RESEARCH ARTICLE

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Molecular Biology of Atherosclerosis Formation, Diseases Mechanism and Diagnosis Application Development

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Abstract

Atherosclerosis is a disorder related to levels of lipids and cholesterol in the bloodstream. The process consists of irritation of the endothelium followed by a buildup of LDL cholesterol on artery walls. Over time these lipids form into plaques that block part of the bloodstream, and when plaques rupture, they cause thrombosis, or blood clots, which inhibit blood flow. This condition can be extremely dangerous, especially when it occurs in the coronary arteries. Common risk factors for atherosclerosis include hypertension and diabetes. Treatments include PCSK9 inhibitors, colchicine, and statins. These therapies lower LDL cholesterol levels by inhibiting proteins involved in LDL synthesis, acting as competing substrates, or reducing immune system activity. Other treatments, such as clot busters, destroy thrombosis after it occurs.

The main component of this research is viscosity. Viscosity is the measure of how thick a substance is, measured by viscometers, which are expensive instruments that use rotation or gravity to simulate flowing dynamics. Simple viscometers cannot calculate blood viscosity accurately because of shear rate. Shear rate refers to the concept that fluids can flow at different speeds at the center of a tube compared to friction on the outer walls.

Keywords

Biology; Molecular Biology; Cardiovascular Biology; Atherosclerosis Mechanisms; Plaque Formation Diagnostics

Introduction

Atherosclerosis was discovered in 1913 by Nikolai N. Anichkov, along with Semjon S. Chalato after the analysis of previous research from other scientists such as Rudolph Virchow[1]. This research is important because it delves into methods of discovering plaque formation in the arteries before they can do harm[2]. In the current medical field, research has been conducted on the study of different stages of atherosclerosis[2],[4]. This includes the study of thin-capped fibroatheromas, which is the stage where atherosclerosis is at its climax and plaque rupture is imminent[4]. Plaque rupture is the process where a thin capped fibrous cap breaks causing lipid-rich fat to be exposed to the bloodstream[5],[4]. This causes blood to clot in the artery, which is called thrombosis[5]. Thrombus in the blood can lead to dangerous symptoms such as a pulmonary embolism[6]. This severely slows down blood flow and can lead to stroke, swelling, and long-term circulation problems[6]. If unfortunately caused in a coronary artery, this can block blood flow to the heart causing chest pain and death[7]. Atherosclerosis is an underlying cause of most CVDs, which continue to kill people across the globe[1]. Heart attacks can kill within minutes or hours, making the prediction of plaque rupture an imperative topic in today's society[6].

After the discovery of atherosclerosis, modern research has progressed with treatment tenfold[16]. This includes the discovery of stents, statins, and other medications[9]. Statins block HMG-CoA reductase, the enzyme required for cholesterol production[11]. This causes liver cells to pack less cholesterol into LDL cholesterol as well as less cholesterol esters[13]. This means that less cholesterol is built up and smaller sizes of LDL molecules[18]. On a molecular level, statins serve as a competitor to HMG-CoA[18]. HMG-CoA is the substrate that causes the creation of LDL cholesterol molecules[11]. Statins serve as an alternate substrate to take up space and prevent HMG-CoA substrates from inciting LDL creation[18](Figure 1).

This discovery provided a revolutionary medication to prevent and slow down the progress of atherosclerosis[16]. However, they do not fully prevent it, meaning that rupture is still a chance[6]. This is why this research is so imperative. With atherosclerosis and CVDs being an almost inevitable disease, the prediction of fatal plaque ruptures is necessary to prevent many deaths across the globe[1]. Atherosclerosis is also a genetic disorder[22]. Treatments such as PCSK9 inhibitors and more treat and slow the progress of atherosclerosis; however, they do not fully prevent the disease[9]. This is why the prediction of rupturing plaques is important to prevent many deaths across the globe[6]. Specifically, blood viscosity is a major component in predicting the risk of heart disease in any person[6],[8]. High blood viscosity poses threats of

cardiovascular diseases such as atherosclerosis and hypertension[6]. Rarer occurrences such as low blood viscosity can also show signs of different medical ailments[6]. Through this research, we will explain how the prediction of plaque rupture thrombosis is an imperative topic in the current medical world[5]. As well as explain different biomarkers, risk factors, medications, and processes of atherosclerosis[4].

