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ABSTRACT

Cholesterol is a molecule central to all human physiological processes at systemic as well as cellular levels. Cholesterol, combined with Apolipoprotein B as low-density lipoprotein (LDL) has been the focus of scientific research because the molecule has been proven to play a role in the development of cardiovascular disease, a disease of pandemic proportions. Considerable scientific and medical attention has been devoted to identifying the role and management of high levels of total serum cholesterol in order to address this global health burden, creating large scale awareness regarding lowering cholesterol concentration in circulation. However, the same molecule, combined into various lipoprotein moieties, is also involved in 'normal' physiological processes. In this review, an attempt has been made to elucidate some of the physiological events at the other end of the spectrum, when serum cholesterol levels are lower than normal. These health risks may need to be managed by going against the grain and actually raising serum cholesterol levels. Hypocholesterolemia is perhaps as much of a health risk as is hypercholesterolemia. These phenomena emphasize the fact that where cholesterol is concerned, maintenance of optimal systemic levels of cholesterol is more crucial than going towards either end of the cholesterol scale.

INTRODUCTION

Cholesterol has been in the center of many debates concerning its role in the human metabolism. Cholesterol is considered as the main culprit behind modern lifestyle diseases like atherosclerosis, which leads to cardiac arrest, obesity and metabolic syndrome. Although implicated as a causative agent of all of the above, cholesterol is also an important component of cellular membranes and is a mediator of several cellular processes. Cellular membranes owe their fluidity to the presence of cholesterol and lack of cholesterol is likely to have an impact on several physiological processes. Cholesterol is an important precursor for synthesis of steroid sex hormones (Payne and Hales 2004) as well as vitamin D (Lehmann et al. 2000). Cholesterol is an important constituent of cell membranes and, being an amphipathic molecule, it interacts with both lipids in the plane of the membrane bi-layer, as well as with water and other electrolytic substances owing to the presence of an –OH group. Cholesterol is thought to play an important role in maintaining membrane fluidity as well as participate in transient membrane specializations called membrane microdomains or 'rafts' (Sharma et al. 2004).

The role of LDL in the development of cardiovascular disease (CVD), when present in excess in human circulation, has been discussed at length (Stein 2009). The consensus is that very high levels of serum LDL-cholesterol and triglycerides are the causative factors of atherosclerotic plaques, which can eventually cause blockage of cardiac arteries leading to a heart attack. There have been extensive studies on the interrelationships between diet, obesity, serum cholesterol levels and CVD as well as other co-morbidities like diabetes mellitus (Daniels et al. 2009), leading to the formulation of a general assumption that one must slay the cholesterol beast in order to live a disease-free life. However, cholesterol is also an essential component of biological tissues and is also specifically required for several cellular processes.

Therefore, the issue that begs consideration here is "How low can one go with cholesterol?" Given the importance of having an optimal amount of cholesterol present

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in the human system, it is likely that extremely low levels of cholesterol are likely to bring in another set of health morbidities and risk. This review attempts to understand health risks at the other end of the cholesterol range by looking at cholesterol deficiency disorders. Physiological deficits in cholesterol levels can result from a variety of causes and the effects of these deficiencies on various health parameters are discussed in this review.

CHOLESTEROL METABOLISM

Cholesterol can be synthesized by all tissues in the human body, barring enucleated erythrocytes. In addition to synthesis of cholesterol from acetate, cholesterol is also absorbed from ingested food in the form of chylomicrons. Chylomicrons are a class of lipoproteins that are produced by intestinal mucosal cells, the principal component of which is a small protein apoB-48, produced by alternative splicing of mRNA from the apoB gene. Chylomicrons are generated in the intestinal cells after the absorption of free fatty acids and cholesterol and are secreted by the intestinal cells into the lacteals and are redistributed to other organs and peripheral tissues. Chylomicrons are capable of exchanging apolipoproteins with high-density lipoproteins (HDL) to generate mature chylomicrons. Cholesterol from peripheral tissues is exported in the form of HDL, which is brought to the liver via the vascular system. HDL-associated cholesterol and phospholipids are degraded in the liver. Cholesterol breakdown products are excreted in bile as bile salts, which, after storage in the gall bladder, are secreted into the digestive system. Bile salts help in emulsification of dietary fats until they are absorbed in the small intestine.

