resulting in the recognition of the chylomicron remnant by macrophages.

Generally, there are numerous dilemmas surrounding the role of specific lipoproteins in the emergence of atherosclerosis, and, although there is no accurate clinical study yet which would show that important, perhaps, a decisive correlation between apo B48, i.e. Chylomicron, and cardiovascular diseases, everything points to the fact that there are sufficient indicators for such a conclusion [1,16].

Chylomicrons generated in the endoplasmic reticulum of the small intestines from the absorbed fatty acids and cholesterol with the help of apoproteins, apo-B48 is mandatory, enter the lymphatic system, the cisterna chyli, and through ductus thoracicus, the main lymphatic blood vessel, enter the jugular vein of the cardiovascular system which is located close to the heart. Chylomicrona are a mixture of particles the diameter of which ranges from 800 to even 3600 A. On the way towards the jugular vein, in ductus thoracicus and from the lymph as well, the chylomicrons, probably, take onto themselves and from the lymph as well, various apoproteins with which the necessary stability of the surface layer of such a large particle is achieved, as well as some other components (protein receptors or their parts, cholesterol, phospholipids), which are removed from the organs through the lymphatic system as remnants after the decomposition and hydrolysis of the lipoproteins in the cells of the organs. The role and importance of each apoprotein embedded into the surface structure of chylomicron is well-known. When chylomicrons enter 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 all the other organs ad tissues in the body. In 1976, in a n article published in Per. Biol. ... we have observed that, chylomicrons, obtained from d. thoracicus, by passing , through the lungs, become much better substrate for the LPL activity [17]. From this we can conclude that the lungs play an important role in the chylomicron metabolism, assuming that the heparinization process takes place in them, i.e. the binding of heparin from mast cells in the pulmonary capillaries onto apoE, or heparan sulphate which exists as a weaker anticoagulant than the heparin on all the cells, or the heparin sulphate proteoglycan from the pulmonary mast cells, thus completing the chylomicron maturation process, after which they are ready for entering the arterial circulation and are capable of binding and hydrolysis with LPL at the surface of arteries and capillaries.

The lymphatic system is part of the immune system of the body of mammals, the role of which is to collect and deliver the excessive intercellular fluid into the blood, the transport of lipids from the intestine into the blood, the generation of lymphocytes and the protection of the body from various diseases. The system consists of the lymph, the lymphatic vessels (lymphatic circulation) and lymphatic organs, such as: bone marrow, thymus, spleen, tonsils and lymph nodes . Lymphatic vessels are very thin, and their anatomy is similar to the ones of the veins, with valves which direct the lymph towards the circulation. Unlike the blood flow which is a closed system with a drive pump, i.e. the heart, the lymphatic circulation is a discontinuous system starting at the periphery and ending in the venous bloodstream. The lymphatic fluid flow within lymphatic vessels is controlled by the contraction of adjacent muscles, the movements of the body, the pulsation of arteries, the movements of the diaphragm and the external pressure. The lymphatic circulation starts with lymphatic capillaries which extend into ever larger vessels, which drain into two major lymphatic ducts: ductus thoracicus and ductus lymfaticus dexter. The most important lymph constituents are protein molecules from the intercellular space, particularly the apoprotein ones, alone, soluble in a water medium or bound onto lipoprotein remnants which are also exceted into the intercellular space following the hydrolysis of chylomicron and VLDL in endothelial cells, the composition of which differs from serum lipoproteins, with a much larger content of cholesterol and phospholipids. Results of apolipoprotein measurement in lymph and plasma, (MN Nanjee et al.), showed that concentration of all apolipoproteins were much lower in lymph than in plasma. ApoA-IV had the highest mean L/P ratio and apoB had the lowest. The concentrations of apolipoproteins A-II, C-III, E, and A-IV in lymph were all positively correlated with those in plasma [18]. The difference in the concentration of apoB in the lymph in a healthy person and a person with the familial LPL deficiency disease is noticeable, which indicates that after the hydrolysis of chylomicrons in the blood vessels endothelium apoB diffuses into the lymphatic system, while in LPL deficiency the diffusion into the lymph is significantly reduced. A similar conclusion may be drawn for other apoproteins as well.