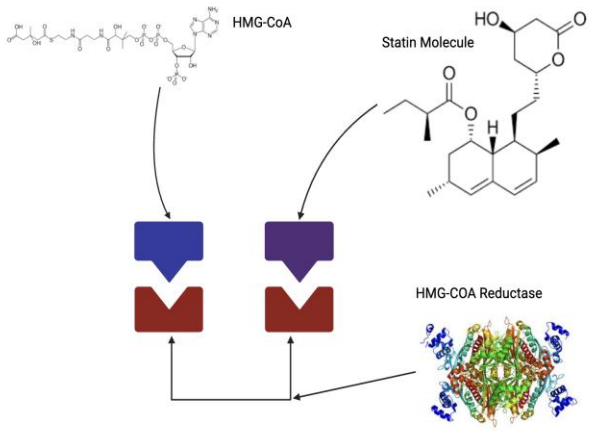

Figure 1: *An illustration of how statin molecules act as a competing substrate for the enzyme HMG-CoA reductase. By serving as a competitor, they prevent HMG-CoA substrates from bonding with the enzyme, hindering LDL cholesterol synthesis.*

Atherosclerosis is a multi-step process that occurs in the arteries. It begins with endothelial dysfunction. The endothelium is the inner layer of blood vessels[1]. The endothelium of the plaque becomes damaged due to several risk factors[2]. This signals possible inflammation in the artery[3]. The next stage of atherosclerosis is called fatty streak. In this stage, cholesterol enters damaged endothelium and gets oxidized[11]. Macrophages ingest oxidized cholesterol and become foam cells[3]. Foam cells build up and turn into fatty streaks[5]. Macrophages are special leukocytes that consume pathogens in the body[4](Figure 3).

During intermediate lesion, muscle cells migrate into the intima, the innermost layer of a blood vessel[5]. Due to this, foam cells and lipids build up in the endothelium[3]. After these events, in a stage called atheroma, a lipid core is formed and is covered by a fibrous cap which blocks off parts of the artery[5]. From here, the plaque begins to calcify and the fibrous cap hardens. In this stage, if the cap is thin and the lipid core is soft, then the plaque is unstable[4]. If no measures are taken to provide aid, then the plaque turns into a complicated lesion which blocks off the artery and creates a thrombosis in the artery[5],[4].

Some tools for basic prediction of atherosclerosis are biomarkers. Biomarkers such as C-reactive protein (hs-CRP), interleukin 6 (IL-6), and lipoprotein-associated phospholipase A2 (Lp-PLA2) can all show signs of atherosclerosis later during lifetimes[18],[5]. However, as stated before, atherosclerosis can be slowed down through different treatments. These include statins, PCSK9 inhibitors, and colchicine[9],[16]. Statins are a medication that fight LDL cholesterol production[18]. They do this by providing competition for the substrate HMG-CoA[11]. By binding with the enzyme HMG-CoA reductase, they cause LDL cholesterol molecules to appear in smaller quantities and sizes[18]. PCSK9 inhibitors are used when statins aren't efficient enough[9]. They block the function of the protein PCSK9. This boosts the liver's ability to remove LDL cholesterol from the body[9]. They do this by raising the amount of LDL receptors on liver cells[9]. The last prevention medication is colchicine. Colchicine dampens inflammation on blood vessel lining[16]. This stabilizes plaques and slows down the progression of atherosclerosis[3]. In addition, colchicine hinders inflammatory markers such as C-reactive protein[18]. In dire situations, a medication called clot busters or thrombolytic drugs can be used[6]. This medication removes blood clots, freeing up arteries and preventing death or heart attack[6].

