Preventing Inflammation and Cardiovascular Diseases

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How Food Polar Lipids Can Reduce Inflammation

By

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Cambridge Scholars Publishing

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Life is a sailing journey: to arrive to interesting ports and eventually to the final destination, a skipper needs a compass and bright stars, not GPS. On the journey to my own Ithaca, I am grateful to Nathaniel and Thiseas (my two brightest stars in the sky) and to Breda (my compass for life).

Love always,
Ioannis

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Over the past few years, I was blessed to work with two special scientists and friends: Alexandros and Ronan. Together, we shaped a new approach towards inflammation and the development of Cardiovascular Diseases. Together, we wrote a number of scientific publications and two books on this topic. They were the inspiration for this book.

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This book wouldn’t have become a book without the support and help of all the people in Cambridge Scholars Publishing, particularly Alison Duffy, Sophie Edminson and Amanda Millar.

PREFACE

The reason for writing this book is to propose a different approach to Cardiovascular Diseases (CVD) and the underlying causes for these diseases.

Today, the most dangerous and on-going pandemic is not COVID-19 but CVD that are responsible for the death of 17.9 millions of people every year, worldwide.

This number is increasing at an alarming rate. Surely, our approach against CVD is flawed.

But what is the problem?

What could we do better to stop this increasing trend?

Can statins (the medication that reduces the levels of cholesterol in our body) be the solution?

These questions were the moving force towards writing this book.

With this book, I hope you will find some answers to these questions.

Statins are not the answer. If they were the answer, then, the number of people dying of CVD would decrease.

Therefore, a different philosophy towards the causation of CVD is needed; this is what inspired me to write this book.

The role of inflammation is described in this book; how foods rich in polar lipids can decrease inflammation and hence the onset of CVD.

In our battle against these diseases, medication is not the answer. But, our diets and lifestyle choices can help us in the fight against CVD.

In this book, I left out all the scientific jargon and I present my views on personalised diet and lifestyle choices in order to reduce inflammation. Key factors here are the foods rich in anti-inflammatory nutrients, such as polar lipids.

This book will have succeeded its purpose if it makes you view CVD through an alternative prism. Each one of us is different and hence we need to approach the cause of CVD (inflammation) in an individual way. The horizontal approach of using statins is not the solution. But, the solution is to adopt lifestyle choices, such as diet and exercise, that suit our daily routine and therefore, it will be easier for us to adopt and keep them for life.

The number of people dying of CVD can't be reduced overnight. At a personal level, we need to modify our way of living. But also, the governments and the nutrition bodies need to create novel policies that will reduce the influence of giant food corporations on consumers by preventing them from promoting unhealthy foods.

Our battle against CVD should be multidimensional; this is the message of this book.

I hope you will find this book a useful tool towards a healthy and prolonged life, without medications.

INTRODUCTION

In our bodies, there are several dynamic balances in a plethora of biochemical reactions. These delicate balances can be summarised as in Figure 1. In a group of people who follow similar patterns of diet and have analogous exposure to various external factors (such as environmental factors), some suffer ill-health, but others do not. So, this leads us to the question: *what are the underlying causes of cardiovascular diseases (CVD)?*

Is there any genetic information in our DNA (i.e., nature) that protects us from falling ill or is it an effect of exposure to disease promoting factorslifestyle(i.e., nurture)? The balance between health and disease is mainly controlled by inflammation. Usually, the balance shifts towards the "health" state; however, under the influence of various risk factors, the balance could be redirected towards the "disease" state.

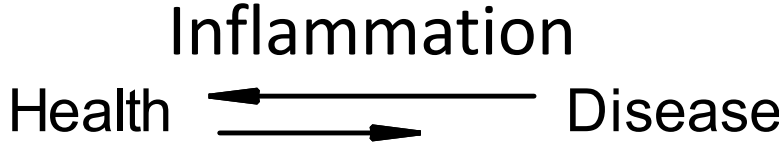

Figure 1: the dynamic balance in our bodies between the states of health and disease

The approach that I advocate is that we view diseases as complex biological processes that are triggered by external factors and various underlying biochemical and cellular processes. These processes can be induced either endogenously or exogenously, either alone or in different

combinations, and may result in cellular dysfunction, damage, or cell death at a cellular level. In the case of *prolonged* cellular dysfunction, tissues and organs may be affected resulting in an array of symptoms depending on the specific type of cellular, tissue, or organ dysfunction that occurs.