Upon the draining into the ductus thoracicus, it gets mixed lymph with chylomicron particles, and apoproteins, probably even phospholipids and cholesterol are bound onto them, thus increasing the stability, firmness and quality of chylomicrons for an optimal functioning within the arterial circulation. Since the flow of the lymph through the ductus thoracicus is relatively slow, the success rate of this operation depends primarily on the quantity and size of the lipid particles delivered from the intestines. The size of the received chylomicron particles depend on the quantity of the lipids absorbed fom the intestinal tract and the possibility of the synthesis of apoproteins, primarily of apoB48, and phospholipids in enterocytes which form the surface layer of the lipid particle. The largest chylomicrons are formed during the peak time of the lipid absorption in intestinal cells [19]. With respect to the duration and frequency of the duration of lipid absorption from the intestines, the question arises about the sufficiency of the newly-created apoproteins and other components from the intestines, as well as of apoproteins, cholesterol and phospholipids accumulated in the lymphatic system for the purposes of the addition of the increased concentrations of ever larger delivered chylomicrons. Chylomicron particles which due to the lack of synthesis and an insufficient inflow of apoproteins from the lymph do not manage to achieve the required stability of their structure, due to insufficient firmness of the surface layer, are probably joined together, forming larger particles (this process is known as coalescence), pose a relatively serious potential threat after they enter the arterial blood flow. Such a situation can have, or has, far-reaching consequences in the development of atherosclerotic changes at the surface of arteries, particularly of those which are in close proximity to the heart, carotid and coronary arteries which are mostly affected by such degenerative changes. In support of such reasoning we must mention the well.known fact that the lack of physical activity, in addition to the excessive consumption of fats (which ones?), is one of the main causes of the development of atherosclerosis. Previously we emphasized that the speed of the lymph flow mostly depends on physical activity, so this fact also leads to such reasoning.

Through vena cava, chylomicrons enter the heart where they also get mixed with the lymph delivered from the right ductus lymphaticus, and the right ventricle pumps them into the pulmonary artery and then into the pulmonary capillaries. So far, nobody has tried to explain what happens in the pulmonary capillaries with chylomicrons (if something happens there at all), except for our attempt [17], where we have demonstrated in vivo that chylomicrons obtained from the ductus thoracicus by passing through the lungs become a better substrate for the LPL activity. The suggestion that chylomicrons in the lungs are conditionally "heparinized" is based on the well-known fact that the presence of heparin significantly enhances the activity of LPL onto the hydrolysis of chylomicrons, and it is the very heparin that is found in the pulmonary mast cells from which is released into the blood circulation. By binding to proteins, heparin generates proteoglycans, with antithrombin becoming a systemic coagulant, while binding to apoE it participates in the decomposition of lipoproteins, binding them to LPL [20]. Unlike heparin which is found exclusively in mast cells of the lungs, heparan sulphate is found as proteoglycan in fatty deposits at the surface of endothelial cells of the small capillaries of tissues containing LPL, serving as a binding site for LPL with chylomicrons [21]. The key question which arises from this is whether the negative charge alone at the binding site with LPL is sufficient to retain a large chylomicron particle, especially the largest ones, in order to enable the hydrolysis of triglycerides from its core or not? Noga O et al. have shown that heparin proteoglycan from pulmonary mast cells represents a physiological macromolecule capable of activating the cellular and humoral contact (cell adhesion) in allergic reactions [23]. Therefore, consequently, it may play the same role in binding chylomicroms onto LPL of blood vessel endothelial cells, binding onto chylomicron apoE.

The question concerning the way in which the native chylomicrons and their remnants are bound onto endothelial cells of arteries is still dubious. There are several potential explanations. One of the possible binding mechanisms is the one of binding the chylomicron to heparan sulphate proteoglycan, which is present in endothelial capillary cells, before the interaction with LPL, while another possibe mechanism is the one of the binding of chylomicron

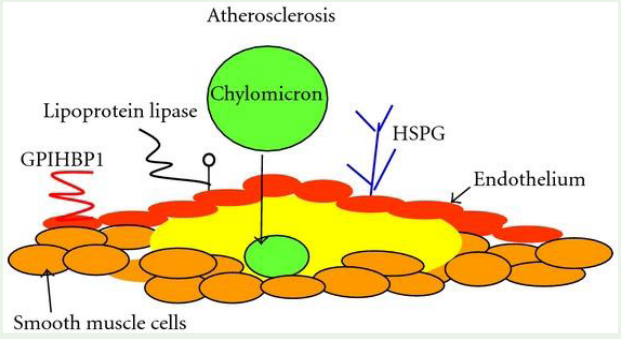

Figure 1: The chylomicron and atherosclerosis. The atherosclerotic plaque is composed of a lipid-rich core containing cholesterol and necrotic tissue and is covered by a fibrous smooth muscle cell cap. Low Density Lipoprotein (LDL) is the major contributor to plaque.