In the primary stage of atherosclerosis, the endothelium becomes damaged[1]. This causes LDL molecules and leukocytes to build up inside the artery walls[11],[3]. The process preceding this one is known as “fatty streak,” during which LDL molecules enter the intima and get trapped[5]. There, the molecules oxidize[11]. Visually, the vessel appears to thicken. However, on most gross exams, the condition still appears asymptomatic[6].

During foam cell construction, monocytes begin to attach to the endothelium and press together[3]. After this process, the monocytes transform into macrophages and begin to consume the oxidized LDL[3]. This causes them to appear fat and foamy as well as inciting the wall to start bulging[5]. These are early signs of a fatty lesion[4]. When foam cells amass, they create structures called yellow fatty streaks on the endothelium[5].

The fibrous cap is formed by muscle cells from a deep arterial layer moving up and laying down different types of scar tissue such as collagen, elastin, and proteoglycans[13]. This narrows blood flow; however, it cannot cause any lethal damage[6]. From here, when foam cells die, the compositions of them are dispersed. This is what causes the lipid-rich necrotic cores to form plaques[5].

In this stage, if the plaque calcifies and the fibrous cap thickens, then the plaque will be stable[4]. Some other underlying conditions can make you predisposed to atherosclerosis. Diabetes damages the inner wall of the endothelium[2]. Damaged artery walls can lead to an increased amount of LDL and HDL cholesterol to sneak inside the artery wall[11](Figure2)

The immune system also plays a major role in the progression of atherosclerosis[3]. At the beginning, when the endothelium is damaged, it disperses special signals which cause white blood cells to travel to the site and enter the endothelium[4]. Macrophages attempt to control the situation by consuming LDL cholesterol to the point where they swell and become foamy; this, in turn, leads to more leukocytes being called to the endothelium[3].

Special cells known as T-cells further worsen the issue; they prevent smooth muscle cells from creating a substance known as collagen, an abundant protein found in the body which specializes in connection and support[4],[13]. Collagen makes the fibrous caps on plaques tough and thick. Without this crucial substance, the fibrous caps grow thin and weak, greatly increasing the risk of plaque rupture[4].

On top of this, another type of immune cell that further worsens the process is neutrophils[3]. Neutrophils break down the tissue in the fibrous cap by releasing enzymes and molecules. This further raises the risk of plaque rupture and the lethality of the condition[3]. These are some examples of how special immune cells can further worsen the problem[4].

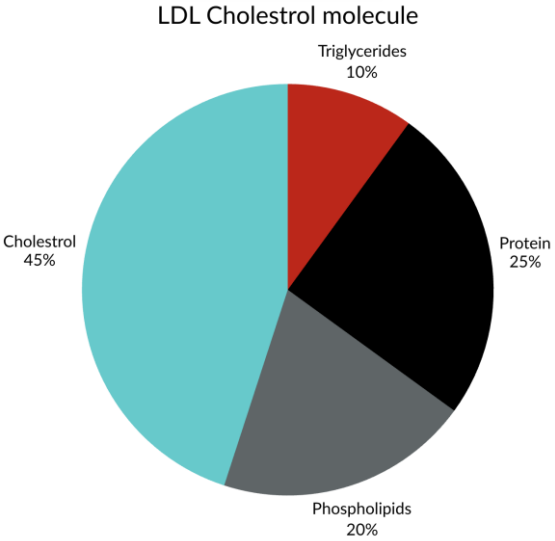

Figure 2: *An outline of the components of an LDL cholesterol molecule. LDL cholesterol is made up of 45% cholesterol, 10% triglycerides, 25% protein and 20% phospholipids.*

Mechanism of atherosclerosis plaques formation:

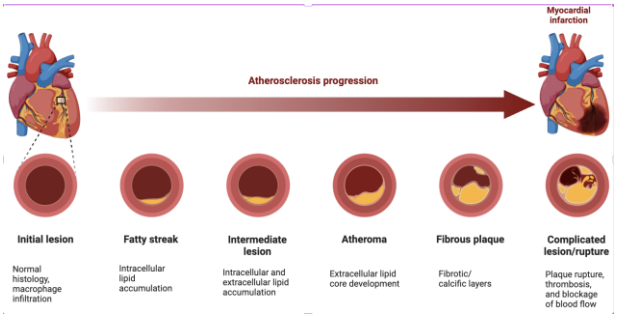

Figure 3: *The atherosclerotic process is shown here. Atherosclerosis is gradual and asymptomatic; the diagram here shows that through lipid accumulation the artery starts to slowly fill up. At the end of the process when the plaque has ruptured and the thrombosis is present; we can observe a red botch on the heart. This is because when the coronary arteries are blocked and as such, they stop blood-flow through the heart causing parts of it to die which can end up being a fatal outcome.*

A major overlooked component is blood viscosity or the thickness of your blood[6]. But why does this matter? The blood viscosity of your blood can surface several underlying diseases or illnesses[8], and most importantly, show key signs of atherosclerosis. When blood viscosity is thick, it means that blood is flowing slowly and is dragging on the endothelium[6]. This process causes the cholesterol and inflammatory cells to attach to the endothelium[3].

On top of this, the slow flow of blood may cause minor injuries on the endothelium[6]. This can make the endothelium more prone to inflammation and atherosclerosis[1]. Other than making atherosclerosis more prone, it makes the effects of it worse. Thick blood is more likely to clot, which means that during plaque rupture, the thrombosis that occurs from atherosclerosis is more condensed and hinders blood flow even further[6].

The analysis of blood viscosity can help patients maintain better hydration. Dehydration causes plasma volume to decrease while the concentration of red blood cells and plasma proteins is increased. This causes hyper viscosity and can contribute to vascular dysfunction to patients already prone to CVD's

With how important blood viscosity is in the fight against heart disease, it is a shame that it comes at such a high cost. The cost of an average rotational viscometer comes to an astonishing $2000–$5000[6]. This is unfortunate because it means that many rural hospitals cannot afford this costly equipment[6].

To deduce if a patient has atherosclerosis, many factors are involved. These factors include blood pressure,

viscosity, sugar, cholesterol level, and BMI[2]. Atherosclerosis cannot be explained by just one aspect of the body. It takes a combined effort of many different tests to discover signs of the progression of atherosclerosis[5].

The reason that standard rotational viscometers are so complex is that blood is identified as a non-Newtonian liquid[6]. This means that it does not have constant flow[6]. Newtonian fluids such as water have a constant flow rate based on their surface[6]. The reason blood is non-Newtonian is due to a factor called shear rate[6].

Mathematically, shear rate = velocity / distance[6]. But on a more descriptive level, shear rate is the factor of when liquid flows in a tube, the fluid on the edge of the tube flows slower than the fluid in the center[6].

One untouched feature of atherosclerosis is that it is caused by inflammation in the arteries[3]. This means that it should be prominent everywhere in the arteries, correct? However, this introduces an aspect called laminar and tubular flow[6]. A brief definition of both is that laminar flow is straight. It occurs in tubes with parallel edges and is normally very smooth and orderly[6]. Turbulent flow, on the other hand, is the exact opposite. It occurs in tubes with swirls and turns. Turbulent flow is not smooth and can vary in speeds[6].