However, when patients present with clinical symptoms of a chronic disease such as CVD, underlying disorders at the cellular or even tissue level (e.g., endothelial dysfunction and formation of atherosclerotic plaques) are sometimes *not clinically observed* until *many* years *after* the initial pathological processes have been triggered and progress undetected. Physicians generally view symptoms as an *end-result* for diagnostic purposes. However, should the symptoms materialise due to a process initiated *many years* before clinical observation, then these individuals would not be aware of their developing condition and thus would be unable to prevent the manifestation of their condition. In some cases, individuals, who are free of lifestyles or risk factors associated with a disease, can often develop a disease due to genetic and environmental factors unknown to themselves (e.g. air pollution).

The number one killer disease or rather group of diseases today is CVD. The World Health Organization (WHO) has estimated that one in three global deaths are because of CVD related events such as myocardial infarction (MI) and stroke. Today, there are approximately 17.9 million global deaths annually due to CVD related events. According to Ireland's Health Service Executive (HSE), approximately 10,000 Irish people die each year due to CVD, including coronary heart disease (CHD), stroke, and other circulatory diseases. CVD account for 36 % of all adult deaths, surpassing cancer, and respiratory diseases as Ireland's leading cause of death. Of those who die from CVD, 22 % are premature deaths (under 65 years old), with the majority of these deaths being related to CHD (5,000). In the UK, CVD cause more than a quarter (27 %) of all deaths, or around 155,000 deaths each year - an average of 425 people each day. According to the American Heart Association, a similar worldwide trend exists; CVD globally account for more than 17.9 million deaths per year, a number that is expected to rise to more than 23.6 million by 2030. In the US, 92,1 million American adults are living with some form of cardiovascular

disorder or after-effects of stroke costing over $316 billion per annum accounting for both direct and indirect costs.

Clearly, the development of CVD is a major global concern, and for several reasons, the balance of Figure 1 has been tipped towards the disease state for an increasing number of people. Considering that CVD are a significant challenge for the healthcare systems around the world and thus a major economic burden, there is a greater need to discover *new ways to tackle* CVD.

In this book, I focus on the role of inflammation on developing CVD and the role of *diet and lifestyle choices* in preventing the onset of CVD. This is because, I believe that *prevention is key* in reducing global mortality due to CVD. Therefore, it is important to separate the underlying *causes and processes* of disease (i.e., inflammation and inflammatory biomarkers) from the *symptoms* of the disease. Focusing on atherosclerosis and the corresponding onset of CVD, it is of vital importance to distinguish the underlying causes of the disease from the formation, progression and expansion of plaque in the walls of coronary arteries that occurs over a period of several decades *before* clinical symptoms appear.

People with subclinical atherosclerosis are free of symptoms throughout most of their life, however often we forget that to have a disease the patient *does* not *necessarily* have to exhibit the symptoms. In westernised and developing societies, where the global burden of CVD is most prevalent, people seem to be diagnosed with CVD in their 50s unaware of the *biochemical time bomb within*.

Since the Seven Countries Study (SCS), dietary cholesterol and the levels of serum cholesterol in relation to the development of chronic diseases have been somewhat demonised. However, the principles of the Mediterranean diet and relevant data linked to the examples of people living in the five blue zones in the world demonstrate that *the key to longevity* and the *prevention of chronic disease development* is not the reduction of dietary or serum cholesterol but *the control of systemic chronic inflammation*.

In this book, I present all the relevant data that support the view that it is the inflammation induced by several factors that leads to the onset of CVD *rather than* serum cholesterol. The key to reducing the incidence of CVD is to control the activities of key inflammatory mediators via diet, exercise, and healthy lifestyle choices.