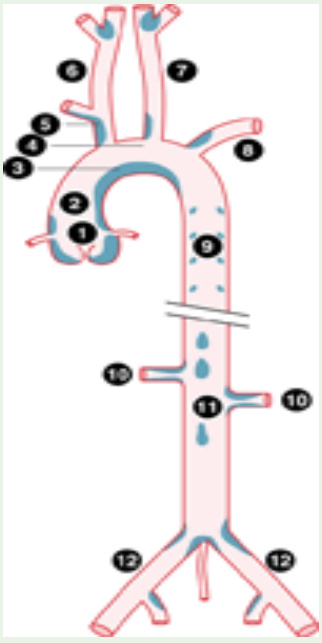

Figure 2: Atherosclerosis preferentially develops at arterial branches and curvatures. Schematic drawing shows a longitudinal representation of the major arterial vasculature illustrating the observed distribution of atherosclerotic plaques (gray shading) in the arterial branches.

directly onto LPL which depends on GPIHBP1 with the help of which it is localized onto the endothelial surface. The third possibility is for the chylomicron to be bound directly onto GPIHBP1. The answer to all these questions, as well as to many other questions related to the problems with chylomicrons is still to be found [24-26] (Figure 1).

What is the way in which large chylomicron particles can initiate atherosclerotic changes at the surface of arteries? (Figure 2).

In the article entitled "Triglycerides and Heart Disease, Still a Hypothesis?", Ira J Goldberg, Robert H Eckel and Ruth McPherson [26], provide us with a review of the current knowledge about the lipoprotein metabolism, and chylomicron in particular, as well as the changes and their impact on the development of numerous cardiovascular diseases, based on the basic and clinical trials. As we can see, a number of issues have been researched and explained, but these are all just the effects having their origin and cause in the very process of the emergence of atherosclerosis. Why, in what way, and when does the true emergence of atherosclerosis occur? This is still unknown. The two alternatives to the potential solutions, which are shown in the figure 3. in this reseaarch paper, do not provide the right answer or complete one to such vital issues.

Does this mean that each chylomicron particle behaves in the same way, or could behave in such a way, meaning that each chylomicron is a potential cause of atherosclerosis? What is the reason behind the fact that, probably, only some of the chylomicrons cause, or can cuse, the inflammatory process in the blood vessel endothelium, and under what circumstances?

We mentioned the way in which and the reason why such large chylomicron particles are generated, for which we can assume with certaintly that the stability and firmness of the surface layer which mostly consists of apoproteins, phospholipids and cholesterol are reduced significantly [26]. The fact is that large chylomicron particles are removed from the circulation more slowly. When such a large particle collides with the surface arterial endothelium, the binding process starts immediately, in one of the assumed ways, which has to take long enough to start the process of transport of triglycerides from chylomicron core into the interor of the arterial endothelium through LPL activity. Since the entire process takes place within a strongly pulsating and turbulent blood current, particularly in the previously shown parts of the arterial circulatory system, strong binding forces are required in order to hold a heavy chylomicron particle of large diameter "in one place" on the surface of the artery, and the stability and firmness of the chylomicron surface layer needs to be large enough not to allow for the particle to disintegrate itself under such circumstances. The previously mentioned fact is to be emphasised once again, stating that the chylomicrons range in size from 800A to up to 3600A, resulting in the increase of the particle mass of up to 80 times its size!!!! When such a large particle gets fixed to the endothelial surface, there are two possible scenarios in this case.