This is important because in certain areas such as coronary arteries, aorta, and carotid bifurcation, blood flow has low shear stress[3]. Meaning it is extremely easy for cholesterol and lipids to stick to the endothelium as well as expediting inflammatory markers[3]. Low shear stress zones are extremely prone to develop atherosclerosis plaques, and blood viscosity can help us understand not only the overall risk of atherosclerosis, but where the atherosclerosis is and where plaque rupture may be imminent[6](Figure 4)

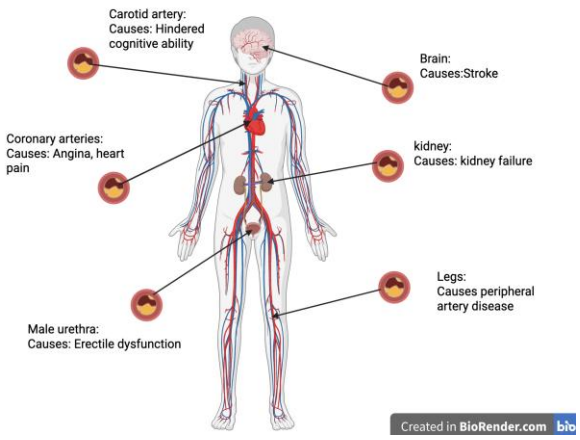

Figure 4: *This outline of the human body shows the most common areas where atherosclerosis takes place.*

It can be observed that different symptoms are observed in different areas. For example, when atherosclerosis occurs in the brain it can cause lethal strokes, on the other hand when it occurs in the kidney it can lead to kidney failure. Through the use of blood viscosity, we can help predict and prevent these dangerous plaques from forming and save countless lives.

High shear stress, on the other hand, is also, if not more harmful than low shear stress locations[3]. High shear stress causes lots of strain on artery walls, meaning that it can damage the endothelium, increasing permeability which causes more cholesterol to seep into the endothelium[11]. High strain can weaken fibrous caps, making plaques more prone to rupture[4].

Finally, hyper viscosity causes an increase of platelet activation in the bloodstream[5]. This means that after plaque rupture and the forming of the thrombus, more platelets will be activated, leading to an increase in size and raising the danger level for the patient[5], this causes increased stress on the endothelium and activates inflammatory markers for atherosclerosis. High shear stress is most common in coronary bifurcations as well as arteries in the shoulder; overall it is most common in laminar vessels with extreme narrowing, mostly due to plaques[3]. High blood viscosity further amplifies the issues stated above, revealing how imperative it is to the quick suppression of dangerous and imminent plaque rupture[6,8].

In addition, conditions such as anemia that lower hematocrit levels can decrease blood viscosity signaling illness before it fully takes place. On the other hand

This then leads to the development of my prototype: a smart Ostwald viscometer that specializes in the measurement of blood viscosity efficiently and effectively[6]. While unwieldy and exorbitant rotational viscometers already do this, they are extremely ineffective and very pricey[6]. With my smart viscometers measuring at an astonishing 100 × 65 × 40 mm, they can do the same calculations with the same accuracy at a fraction of the price[6]. This innovation can aid rural hospitals and healthcare facilities around the globe by providing an easy-to-use, cheap, and accurate substitute for extremely expensive rotational viscometers[6].

Overall effects of atherosclerosis on the world

I have been explaining on and on about my research on atherosclerosis, but one thing that must be clarified is the effects on atherosclerosis across the globe to understand the gravity of the situation[6,7].

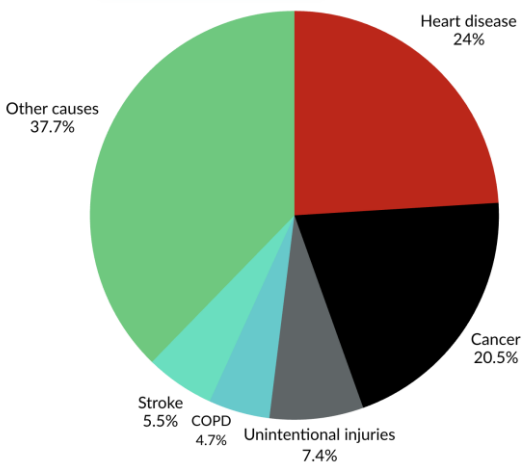

Figure 5: *This pie chart consists of the 5 leading causes of death from 2024. This data shows that heart disease and stroke account for 29.5% of deaths worldwide. This makes atherosclerosis the deadliest condition known to man and further signifies the need for efforts to help prevent atherosclerosis.*

From this graph, which shows data including the number of deaths from cardiovascular disease as well as stroke (also caused by atherosclerosis), it amounts to over a quarter of deaths around the world[6,7]. This further emphasizes the need for research on atherosclerosis. Overall, heart disease is THE leading issue in today's society[1,3]. A single step towards solving heart disease is bound to save millions of lives around the world[1,18](Figure 5).

