International Journal of Innovation and Applied Studies
ISSN 2028-9324 Vol. 4 No. 3 Nov. 2013, pp. 512-523

http://www.issr-journals.org/ijias/

Insights on cholesterol nutrition: shift to a new paradigm for better cardiovascular health

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ABSTRACT: Cholesterol is an extremely important biological molecule involved in a multitude of biological processes regarded as vital for our survival. Yet, the function that has attracted more attention is its contribution to the development of atherosclerosis, a chronic inflammatory disease of blood vessels, which constitutes an underlying cause of coronary heart disease. Atherosclerosis is the principal cause of myocardial and cerebral infarction and remains the chief cause of death across many parts of the globe. Shockingly, despite its extreme physiological importance, cholesterol remains the most controversial nutrient ever. Misconception continues to exist not only among the people lacking knowledge in nutrition, but also among many nutrition researchers. The misconceptions surrounding cholesterol have been so pronounced and persistent that its beneficial effects are hardly heard of. Pharmaceutical companies are using this mass (cholesterolphobia) to flourish their business. However, recent studies demonstrate that cholesterol plays a minor role in cardiovascular disease. The objectives of this article are twofold. Firstly we review research articles to analyze the existing ideas regarding the link between heart diseases and cholesterol. Then we provide an up-to-date information about some health impacts of cholesterol and highlight the effects of anti-cholesterol drugs based on the researches performed to date.

KEYWORDS: Cholesterol, Cardiovascular disease, Atherosclerosis, Inflammation, Anti-cholesterol drugs.

1 INTRODUCTION

Cholesterol ($C_{27}H_{45}OH$) is an extremely important biological molecule that plays major roles in membrane structure and serves as the sole precursor for the synthesis of the steroid hormones and bile acids. Cholesterol is a type of sterol, a class of lipid molecules, waxy substance found in all parts of the body. Body gets cholesterol from two different sources, dietary and from synthesis in liver. Biosynthesis in the liver accounts for approximately 75% of the amount produced each day [29]. Both dietary cholesterol and that synthesized de novo are transported to the target cells to be used in the manufacture of hormones and cell membranes through the circulation in lipoprotein particles known as LDLs and HDLs. A low level of LDLs and high level of HDLs are believed to lower the risk of heart disease. In general, healthy adults synthesize cholesterol at a

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rate of about 100mg/day and consume approximately 300mg/day and blood maintains a relatively constant level of cholesterol of 150–200 mg/dL primarily by controlling the level of de novo synthesis [1]. The greatest proportion of cholesterol is used in bile acid synthesis. The medical establishment commonly incriminates cholesterol for everything from all types of cardiovascular diseases (CVD) disease to neurodegenerative diseases such as Alzheimer's. But recent epidemiological and clinical studies show that high cholesterol level is not the main cause of CHD. On the contrary it has proved to be beneficial in the normal regulation of many biological pathways. For example cholesterol is indispensable in the brain for its significant role in the process of memory formation and optimal functioning of neurotransmitters. Though cholesterol has involvement to the development of arthrosclerosis, many cardiologists now beginning to believe that it's a minor contributor to CHD and the most deleterious cause is actually inflammation. Inflammation is body's innate immune response to injuries resulting from infection and/or other physical injuries. Various kinds of anti-cholesterol drugs are presently available on the market. But it appears that doctors are prescribing such drugs before their safety measures are tested on all target population. Drug companies are more mindful in disseminating their products and hiding many side effects that occur on long-term use of these drugs. Thus it appears that by avoiding cholesterol in diet and by taking medication to keep blood-cholesterol level low, people are engendering greater health hazards. We need to avoid the misconceptions about this vital nutrient and have to maintain proper dieting that is conducive to cardiovascular health.