In the first scenario, (Figure 4) the forces maintaining the surface stability are weakened, and it can therefore disintegrate easily due to a strong flux of blood, and probably even due to the collision with other large particles in the blood (erythrocytes, leucocytes, platelets). Part of the particle bound to the endothelial surface by the action of the lipoprotein receptor, proteoglycans, LPL and GPIHBP1,

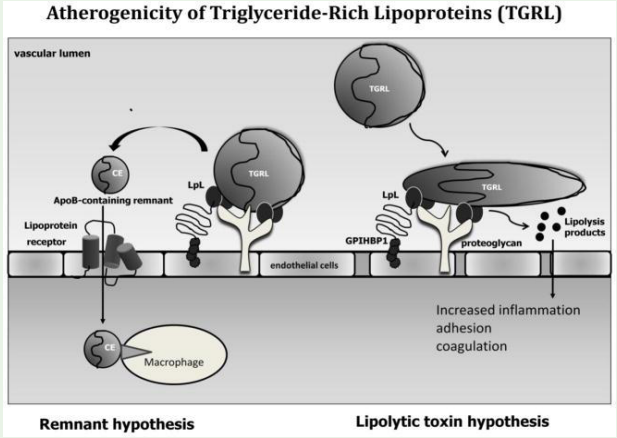

Figure 3: Two hypotheses for pathways by which Triglyceride-Rich Lipoproteins (TGRL) might increase atherosclerosis are illustrated. Left panel shows the remnant infiltration hypothesis. Conversion of TGRLs to remnants produces particles that then enter the arterial wall, carrying both triglyceride and cholesterol. Arterial LpL may be important to increase the local concentration of these particles. Remnants can be internalized by macrophages and convert these cells into foam cells. Right panel illustrates the toxic lipolysis product hypothesis. During lipolysis of TGRLs a number of inflammatory lipids are released that alter endothelial biology. These lipids - including fatty acids lysolecithin and oxidized lipids - increase expression of adhesion molecules and cytokines, and promote coagulation.

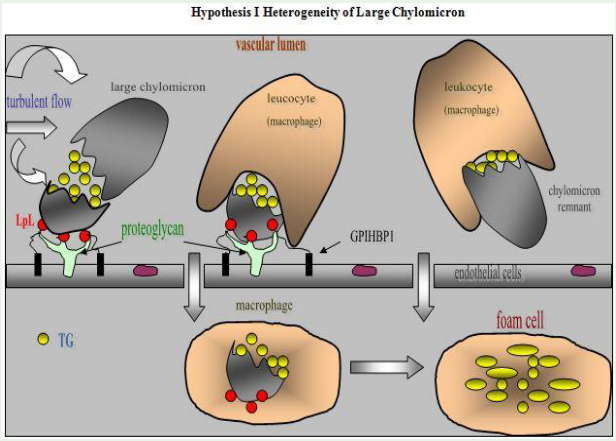

Figure 4: The illustration provided to this research paper shows one of the potential forms of behaviour of large chylomicrons after they enter the blood circulatory system, particularly in the areas of the turbulent flow on the sites where the arteries bifurcate. Namely, large chylomicrons, of the dimeter and mass which are several times the size of the usual chylomicrons, generated in the later postprandial period, due to the reduced presence of apolipoproteins, and thus of the weakened surface tension, in a strong turbulent blood fluid current, after getting attached onto the arterial endothelium, are exposed to strong resistance, which can lead to their disintegration. If the binding force is strong enough, a part of the chylomicron remains attached onto the arterial endothelium, and the other part is carried away by the blood fluid current. It may also occur that the disintegration of the chylomicron particle is caused by its collision with some of the blood particles. The chylomicron particle which has disintegrated itself in such a way on the endothelial surface becomes the inflammation factor which initiates the process of activation and activity of lymphocytes (macrophages), thus initiating the process of their removal from the arterial endothelial cells and from the blood circulation. Parts of chylomicrons and chylomicron remnants which have been introduced into the arterial endothelium in this way with macrophages transform themselves into foamy cells which represent the beginning of the formation of the atherosclerotic plaque.

remains attached to the endothelium, and the rest of the decomposed hylomicrons draws the flow of blood fluid.. The remaining chylomicron which remained bound onto the arterial surface, as a foreign body, is invaded by leucocytes, macrophages or monocytes and T-cells which by binding onto the blood vessel endothelium and by penetrating the subendothelium start the process of increasing the local inflammatory response. In the subendothelium, the monocytes are transformed into macrophages. The lipids remaining on the chylomicron remnant also enter the subendothelium and with the generated macrophages which are transformed into foamy cells full of lipids cause typical early atherosclerotic lesions, fatty streaks, which represent the beginning of the formation of atherosclerotic plaque on the arterial surface.