But narrowing down on my research, you may ask the question: why blood viscosity, and how should we look more into this instead of other areas of heart disease? Blood viscosity is imperative to understand as it is a new frontier of exploration that is not viewed as much as other forms of atherosclerosis research such as blood pressure, genetics, and cholesterol levels[6,22,14]. Predicting plaque rupture is not just a one-trick formula but a team effort from the observation of different factors[8,5]. As explained in the text above, the different properties can reveal where plaques are most likely to form and the overall risk of atherosclerosis[3,4]. In addition, my invention will help bring these ideas to fruition[6].

Methods

The invention has only been talked about briefly; however, not in detail. The invention is a smart Ostwald viscometer[6]. An Ostwald viscometer is a tool used to measure the viscosity of Newtonian liquids[6]. A Newtonian liquid is a liquid that holds constant velocity regardless of the shear rate (e.g., water, oil)[6].

For clarity, the Viscometer described here is a prototype that is currently in development meaning that no physical testing has been performed at this time. Validation of the device will be performed after development of the prototype is completed.

The shear rate is the theory that liquids flow at different speeds due to the friction of their container or vessel[6]. Blood is a non-Newtonian liquid, meaning that shear rate changes its viscosity, which necessitates more complicated tools to measure its viscosity, leading to the $5000 rotational viscometers[6].

Until now, the smart Ostwald viscometer devised uses technological components to calculate the shear rate of blood and produce an accurate viscosity[6]. The marvel is that the production cost is at most around $100–$125 per unit[6]. A fraction of the price of rotational viscometers, this means that rural hospitals and even the general public can use this device to accurately examine their blood viscosity[6]. In addition, the device itself is extremely small, meaning that it is easily portable, further boosting its utility and overall efficiency[6].

The way that the viscometer works is as follows. First, blood from a blood bag is injected into the primary compartment of the viscometer[6]. When the person is ready, they will push a button that begins the test[6]. The blood will flow through a temperature-controlled tube and pass two sensors[6]. These sensors will time the flow from one to the other[6]. Once that has been measured, the viscometer will calculate the viscosity using shear-rate equations which have been coded into the viscometer's mainframe[6]. The viscometer includes heating technology and regulators to make sure that the tube represents human-like conditions and so that the viscometer does not overheat[6](Figure 6)

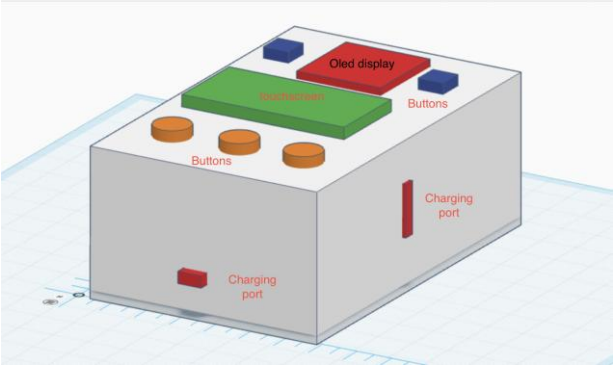

Figure 6: *This is a diagram of the exterior of the designed viscometer. Several key components are outlined above. The orange circles and blue squares represent buttons. The orange buttons are designed for calibrations, temperature control and data recording. The blue buttons are for Test conduction. The red square is the OLED display. This will display test results and the calculated viscosity. The green rectangle is the touchscreen. This serves as the central control and the manipulation of temperature, calibration and test results. The red objects on the bottom and sides serve as chargers for the device. The viscometer does not require a significant amount of charge for the test meaning that it can conduct numerous tests until finally requiring a recharge.*

Conclusion

Atherosclerosis is a leading cause of death around the world, causing 17.8 million annual deaths[6,7]. Predicting plaque rupture is a new frontier of possibility that could save countless lives[1,3]. In modern society, while research is being done to cure heart disease, there are aspects of the cardiovascular system that go largely untouched. Blood viscosity is a crucial part of atherosclerosis formation and process[6].