2 CHOLESTEROL AND CARDIOVASCULAR DISEASE

It's been few decades now since the executive board of the World Health Organization declared coronary heart disease as 'Mankind's greatest epidemic'[33]. Still today cardiovascular disease (CVD) is responsible for approximately one-third of deaths worldwide [34]. Cholesterol has historically been incriminated as an accomplice of all types of cardiovascular diseases. According to a recent WHO report, high blood-cholesterol is estimated to cause 18% of global cerebrovascular disease and 56% of global ischaemic heart disease. Together this amounts to about 4.4 million deaths (7.9% of total) and 40.4 million DALYs (2.8% of total) [36]. It was after the research by a mid-nineteenth century German pathologist Rudolph Carl Virchow (13/10/1821 – 5/9/1902) when cholesterol entered the picture, who first theorized that high blood-cholesterol level leads to the formation of plaques in arterial walls. Since then the link between cholesterol and heart disease has been a very popular venue for many medical studies. Almost a hundred researches and studies have been conducted just to find out how cholesterol's contributes to heart diseases. To date, the most widely accepted underlying pathology of most clinical manifestations of CHD is atherosclerosis. However, whether or not cholesterol contributes to atherosclerosis has always remained controversial [53]. A group of researchers at the Saint Louis University School of Medicine once hypothesized that cholesterol contributes to atherosclerosis by suppressing the activity of a key protein that protects the heart and blood vessels. Some other studies revealed that excess cellular cholesterol induces apoptosis in macrophages, an event likely to induce the development of atherosclerosis. Development of atherosclerosis is associated with the induction of the endoplasmic reticulum stress pathway known as the unfolded protein response (UPR) [31]. It was subsequently proposed that cholesterol channeling to endoplasmic reticulum membranes, resulting in activation of the CHOP (A stress-inducible nuclear protein, also called GADD153) arm of the UPR, is the key signaling step in cholesterol-induced apoptosis in macrophages, which by a certain way influences formation of plaques [32]. However, many epidemiological surveys indicated that the majority of CHD events occur in people who show moderate or low blood cholesterol levels. High levels of blood-cholesterol have consistently been shown to be associated with coronary heart disease risk [41]-[45], [55]. On the other hand, low levels of blood-cholesterol have shown to be associated with marked increase in mortality in advanced heart failure [40], [54]. Lowering blood-cholesterol levels reduced rate of death from coronary disease related causes in both who had coronary complications as well as in those who didn't have [46]- [51]. Thus the relationship between cholesterol and heart failure remains clouded till today. However, in the light of some recent and more comprehensive studies, which focused more on the activity of cholesterol carriers(LDLs and HDLs) rather than cholesterol itself, researcher are slowly coming to accord with the fact that cholesterol itself has no particular link to the development of CVD whatsoever. It is worthy of mentioning that, in all likelihood, the mystery roots not in cholesterol, but somewhere else. The exterior of LDL molecule is made up mainly of lipoproteins and cholesterol. When it becomes deficient in cholesterol, the fatty part in the lipoprotein become more vulnerable to attack by oxygen and also the protein (apoB) part becomes vulnerable to attack by blood sugars, especially glucose and fructose. During a state of increased blood-sugar, more and more sugar molecules get stuck to the protein part which results in relatively less efficient LDL particles as they fail to transport the contents to target cells. Consequently they begin to travel longer in the bloodstream resulting thus evident that blood cholesterol/LDL/HDL level alone is a relatively poor determinant of individual CHD risk. Furthermore, now we know that there are at least five different types of LDL and HDL particles and there is growing evidence that only the small LDL particles are able to squeeze through the artery linings and can do potentials harm when oxidized(turning rancid). There is a natural tendency among many researchers to highlight the most positive findings in their study, particularly where commercial sponsorship is involved. The fact of the matter is that, since there are sufficient evidences both qualifying and rejecting cholesterol to be a

genuine contributor to CVD, it provokes a need for more pragmatic clinical trials based on more personalized treatment rather than randomized trials which involves homogenized sample population. Moreover, risk factors are capable of greatly altering the profile of CVD events in different individuals. *Hence, it is assumable that cholesterol screening is unlikely to reduce mortality and can be misleading or even harmful.*