The liver is also the site of cholesterol synthesis and hepatic cholesterol is secreted into the vascular system in the form of very low-density lipoproteins (VLDL). In the plasma, VLDLs coalesce to form low-density lipoprotein (LDL) particles.

Cholesterol deficiencies can be classified into

a) Inborn errors in cholesterol synthesis or apolipoprotein synthesis
b) Clinically observed hypocholesterolemia of undetermined origin such as in HIV-positive patients (Miguez et al. 2010; Shor-Posner et al. 1993)
c) Cholesterol deficiency induced by surgery and critical illness

THE ROLE OF HDL IN CARDIOVASCULAR DISEASE

Cholesterol is present in serum in three forms: very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), with each form serving a distinct physiological function. Very low-density lipoprotein is the form that is created by processing of HDL and LDL by the liver into smaller particles meant for excretion. LDL has been implicated as a causative factor principally in atherosclerosis especially when plasma concentrations of LDL are high (Daniels et al. 2009). HDL, on the other hand, functions to transport cholesterol from peripheral tissues to the liver for degradation (Podrez 2010). HDL is chiefly composed of apolipoproteins A I and II (apoAI and apoAII) with apolipoproteins C, D, E, M and A-IV(apoC, apoD, apoE, apoM, apoA-IV) and other enzymes forming the protein components of the particles. Cholesterol is the main lipid component but other phospholipids as well as free fatty acids have also been reported to be included in HDL.

A sum total of 75 proteins have been found to be included in HDL in proteomic studies. These findings suggest that HDL may exist in several distinct forms engaged

in several functions apart from transporting cholesterol to the liver (reviewed in Podrez 2010). In fact, HDL plays a prominent role as an anti-oxidant molecule by preventing oxidation of LDL and acting as a 'sink' for oxidized lipids from LDL (Podrez 2010; Terasaka et al. 2007). The role of HDL as an antioxidant is thought to help in preventing the formation of dysfunctional LDL molecules that may play a role in initiating atherosclerotic plaques (Terasaka et al. 2007). HDL is thought to have a cardioprotective role and help prevent cardiovascular disease. Low HDL is considered as a positive predictor for cardiovascular disease (Schaefer et al. 2010). Patients with mutated apoA-I show normal levels of LDL and serum triglycerides and yet are at greater risk of developing coronary heart disease (Schaefer et al. 2010).

The link between circulating levels of HDL and coronary heart disease has been demonstrated by other researchers as well. In a 16-year follow-up study with 3,026 patients, treatment with bezafibrate reduced the risk of coronary heart disease and death by myocardial infarction by 22% as compared with patients who had been prescribed a placebo (Goldenberg et al. 2009). In this study, patients who showed a greater increase in serum HDL levels in response to bezafibrate were at lesser risk for developing coronary heart disease. The study vindicates the role of HDL in preventing atherosclerosis as well as coronary heart disease. In a Finnish population study of 148 people who presented with low HDL levels, a reduction in HDL particle size was positively correlated with increased carotid intima-media thickness (Watanabe et al. 2006). Increase in the thickness of carotid intima and media, as assessed by ultrasonography, is considered as a reliable marker for atherosclerosis. In this study, people with low serum concentrations of HDL also showed a significant reduction in the HDL particle size and were consequently deemed to be at greater risk for development of coronary heart disease.

Given the diversity of proteins and lipids associated with HDL in addition to cholesterol (Podrez 2010), heterogeneity in size and diversity of functions of HDL is to be expected. In a study that sought to understand the relationship between HDL particle size and coronary heart disease, Arsenault and colleagues found that smaller HDL particle size (which can possibly be attributed to deficiencies in proteins as well as associated cholesterol and other lipids) (Arsenault et al. 2009) was positively correlated with increased risk for coronary heart disease. Patients with smaller sized HDL particles also had greater co-incidence of other unfavorable cardiometabolic factors like elevated waist circumference and higher systolic blood pressure and elevated serum triglyceride levels. The study does indicate that predominance of HDL and large sized HDL particles are indicators of cardiovascular risk, however; analysis of the specific contribution of serum cholesterol was not carried out in this context.