The demonisation of cholesterol led to the design of statins, i.e., drugs that block completely the biosynthesis of cholesterol in our bodies. However, cholesterol is an essential biomolecule for the normal function of all our cells. Thus, we would need to consider: how much do we need to lower the levels of cholesterol? Given the fact that cholesterol plays a crucial role in several of our cellular and tissue mechanisms, it is not surprising that there are several consequences due to the aggressive reduction of cholesterol levels in the body. This has been common practice over the last few decades. Today, we can say for sure that statins do *not* lower the cardiovascular risk (CR) but also that they are the cause of the onset of a number of side effects after chronic use.

Since the COVID-19 pandemic, it became apparent that the virus causes another type of inflammation, *acute inflammation.* This acute inflammation when it takes place in humans with chronic inflammation leads to more severe clinical symptoms and higher mortality. Thus, this is one more reason why we would need to re-address acute and chronic inflammation under a new prism.

The view that I advocate in this book is this: diet and lifestyle are valuable preventative tools against inflammation and CVD and they need to be considered as *a lifelong target* and not just a middle-aged response to a debilitating disease. Our commitment to following a healthy diet and lifestyle in combination with moderate exercise is integral to minimising our risk of developing CVD. We believe that personalised nutrition should be regarded as a lifestyle parameter and a powerful and important biochemical tool for preventing chronic diseases such as CVD. In this book, we are going to explore all the biochemical processes that lead to acute and chronic inflammation and hence the onset of CVD. Having understood these processes, the missing link between CVD, diet and

lifestyle will be explained with the view to combating CVD via diet and lifestyle choices *rather than* medicines.

Selected references for further reading

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CHAPTER 1

THE ROLE OF INFLAMMATION TOWARDS CVD

1.1 The Seven countries study and the Mediterranean diet

The story begins in the mid-50's when Ancel Keys (1904-2004) a physiologist in Minnesota, conceived the idea to study the diet and the lifestyle of populations in seven countries in the World in an attempt to link dietary habits to the causes of cardiac heart disease (CHD) and vascular diseases. This is how the Seven Countries Study (SCS) began and it took place from 1958 to 2000. The SCS was the first major study to correlate diet, lifestyle and other risk factors to what collectively today we call Cardiovascular Diseases (CVD). The seven countries that were chosen were: US, Finland, Netherlands, (former) Yugoslavia, Italy, Greece and Japan. The researchers measured the levels of serum cholesterol and the percentage of incidence of CHD in all seven populations and they tried to find some correlations between these two parameters. Their whole working hypothesis was based on the fact that cholesterol is the cause of CHD. But is this the case?

Kromhout reported that at a serum cholesterol level of 200 mg/dL, the 25-year cardiovascular mortality rate was five times higher in the Northern European populations of the SCS compared to the Southern Mediterranean populations, and thus the relations between diet, serum cholesterol, and cardiovascular mortality are more complex than originally thought. This is because it is not only dietary cholesterol that is involved, but other lipids

and antioxidants may play a role in the onset and prevention of atherosclerosis.

So, the first paradox starts here: there was *no clear association* between serum cholesterol and cardiovascular mortality in all seven countries. While, a linear relationship between the levels of serum cholesterol and CHD could be observed for the US, Netherlands and Finland, there was no such correlation in populations in Yugoslavia, Italy, Greece and Japan (figure 1.1).