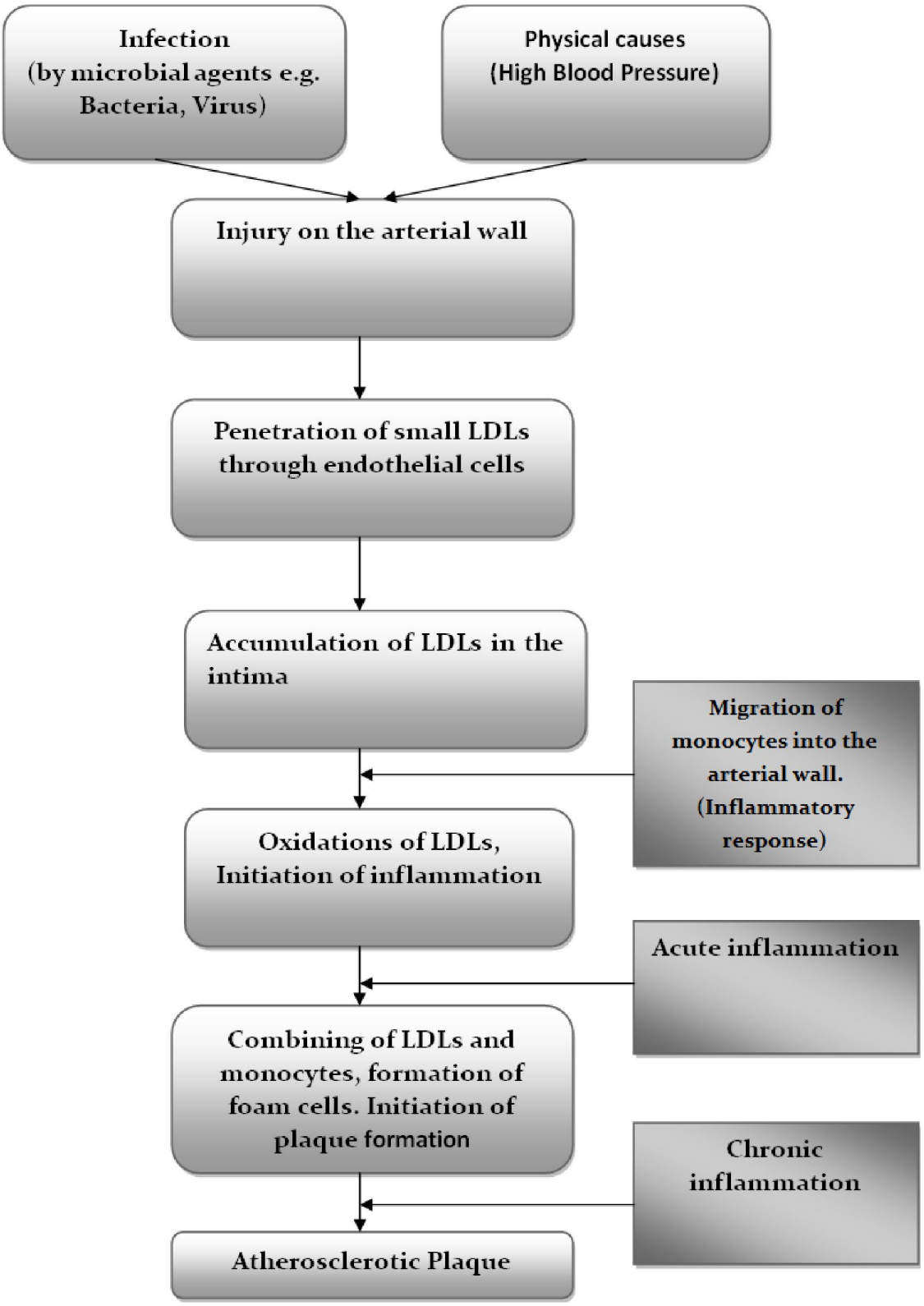

Fig. 1. Steps of the development of atherosclerosis

3 NEUROLOGICAL IMPLICATIONS OF CHOLESTEROL

Cholesterol is an extremely important molecule for maintaining a healthy brain where it functions as an antioxidant, as a structural scaffold for the neural network and a functional component of all membranes. Scientists in the early 19th century regarded it as 'a principal element' for the nervous system [83]. The central nervous system accounts for only 2% of the whole body mass but contains almost a quarter of the unesterified cholesterol present in the whole body [20]. Around 95% of the cholesterol content in the brain can be accounted for by de novo synthesis ([92], [93]). The cerebral production appears to be relatively constant, although the hepatic metabolism varies with age. Cholesterol helps in the formation of memory and vital for neurological function. The brain's dry weight is 60% fat and cholesterol plays a vital role in neuron signaling and brain structure. Brain signaling is all about membranes, and cell membranes contain a good amount of cholesterol. Cholesterol is required for myelination, dendrite differentiation, and synaptic activity. It has been estimated that up to 70% of the brain cholesterol is associated with myelin. The brain has an independent and isolated pool of cholesterol which reflects a high need for constancy in the cholesterol content of membrane and myelin. Patients with defected 7-dehydrocholesterol-7-reductase in the brain show mental retardation, most likely caused by a deficiency in myelin function [84]- [85]. The blood-brain barrier effectively prevents it from exchange with cholesterol in the circulation [86]- [88]. Brain Cholesterol homeostasis is regulated through *de novo* synthesis by the action of 24S-hydroxycholesterol, most of which are found in brain [89]. Some researchers showed that Oxysterol, an oxidized form of cholesterol, is necessary for the formation of dopamine-producing neurons during brain development. The process requires the activation of a specific receptor in the brain which is mediated by Oxysterol. Cholesterol is also known be an important chemical in dopamine transporter function [90]. Disturbances in central nervous system cholesterol homeostasis are implicated in neurodegenerative disorders, including Alzheimer and Huntington diseases [84]. Recent results indicate that both cholesterol synthesis and degradation are active in the adult brain as well and that alteration in these mechanisms profoundly effects higher-order brain functions [91]. Some studies found that individuals with type 2 diabetes (who tend to run raised blood sugar levels) have a 2- to 5-fold enhanced risk of Alzheimer's disease (AD) due to impaired cholesterol availability to the brain [94]. Brain cholesterol homeostasis misregulation causes the key AD feature of learning and memory failure as a result of the impairment of neuronal function, neurotransmission and synaptic plasticity [22]. The normal functioning of serotonin in the brain is profoundly influenced by the availability of cholesterol in the central nervous system [17-19]. Though brain appears to be independent in its own cholesterol