In the second scenario, (Figure 5) due to a strong resistance to the blood fluid current, the links by means of which the large chylomicron got fixed to the arterial endothelium get broken, and the chylomicron particle takes away the remnants of LPL, GPIHBP1 and proteoglycan with it, thus causing damage to endothelial surface cell. On both the damaged site begins inflammation and leukocyte lymphocytes, macrophages or T-cells reaction , which can also contain the remnants of the previously absorbed chylomicron remnants, as well as the other absorbed lipoprotein particles, VLDL and LDL. By introducing such cells into the arterial subendothelium, the process of foamy cell creation initiates, ultimately leading to the formation of the atherosclerotic plaque.

It is considered that an inadequate inflammatory response to subendothelial lipoproteins may be the cause of the further progression of the disease. The key aspect of this response is failing to eliminate the inflammation, which usually includes the inhibition of further inflow of inflammatory cells, an effective action time of apoptotic cells and the stimulating of the release of inflammatory cells. The shortfalls in these processes stimulate the development of atherosclerotic lesions into health-threatening plaques [27].

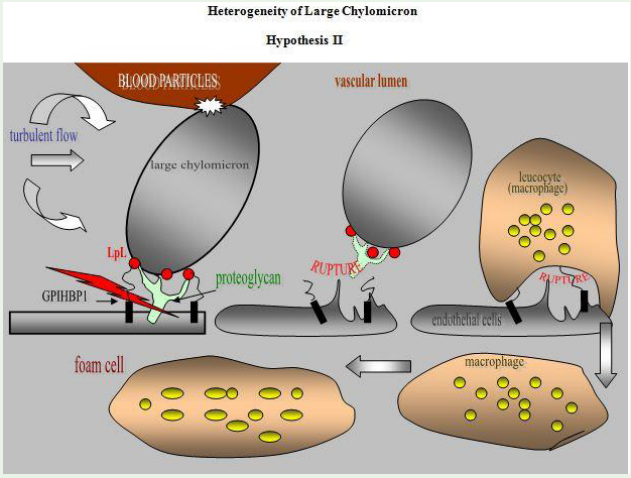

Figure 5: This illustration represents the second potential form of behaviour of chylomicrons in turbulent parts of the cardiovascular system. Namely, due to a strong resistance to the blood fluid current, or due to the collision of some of the blood particles with it, the links attaching the large chylomicron onto the arterial endothelium get broken, and the chylomicron particle carries away the remnants of LPL, GPIHBP1 and proteoglycans with it, thus causing damage to the blood vessel endothelium surface layer. On the damaged site, the inflammatory process initiates, as well as the reaction of leucocytes, lymphocytes, macrophages or T-cells which may also contain the remnants of the previously absorbed chylomicron remnants, as well as the other absorbed lipoprotein particles, such as VLDL and LDL. The lymphocytes introduce parts of the damaged endothelium cells into the subendothelial space, causing the lymphocytic cells to transform themselves into a form of a macrophage, and then with the introduced lipoprotein components they create foamy cells which represent the initiator of the atherosclerotic plaque.

In their review article, McLaren DR et al. [28] state and confirm that macrophages participate in the absorption of native and modified lipoproteins into the endothelium of large and middle-sized arteries, and in the creation of foamy cells as a beginning of the formation of the atherosclerotic plaque, leading to atherosclerosis. However, they do not provide any answer as to what may represent a trigger for such a reaction of macrophages, nor how the inflammaton and immune response occur.

It needs to be emhasised that in both cases endothelial cells get damaged, causing the inflammatory process in such areas, which leads to a strong reaction of all types of lymphocytes. In the works of Marijka A de Vries et al. [5,30], clinic trials have shown that in the postprandial lipemia leucocytes are excessively activated. Although they suggest that chylomicron remnants are responsible for the increased postprandial activation of the serum leucocytes, which they probably are to a certain degree, the author of this research paper believes that the changes and damage on the blood vessel endothelium, generated as a result of action of large chylomicron particles in the way described above, are the primary cause of their increased activation.

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