The predominant question that arises from the previous discussion is whether HDL particle size is regulated by cholesterol levels or not. HDL particle size analysis was undertaken in a study of people who were heterozygous for Tangier disease (TD) (Brousseau et al. 2000). Tangier disease is characterized by the presence of orange tonsils, very low levels of HDL and enlarged spleen and liver. The essential mutation in Tangier disease is one that causes a dysfunctional ATP-binding cassette transporter protein ABC1 on chromosomes 9q31. This transporter protein regulates the efflux of cholesterol from peripheral tissues and allows it to complex with apoA-I and apoA-II to form HDL. In patients heterozygous for Tangier disease mutation, HDL particle size was significantly smaller than that seen in controls. Efflux of cholesterol from TD-

heterozygote cells was reduced by 50 % to that of control cells and this reduction in serum cholesterol correlated positively with serum HDL concentration as well as HDL particle size (Brousseau et al. 2000). Cholesterol efflux may also influence the HDL-subtype distribution in Tangier disease heterozygotes (Asztalos et al. 2001). HDL subpopulations can be characterized on the basis of size as well as the predominant apolipoproteins associated with them. In a study of people heterozygous for Tangier disease as confirmed by low HDL levels, the prevalence of large alpha1, pre-alpha1, alpha 2 and pre-alpha2 particles was significantly lower as compared to healthy control subjects. The loss of these specific HDL subpopulations may be the result of reduced cholesterol efflux mediated by the Tangier mutation in the ABC-1 gene (Asztalos et al. 2001). Concurrently, the incidence of coronary heart disease was also found to be greater by 60%, in the heterozygote group as compared to unaffected healthy subjects. Therefore, cholesterol deficiency is likely to influence the particle size as well as the specific nature of HDL particles; it is likely that very low levels of cholesterol in the serum may actually contribute to increasing the risk of coronary heart disease. Although this sounds contradictory to conventional wisdom that cholesterol in the form of LDL IS the 'seed' molecule for formation of atherosclerotic lesions, the lack of HDL particles of appropriate size and functional properties is a serious concern for people with very low levels of serum cholesterol.

CHOLESTEROL AND NUTRITION

Lipoproteins are involved in the transport of vitamin E from the digestive system as well as from the liver to the peripheral tissues. Vitamin E or alpha-tocopherol is known to bind to HDL, specifically HDL-3 (Goti et al. 1998). HDL-3 bound tocopherol can be taken up by hepatocytes (in in vitro studies) and is secreted out in the form of LDL by hepatocytes. Thus both metabolic forms of cholesterol in the form of lipoproteins are involved in the systemic transport of vitamin E.

Cholesterol is known to participate in transient membrane specializations termed as membrane microdomains, along with sphingolipids (Sharma et al. 2002). These microdomains are formed laterally in the plane of the plasma membrane and are especially important for the endocytosis of the folate receptor. Depletion of cellular cholesterol, in in vitro systems has been shown to alter the endocytic pathway (Sabharanjak et al. 2002), recycling time as well as intracellular endosomal destination of the folate receptor (Sabharanjak and Mayor 2004). The overall efficiency of accumulating folic acid in the cytoplasm is also reduced. Although it is unclear whether physiological depletion of cholesterol either by suppression of synthesis or by reduced dietary intake results in similar disruption of microdomains, the role of cholesterol in uptake of water-soluble vitamins is also important.

DEFICIENCIES IN CHOLESTEROL BIOSYNTHESIS

Cholesterol in circulation can be derived from dietary components as well as from de novo synthesis. Cholesterol is synthesized from hydroxymethylglutaryl co-A (HMGco-A) in a series of steps with intermediates like squalene, lanosterol and lathosterol. Cholesterol thus synthesized may also get converted into steroid hormones like testosterone. Incidentally, low testosterone levels in men are also correlated with increased risk of coronary heart disease and show a positive correlation with low levels of HDL as well (Nettleship et al. 2009).