supply, several epidemiological and clinical studies have demonstrated that low serum cholesterol reflects reduced cholesterol content in the brain, specifically in brain cell membranes which affect the serotonergic system, due to the lowering of the lipid microviscosity of the brain cell membranes [10]. Cholesterol and the omega-3 fatty acids are two most important molecules for normal synaptic transmission. Depleting cholesterol impairs the function of the serotonin 1A receptor and the serotonin 7 receptor, and reduces the ability of the membrane serotonin transporter. Reduction of serotonergic function profoundly affects brains natural performance and causes severe mood disorders, mixed-anxiety and depression. Low serum cholesterol has been linked in numerous scientific papers to suicide, accidents, impulsive acts, hostility, aggression and violence [2]-[11].

4 ROLE OF IMMUNITY AND INFLAMMATION IN ATHEROSCLEROSIS

Cholesterol is vital for immune function. It is a precursor to vitamin D which is essential for immune system function. It is also a precursor to corticosteroids, hormones that support immune system by protecting the body against stress. Many researchers have suggested that the blood lipids play a key role in the immune defense system [68]-[73]. Immune system plays an important role in the development, progression, and the complications associated with atherosclerosis [75]. High cholesterol is believed to be protective against infections and atherosclerosis [77]. Apparently, microorganisms play a role in cardiovascular disease. A large number of studies have reported on the associations between of coronary heart disease and various bacterial and viral agents and clarified the role of chronic infection and inflammation in CHD. Some studies have mentioned that during the weeks preceding an acute cardiovascular attack many patients have had a bacterial or viral infection [78]. They may be one of the factors that start the process by injuring the arterial endothelium. A secondary role may be inferred from the association between acute cardiovascular disease and infection. Infectious disease causes deleterious effects on blood clotting with sludgy blood flow which promotes vascular occlusion. During infections an inflammatory infectious reaction may be occurring in the arteries. Inflammation is a natural protective response intended to eliminate the initial cause of cell injury and thus it is intimately associated with the repair process which include clogging of the injured area, regeneration of tissues and scarring. But chronic inflammation is associated with the risk of excessive plaque formations and subsequent coronary complications. Evidence of bacterial and viral infections in the walls of arteries have been found by electron microscopy and immunoflourescence microscopy in many patients [80]. Infection is caused by a bacterium, virus or fungus, while inflammation is the body's response to it and a part of body's innate immunity. A medical

team in Germany found that the strongest predictor for death in a patient with heart failure was the concentration of cytokines type of hormones secreted from white blood cells in response to inflammatory process in the body [79].