Through deep research into how blood viscosity affects atherosclerosis, as well as other new factors of atherosclerosis, we can uncover major findings[8]. Areas of research other than blood viscosity include how the immune system plays a substantial role in atherosclerosis[3,4]. From endothelial dysfunction to intermediate lesion, the immune system, in an effort to bring the body back to homeostasis, actually worsens the condition[3]. Macrophages, in an effort to remove the increasing amount of LDL cholesterol in the body, consume substantial amounts of LDL, which then turns them into foam cells that build the lipid plaques on artery walls[5,11]. Other examples include how T-cells prohibit the production of collagen, which is required for plaques to be stable and relatively safe[4,13], and how neutrophils eat away at those fibrous caps, which further worsens the condition and expedites plaque rupture[3].

Blood viscosity is an untouched horizon of possibility. It can be used to predict where and when atherosclerotic plaques will rupture[6,8]. By using information such as laminar and tubular flow, we can correctly deduce the most probable location for plaque rupture as well as the imminence of the plaque rupture[3,6]. With this information combined with our other methods for understanding atherosclerosis, we can collectively combine our information to save millions of lives[5,18].

In addition, to combat the egregious prices of modern-day healthcare equipment, the smart Ostwald viscometer brings a new revolutionary weapon to rural clinics and emergency centers across the world[6]. Healthcare is not a privilege, and through this tool, we can aid hospitals and clinics which are not able to afford standard viscometer technologies[6]. Not only that, but we can also help people individually by letting them examine their own bodies. This can alert those in imminent danger and stop disaster before it strikes[6].

Viscosity provides such a powerful weapon in the battle against heart disease[6,8]. On a general view, blood viscosity can communicate how predisposed someone is to the perpetuation of atherosclerosis[6]. A scientific explanation: dangerously high blood viscosity shows that when blood flows, it will drag on the endothelium. This, in turn, causes the endothelium to slowly be damaged and allows more cholesterol and lipids to seep into the artery walls[3].

Going beyond the boundaries for atherosclerosis, low blood viscosity can unveil underlying issues such as anemia[6]. In addition, understanding blood viscosity correlates with understanding LDL and HDL cholesterol levels in the body[7,11]. High viscosity reveals an increased number of inflammatory cells[5]. This means that through the higher inflation, more macrophages are called, which in turn further expedites the inflammatory process of atherosclerosis[3]. Vice versa, high viscosity levels indicate an absence of HDL cholesterol since HDL cholesterol stops the oxidation of LDL and overall reduces blood inflammation[13]. High viscosity levels can reveal that HDL cholesterol levels may be low[13].

Other than LDL levels, high blood viscosity generally states high stress on the endothelium[6]. In addition, thick, slow-moving blood can inhibit platelet movement. This causes an increase in the amount of LDL that oxidizes[3]. Therefore, we can use blood viscosity to predict plaques and plaque rupture of atherosclerosis[6,8].

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About the Student:

Ahroosh Vydyula is a sophomore at Carrollwood Day School. His research interests include biology, chemistry, and the study of cardiovascular disease.

About the Mentor:

Prof. Rajagopal Appavu is a dedicated mentor at Research Rising Stars, guiding students in STEM, biomedical research, artificial intelligence, scientific writing, and publication.

Peer-Review Decision: Unanimously Approved
Reviewer 1: ✅ Approved
Reviewer 2: ✅ Approved
Reviewer 3: ✅ Approved
Final Status: Approved by all three peer reviewers.