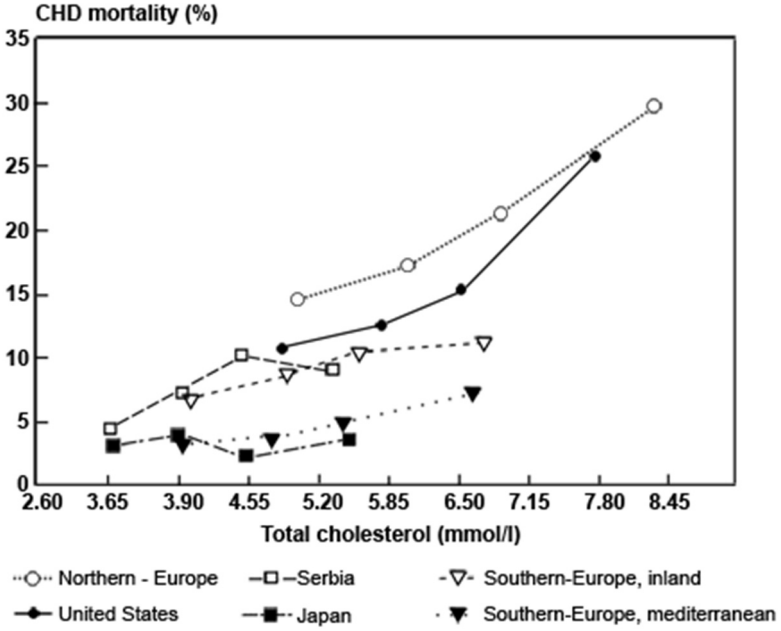

Figure 1.1: the correlation between total serum cholesterol and CHD mortality in the SCS: source https://www.sevencountriesstudy.com/serum-cholesterol-and-coronary-heart-disease/figure-1-small/

So, why did we demonize cholesterol? The answer to this question is not straightforward. However, we would need to remember that if cholesterol is the route cause of CVD, then the same linear correlation for all seven

populations in the SCS would be observed. This topic is further discussed in the second part of this chapter.

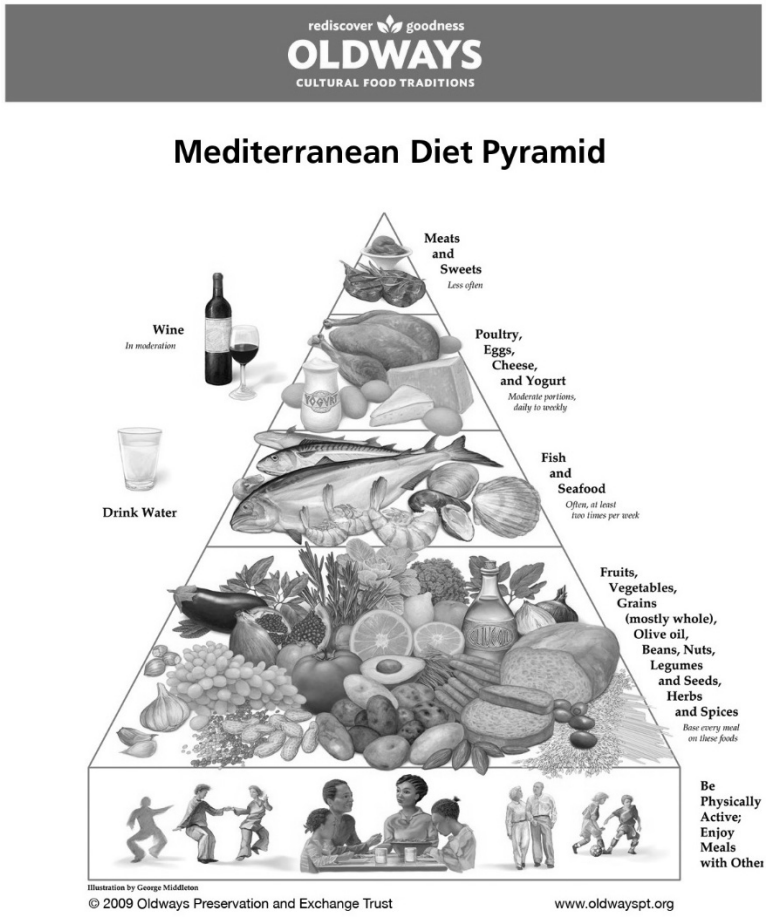

Figure 1.2: The Med-diet pyramid. Source: https://oldwayspt.org/resources/oldways-mediterranean-diet-pyramid

Today, we know that the low prevalence of cardiovascular mortality in the Mediterranean cohorts of the SCS is attributed to their lifestyle and especially to their dietary habits, namely the traditional Mediterranean diet (Med-diet) (figure 1.2.). A common feature of the diet amongst

populations in the Mediterranean is a relatively high dietary intake of vegetables, fruits, legumes, whole grains, monounsaturated fats, and nuts, followed by moderate consumption of fish, dairy products (mainly cheese and yogurt), alcohol, and low consumption of red and processed meats.