5 IN SEARCH OF THE REAL CULPRIT

The most apparent link between CVD and cholesterol is atherosclerosis. Atherosclerosis, sometimes called hardening of the arteries, which is a condition that causes the arteries of the heart and other tissues to become hardened and narrowed, preventing normal flow of blood and increasing the risk of heart attack. In Greek the term 'Arthero' means the building up of fatty gunk in arterial walls which is also known as plaques and 'sclerosis' means hardening or thickening. Generally it takes years to for atherosclerotic plaques to become bulky enough to hinder normal flow of blood. When there is damage to the arterial wall initiated by certain causes, small LDLs penetrate the endothelium and begin to accumulate in the intima (the innermost layer of arterial wall). In the intima the LDLs gets oxidized which is harmful for health and causes inflammation. In response to this inflammation liver begins to release more cholesterol in the blood stream. Problem arises if inflammation is prolonged which causes more cellular damage and liver starts to send out more cholesterol to take part in tissue repairing process. Were there no inflammatory damage, no extra cholesterol would have released in bloodstream by liver. Thus a rise in blood-cholesterol level indicates the occurrence of an inflammation. Thus, raised blood-cholesterol actually serves as a symptom of the underlying problems. Atherosclerosis, which manifests itself as acute coronary syndrome, stroke, and peripheral arterial diseases, is a chronic inflammatory disease of the arterial wall [62], [76]. The atherosclerotic plaque is characterized by an accumulation of lipids in the artery wall, together with infiltration of immunocytes [81]. The defense of the normal artery depends on innate immuneresponses of endothelial cells and, which after an inflammatory signal, by macrophages and other cells of the immune response that are recruited to the artery wall. Such innate immune responses also have a major role in the initiation of atherosclerosis [82]. Cholesterol is body's natural response to inflammations. Therefore it is INFLAMMATION, which is the real culprit behind heart disease, while we've been obsessed with cholesterol for around a century. Inflammation is triggered when innate immune cells detect infection or tissue injury. Chronic inflammation as measured by high sensitivity C-reactive protein which predicts future risk of acute coronary syndrome independent of traditional cardiovascular risk factors. *Inflammation*, not high *cholesterol*, is the primary cause of heart disease. Harvard researchers have discovered that a high blood level of C-reactive protein, a marker of inflammation, is more predictive of heart disease than cholesterol. More recent studies claim that stem cells also play a certain role of in the development of Atherosclerosis, which are able to produce various types of cells including adipocytes and osteocytes. So the deal is to avoid foods that causes inflammation (e.g. trans-fat, omega-6, refined sugar rich food) rather than cholesterol-rich foods(e.g. egg, butter, red meat, organ meat). The typical American, however, consumes 15 times more Omega 6 fats than Omega 3s. This imbalance creates the path for increased inflammation and accounts for the high morbidity and mortality from CHD.

6 FACTS ABOUT ANTI-CHOLESTEROL DRUGS AND PHARMACEUTICAL COMPANIES

With anti-cholesterol drugs begins the second chapter of cholesterol-cardiovascular tragedy. Nowadays there are around hundreds of different types of anti-cholesterol drugs on the market. Statins and Lipitors are regarded as some of the greatest triumphs of modern medicine. Statins are potent cholesterol-lowering drugs and claiming them very effective in the prevention of coronary heart disease. It's no surprise that Statins constitute one of the most important sectors of the pharmaceutical industry, with total revenues exceeding $25 billion in 2009. There's no question about their efficacy in lowering cholesterol. Yet there remains something to ask- *does lowering cholesterol actually benefit patients with coronary artery disease*? These drugs have a range of well-documented negative effects. The evidence of the adverse effects of statins in the treatment of stable coronary heart disease continues to grow. Besides that, Statin treatment has found to be effective only when the initial LDL level is high. Large-scale, randomized, secondary-prevention trials involving patients with CHD have shown that statins reduce the clinical consequences of atherosclerosis, including death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina pectoris and heart failure, as well as the need for coronary revascularization. But almost all of those studies were short lived, and/or weren't carried out for long enough to observe the long-term effects. Statin therapy is associated with excess risk of developing diabetes mellitus [39]. Besides that, cholesterol-lowering drugs are also lipid-lowering drugs which cause myopathy, even rhabdomyolysis. Few Studies have also shown that Statin drugs exert their anti-cholesterol properties by inhibiting the function of HMG coenzyme-A reductase(3-hydroxy-3-methylglutaryl-coenzyme A), which catalyses an early step in the biosynthesis of cholesterol. This step also generates few other vital biological substances (for example Coenzyme Q10, also known as CoQ10) that are required for normal functioning of cells. CoQ10 is a fat-soluble antioxidant present in almost all cell membranes, required for the proper functioning of Vitamin E. It is also an essential component of the mitochondria. CoQ10 is known to prevent arteriosclerosis by reducing the accumulation of oxidized fats in blood vessels. Several studies revealed that the function of the heart may be