In the biosynthesis of cholesterol, lanosterol is converted via seven steps to lathosterol, which in turn in converted into 7-dehydrocholesterol by the action of lathosterol-5-desaturase. Mutations in this enzyme lead to the accumulation of lathosterol instead of cholesterol, a defect known as lathosterolosis. This defect has been replicated in a mouse model for lathosterolosis. Likewise, the final step in biosynthesis is the conversion of 7-dehydrocholesterol to cholesterol catalyzed by 7-dehydrocholesterol reductase. A genetic mutation of this enzyme has been described as the Smith-Lemli-Opitz syndrome (SLOS), which is characterized by severe developmental abnormalities including mental aberrations (Gondre-Lewis et al. 2006).

Both these defects have been established in mouse models described by Y Peng Loh and colleagues (Gondre-Lewis et al. 2006). In order to examine the effect of abnormal sterol accumulation in membrane trafficking events, these scientists characterized and quantified the occurrence of dense core secretory granules in exocrine pancreatic tissue as well as neuroendocrine cells. In *Sc5d-/-* as well as *Dhcr7-/-* mice, the number of secretory granules in pancreatic tissues was significantly lower than that found in wild type or heterozygous mice. (Gondre-Lewis et al. 2006). Additionally, the fission of dense core granules from the endoplasmic reticulum was seen to be impaired in *Dhcr7-/-* mice, suggesting that lack of cholesterol had interfered with formation of dense core granules at the Golgi. The proportion of immature granules lacking the dense core was higher in the mutant homozygous mice as compared to wild type mice. The accumulation of sterols other than cholesterol is likely to hinder secretory processes. Although alpha-amylase was produced by normal as well as homozygous mutant mice with both genetic defects, the enzyme was found to be constitutively secreted in *Dhcr7-/-* mice, indicating that cholesterol in the granule membrane as well as plasma membrane of pancreatic acinar cells is essential for regulated secretion of digestive enzymes.

This study highlights the importance of having the right sterol in the right cellular membranes. The mutant phenotype can be rescued by culturing cells from these mice in normal LDL-containing serum (or by dietary supplementation in the live animal), which vindicates the requirements of cholesterol in cellular membranes in regulated membrane trafficking events.

Although the lipoprotein measurements in the mouse models have not been reported in this study, HDL deficiency has been shown to be associated with SLOS in children (Behulova et al. 2000). In this study, serum lipoprotein levels were recorded in children suffering from SLOS, ranging from five days to seven years of age. Total cholesterol levels were certainly depressed in these children as compared to normal children but the authors note that the severest symptoms of SLOS were exhibited by children with significantly depressed levels of HDL and HDL-bound cholesterol (Behulova et al. 2000). Developmental abnormalities resulting from cholesterol deficiency in this syndrome usually mean that children are not able to attain adulthood. Heterozygous individuals show normal development owing to the presence of the normal DHCR7 allele.

HYPERCHOLESTEROLEMIA AND SURGICAL AND CRITICALLY ILL PATIENTS

In order to understand hypocholesterolemia, 'normal' levels of cholesterol have to be defined. From studies of primates as well as 'primitive' humans like tribals, the

optimal serum concentrations of total cholesterol was found to be 3.0 to 4.0 mmol/l. Plasma total cholesterol levels ranging from 2.6 to 3.5 mmol/l have been considered as low cholesterol levels in certain conditions (Vyroubal et al. 2008). However, these values show a large overlapping range. In another study, the plasma cholesterol concentration of patients undergoing hepatectomy was judged relative to their own total cholesterol estimations before and after surgery (Giovannini et al. 1999). This study shows that patients whose total plasma cholesterol levels were reduced to 55% of the pre-operative values were judged as hypocholesterolemic and tended to develop fatal health complications.

In some papers, patients with cholesterol levels <150 mg/dl have been considered as being hypocholesterolemic (Miguez et al. 2010; Shor-Posner et al. 1993).

Cholesterol levels may become a useful diagnostic tool in the prognosis of critically ill or surgical patients in the recovery period. Dunham and colleagues have demonstrated an association between the hypocholesterolemic state and likelihood of recovery in patients who have suffered severe injuries (Dunham et al. 2003). In their study of 28 patients maintained on ventilator support, reduction in plasma cholesterol levels was observed in the beginning of the convalescence period. Those patients for whom cholesterol levels rose to the normal population average were able to recover from the trauma and were at reduced risk for sepsis. In contrast, patients with persistent hypocholesterolemia tended to develop secondary infections as well as organ failure and metabolic dysfunction (Dunham et al. 2003). The association between development of sepsis and reduced levels of cholesterol is attributed to the fact that lipoprotein complexes are able to sequester bacterial lipopolysaccharides and prevent toxicemia. Reduced levels of serum lipoproteins are therefore a predisposition towards developing secondary bacterial infections.