1.2 The role of cholesterol

On a personal note, a friend of mine few years ago (Joe, not his real name) had some chest pains and he visited his GP. After the tests were done, the levels of serum cholesterol were deemed high by his GP and the doctor prescribed Joe statins. Two years after this, Joe developed diabetes type II. Now Joe is taking statins for his cholesterol levels but also medication for his diabetes. Why did this happen? What should have happened instead? This personal story was the catalyst for me to embark on studying the underlying causes of CVD and how statins and reducing serum cholesterol *cannot be* a part of the solution.

As discussed before, we have demonized cholesterol and this demonisation has led to the creation of statins. Statins, in lay terms, are medications that block completely the biosynthesis of cholesterol in our body. In fact, statins cause our bodies to be starved of cholesterol!

However, *cholesterol is an essential lipid* in our body that interacts with the phospholipid bilayers in the cell membrane and it increases membrane packing. The role of cholesterol in membrane fluidity and integrity is vital. Also, cholesterol takes part in signal transduction, intracellular transport, nerve conduction and in a number of signalling pathways. Apart from these roles, cholesterol is an important precursor molecule in several biochemical pathways, such as the biosynthesis of vitamin D and steroid hormones, e.g., adrenal gland hormones and sex hormones.

Cholesterol ($C_{27}H_{46}O$) is a non-water-soluble steroid and hence it can't reach the blood stream. In our body, hepatocytes synthesise more than 20% of cholesterol and release it endogenously into the blood while the intestines produce significant amounts which is excreted exogenously into the bowel. The rate of endogenesis is controlled by the available quantity of cholesterol in cell membranes through a complicated process of

constant cellular feedback. Therefore, by controlling the activity of the HMG-CoA (3-hydroxy-3-methylglurary-co-enzyme A) reductase enzyme (i.e., which is the rate limiting enzyme in the biosynthesis of cholesterol in our body) can alter the levels of cholesterol in the body. Once cholesterol is produced, along with triglycerides, it is transported around the body with the help of lipoprotein molecules that render the hydrophobic cholesterol to hydrophilic molecules. These molecules are summarised in table 1.1, where they are categorised by density and they help solubilize hydrophobic lipids (e.g., cholesterol) in our water-based blood, while also containing cell-targeting signals.

When we address cholesterol, we need to remember that cholesterol is an essential lipid that helps maintain the structural integrity and fluidity of cell membranes in a number of varying physiological conditions. Cholesterol interacts with phospholipid fatty acid chains in the cell membrane and it increases membrane packing, which in turn alters the fluidity of the membrane and helps the membrane to maintain its integrity. The resulting fluid nature of the cell membranes in our body allows our cells to change shape and move. Also, from the cellular function point of view, cholesterol takes part in signal transduction, intracellular transport and nerve conduction. When we deplete cellular cholesterol, we practically disrupt cell signaling. Cholesterol and phospholipids act as an electrical insulator and help in nerve conduction. Finally, cholesterol serves as a precursor in biochemical pathways such as the synthesis of vitamin D and all steroid hormones (i.e., adrenal gland hormones and sex hormones). For all these reasons, the role of cholesterol is enormous and disrupting the biosynthesis of cholesterol (i.e., when using statins) has severe implications, as discussed further in chapter 3.

Table 1.1: Lipoprotein particles.

Lipoprotein particles	Major Core Lipids	Function in the body
Chylomicrons (ultra low-density lipoprotein – ULDL)	Dietary triacylglycerols	Transporting triglycerides and cholesterol from the liver to sited of usage throughout the body via blood
Very low density lipoproteins (VLDL)		Transporting triglycerides and cholesterol from the liver to sites of usage throughout the body via blood
Intermediate low-density lipoproteins (IDL)		
Low-density lipoprotein (LDL)		
High-density lipoprotein (HDL)		Mediates severe cholesterol transport where excess serum cholesterol is removed from the blood