improved after major heart surgeries if CoQ10 is given to patients before or during surgery [38]. It is even found to be necessary for brain functioning. Statin drugs inhibit not only cholesterol biosynthesis, but also that of CoQ10, as they are synthesized from the same precursor (mevalonate). The loss of CoQ10 leads to loss of cell energy and increased free radicals which in turn can damage mitochondrial DNA and sets the way for farther cellular damages. Gradual depletion of CoQ10 causes fatigue, muscle weakness and soreness, and eventually heart failure. Thus while lowering blood-cholesterol; Statins also decrease energy supply to nerves, muscle and heart by lowering CoQ10. However, anyone who has no choice but taking statin must also consume sufficient CoQ10 supplements to avoid the consequences of depletion of CoQ10. Another important substance whose synthesis is blocked by Statin is Dolichol, which plays a crucial role in the endoplasmic reticulum.

Table 1. Most widely used Anti-cholesterol drugs

Active ingredient	Example	Efficacy (percent)	Potential Side Effects	Mode of action
Statins	Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin.	Lower LDL-C by 30-50%, triglycerides by 20-40% Raises HDL-C by 10%	Rhabdomolysis, Insomnia, Headache, GI problems, Memory loss, mental confusion, high blood sugar, Renal impairment, Liver disfunction, pregnancy complication.	Inhibit the activity of HMG CoA reductase
Fibrates	Lopid, Tricor, Lopid.	Lower LDL-C by 10%, triglycerides by 40-60% Raises HDL-C by 10-20%	indigestion, headache, muscle weakness and/or pain.	decreases the formation of VLDL, very low-density lipoproteins
Bile acid sequestrants	Questran, Welchol, Cholestagel, Colestid	Lower LDL-C by 20% Raises HDL-C by 10%	constipation, abdominal pain, bloating and gas.	binding to bile acids in the intestine, resulting in their elimination from your body.
Nicotinic acid	Niaspan	Lowers LDL-C by 15% Raises HDL-C by 15-30%	Flushing, itching, rash and high blood sugar.	blocking the formation of LDL, the bad cholesterol, and decreasing the production of VLDL in the liver.
Intestinal absorption blockers (Ezetimibe)	Zetia	Lowers LDL-C by 20%	muscle pain and abdominal pain.	blocking the absorption of dietary cholesterol in the intestine

Moreover, since most anti-cholesterol drugs also lower LDL, which is a carrier of all other fat-like nutrients including fatty acids, fat-soluble vitamins, fat-soluble antioxidants; the bioavailability of these nutrients are significantly decreased and body becomes exposed to the risks which are protected by these nutrients. Consequently liver begins to produce low quality LDL particles, containing insufficient protective cholesterol, which results in increased vulnerability of the LDL particles to the free blood sugars. Several studies showed that people who have extremely low levels of blood-cholesterol have a greater risk to dying in later years from a variety of causes, including suicide, homicide, strokes, certain cancers, liver disease and lung disease. However, there is no controlled study yet to demonstrate the benefit of Statin drugs on women, children, and men over 65. There lipid-lowering statins should not be prescribed for women of any age and for men older than 69 years [63]. In fact, some reviews of clinical studies on cholesterol-lowering drugs suggest that the survival rate is not improved because the observed reduction of deaths from coronary heart disease is offset by a noticeable increase in non-cardiac mortality, including cancer and violent deaths. A recent WHO report says Thanks to population-wide policies and individual risk

management in the past 30 years CV disease has decreased by more than 50% in many developed countries. It doesn't indicate that it is due to the advent anti-cholesterol drugs. One meta-analysis showed that in healthy patients Statin reduced the rate of mortality only by 0.6% [64]. People are beginning to realize that they are actually inviting more serious evils in exchange of a minor one. Heart diseases have many risk factors. Hence the treatment can't be as simple as taking a pill, no matter how effective it is. Emphasis should be given on controlling risk factors too. The fact of the matter is that, people have become overly obsessed about drugs to cure our health problems rather than taking measures to prevent it. Drugs are barely healing patients and at the same time generating other indirect yet serious aftermaths, thereby increasing the necessity for more drugs. And this type of necessity has made drug industry the most lucrative sector of modern day economy. In USA no other industry makes as much profit as the drug industry does. Billions of dollars are being spent to invent new drugs, billions of dollars being spent to advertise them and billions of dollars are being spent to offer free samples. No doubt there are many more billions spent to manipulate the knowledge and data acquired by researchers, doctors, pharmacists and health officers from the experience of their consumers. The ready money serves as a strong deterrent against any legislative proposal that would lower costs for consumers and profits for the drug makers [67]. Prosperity and goodwill of the drug companies are rooted on not only inventing new drugs, but also new diseases. No drug has ever been able to cure any chronic disease, yet drugs for chronic disease remains the most sold ones ever. Lipitor was the highest selling drug for about a decade. Last year Crestor was the third most sold drug worldwide. As is the case with anti-cholesterol drugs, drug companies are targeting to bring more diseases than cures and scam patients for vast amounts of money, by treating the symptoms but not addressing the cause. As a matter of fact, treating high blood-cholesterol is nothing but treating the symptoms, and not necessarily the disease. Not only the anti-cholesterol drugs are being manufactured, but also many unscientific information which are bringing welfare for drug companies, and severe threats to public health. Not surprising, anti-cholesterol and anti-depressant drugs are always on the top selling list. Statin use has increased in recent years as high cholesterol, heart disease, and diabetes are being diagnosed more frequently. Physicians are increasingly influenced to prescribe these drugs. Patients are also becoming increasingly dependent on drugs and in most cases neglecting the fact that life style has a greater effect on health and disease than these magic drugs. Since cholesterol is needed for maintain good memory and brain health, the more there are patients taking anti-cholesterol drugs, the more there is need for anti-depressant drugs. More and more young people are taking anti-depressant drugs nowadays. CVD provides a very lucrative ground for pharmaceutical industry as it's one of the most feared diseases in the world. The guidelines that create the clinical imperative for physicians are manipulated by experts who have financial ties to drug companies. It has been repeatedly shown that doctors prescribing practices are influenced by interaction with industry representatives and attendance at events sponsored by drug companies [66]. In a meta-analysis of statins in *Lancet*, 13 out of 14 studies were commercially sponsored. The industry also maintains a war chest for advertising and grassroots lobbying aimed at altering public opinion. The worst part of the story is that the ordinary folk are kept away from the light of scientific truth and they are bound to obey their physicians' prescriptions, which are in some way other manipulated by the drug industry itself. Once someone is found with high blood-cholesterol, he/she is somehow sentenced for a lifetime use of anti-cholesterol drugs. Patients who already had a heart attack are prescribed to continue these drugs to maintain a constantly low level. And according to the prevailing trend, the level has no lower threshold, the lower the better. The consequences of such medical malpractices are borne mostly by healthy people is more and more people are at risk of falling sick. Heart diseases have become a matter of regular checkups, blood tests and taking costly medicines. These drugs are not only depriving us of our wealth, but also our health. More and more we're falling sick before we really fall sick. More than ever we're dying from drugs than from diseases. It's the high time for a paradigm shift now. Health is a global issue and it exiges for a global approach to bring forth a sustainable healthcare system, and improvement of corporate ethics of the healthcare industry.

7 CONTROLLING THE CONTROVERSIES

Ancient pharmacological knowledge tells us that everything is toxic; it is only the dose that draws the differentiating line between the toxic and the non-toxic. So must be true for cholesterol too. If cholesterol were really so harmful then how come liver goes on producing it every day beginning from birth and not all of us die from heart disease! It's a vital nutrient and body is capable of producing by itself. It does make no sense to cut its dietary intake or inhibiting body's natural ability of producing it by taking medications. Furthermore, absorption rate of cholesterol from diet is relatively low and by removing all cholesterol from the diet the blood cholesterol will only fall by about 20% to 25%. So cholesterol in food may matter, but not nearly as much as we are used to believe. Chronic excessive intake of any nutrient above threshold would cause toxicity. Vitamin and mineral toxicity is well known fact. Even water consumed in an excessive volume (known as Water intoxication) in a short time can cause death [28]. But cholesterol has never found reach toxic level in human body as body has its own mechanism to discard the excess the surplus amount. Besides that, almost 80% of body's cholesterol is finally converted to bile acid which has no such influence on heart diseases. The fact remains that, humans preside over the plant kingdom by virtue of two elements- conscience and cholesterol, and even the first one would go inert without cholesterol. We are

supposed to have cholesterol in our body and not depriving body from the functions it exerts. Life wouldn't be possible if cholesterol were not present in sufficient amount in our body. Cholesterol is the long misunderstood molecule that plays critical roles in human develop and survival. People with high blood-cholesterol are suggested to avoid cholesterol rich food. But unfortunately most cholesterol rich food are also very good source of other vital nutrients. Egg, red meat, organ meat are ideal sources of protein, and many other important nutrients such as Zn, Cu, Fe and CoQ10. Increased consumption of PUFA induces an increased rate of cholesterol synthesis to maintain their stability and proper fluidity in the cell membranes [21]. But almost all of these foods are prohibited by many dieticians due to their high cholesterol content. Such faulty ideas can lead to serious health problems. Blood cholesterol might serve as an important risk factor for CHD but should be considered in the context of other risk factors such as smoking, high blood pressure (HBP), physical inactivity, hypertension, obesity, [51]- [52]. Newly emerging CVD risk factors, such as low birth weight, folate deficiency, and infections, are also more frequent among the poorest segments of the population in low and middle-income countries [35]. Infants require plenty of cholesterol for proper brain development and cholesterol content of breast milk gives a clear evidence of that. Infant formulas are usually made free of cholesterol due to lack of adequate knowledge about the necessity of cholesterol. Avoiding cholesterol rich food is associated with the risk of being deficient in very low cholesterol levels, which make death from other causes more likely. The issue of cholesterol has long been clouded by debate because large-scale studies of people with high cholesterol levels have shown that lowering their cholesterol levels reduces their rate of fatal heart disease, but, paradoxically, no overall reduction in mortality has been seen. Normally people who are at risk of developing heart disease are advised to lower their cholesterol level even if it is already low enough due to the belief that the lower the level of blood-cholesterol, the lesser is the risk of heart diseases. According to certain studies that address the link between cholesterol and heart disease, the best way to reduce cholesterol and prevent heart disease is to adopt a healthy diet rather than avoiding cholesterol in foods and that the link between the two is made possible only with poor diet.

Table 2. Major Risk factors of atherosclerosis

Age	Male: ≥45 years Female: ≥55 years
smoking	Highly associated with smoking habit
Genetic factors	Myocardial infarction or sudden death before 55 years or 65 years of age in parent or first-degree relative, male or female, respectively
Family history of hypercholesterolemia	Individuals with family history of hypercholesterolemia are more likely to develop atherosclerosis
Hypertension	Blood pressure equal or above ≥140/90mmHg
Diabetes Mellitus	Individuals with diabetes frequently have what is commonly referred to as an atherogenic lipoprotein profile: low HDL cholesterol levels and elevated triglyceride levels.
Low LDL	Low high-density lipoprotein (HDL) cholesterol (<40mg dl/1 (1.0mmol l/1))
Obesity, physical inactivity	Increased body weight for height is associated with various primary risk factors for atherosclerosis. These include hypertension, elevated LDL cholesterol levels, and low HDL cholesterol levels.

8 CONCLUSIONS

This article reveals that cholesterol plays a minor role in the development of atherosclerosis and the correlation between cholesterol and CVD is very narrow. On the contrary low blood-cholesterol is likely to increase the risk of mortality from other causes. Furthermore, blood-cholesterol fluctuates depending on a wide range of factors and not everyone respond in the same manner to dietary cholesterol, and hence in no way blood-cholesterol can serve as a suitable predictor for increased risk of heart disease. It is also an unscientific idea that everyone must have or has to maintain exactly the same amount of cholesterol in their blood. The war on cholesterol need to be terminated and its beneficial sides must be emphasized instead to promote health. Cardiologists are slowly realizing that it is inflammation of arterial tissue that leads to heart disease and most strokes, but not cholesterol. Safety tests of anti-cholesterol drugs have not yet been performed on all age and sex groups and have proved to have a multitude of adverse effects on many.

ABBREVIATIONS

AD: Alzheimer's disease
HD: Heart disease
HDL: High density lipoprotein
CHD: Coronary heart disease
CVD: Cardiovascular disease
HBP: High blood pressure
LDL: Low density lipoprotein
UPR: Unfolded protein response
WHO: World health organization

ACKNOWLEDGMENTS

We're greatly indebted to Dr. Yang Wei for his critically reading the paper and giving valuable suggestions for its improvement.

CONFLICT OF INTERESTS

The authors declare that no conflict of interest exists.

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