Although this study is limited by the number of patients included in the study as well as lack of differentiation between the kinds of lipoproteins (LDL or HDL) involved, it is nonetheless an eye-opener for critical care procedures. A study with animal models wherein sepsis had been induced by irradiation showed that HDL is persistently lowered (for up to 10 days in the recovery period) in individuals who developed sepsis following irradiation (Parra et al. 2007).

Hypocholesterolemia has been shown to be associated with postoperative surgical complications as well. Leardi and colleagues have noted that following invasive abdominal surgery, patients whose total cholesterol levels fell below 105 mg/dl showed the highest incidence of sepsis (Leardi et al. 2000) in the recovery period. Likewise, an association between lowered cholesterol levels and increased incidence of sepsis and multiple organ failure has been reported by Giovannini et. al in a comparative study of 135 surgical patients (Giovannini et al. 1999).

Taken together, these studies indicate that cholesterol homeostasis (balance) in circulation is important for recovery from accidents as well as planned interventions like surgery. Hence, hypocholesterolemia is a risk factor to be considered, perhaps, before opting for invasive surgical procedures. This fact is likely to be most relevant for people bearing known cholesterol metabolism disorders as well as for people undergoing statin-based therapy to reduce cholesterol levels.

CHOLESTEROL AND INFECTION

Cholesterol-sequestering lipoproteins are also likely to play a protective role against infection in non-traumatized and non-surgical patients as well. The sequestration of bacterial lipopolysaccharides (LPS) by LDL to reduce the inflammatory response that is launched to counter LPS has been well characterized. Experiments conducted with knock-out mice that lacked the LDL-receptor gene showed total susceptibility towards septicemia and eventually died (Lanza-Jacoby et al. 2003). This research suggests that LDL bound to bacterial LPS may be endocytosed by cells bearing the LDL-receptor in order to inactivate this exotoxin.

In humans, *Staphylococcus aureus* is a bacterium that not only colonizes and persists in the system in the form of biofilms but can also aggressively invade tissues leading to system-wide sepsis. In fact, resistance of *Staphylococcus aureus* to many antibiotics is a major health issue that results in nosocomial (resulting from a hospital stay) infections (reviewed in Falcone et al. 2009). In the colonized state, when the biofilm reaches a certain bacterial population size, an operon termed as *agr* is switched on, triggering an invasive infectious response. Peterson and others have shown that apolipoprotein B is a natural antagonist of the *agr*-mediated aggressive infection. ApoB binds to an auto-inducing cyclic thiolactone peptide (AIP) and prevents the binding of this protein to its receptor AgrC (Peterson et al. 2008). ApoB is also capable of sequestering other forms AIP2-4 and therefore confers protection against *S. aureus* infections. It is therefore likely that extremely low levels of LDL-cholesterol may actually result in loss of protection from *S. aureus* infections. This is especially a risk factor for people bearing implants such as pacemakers since *S. aureus* biofilms are often associated with such implants.

LDL is a defensive barrier against other bacterial toxins like the *Vibrio vulnificus* cytolysin (Park et al. 2005). LDL has been shown to bind and inactivate the endotoxin by causing oligomerization of the toxin. An important feature of this interaction is that this is a dose–dependent inactivation mechanism (Park et al. 2005). Therefore, in hypocholesterolemic conditions, the reduced availability of LDL is likely to enhance the cytotoxicity of bacterial toxins, a factor that may lead to rapid onset of sepsis. Typically, in trauma patients, when total serum cholesterol levels fall to 50% of the normal population average levels, the risk of sepsis as well as multiple organ failure is high (Vyroubal et al. 2008). These interdependencies highlight the fact that an 'optimal' cholesterol balance is required and low levels of cholesterol are just as detrimental to health as elevated levels of cholesterol.

CHOLESTEROL IN MENTAL HEALTH

Cholesterol, being a membrane component, plays significant roles in neural functions as well. In fact, cholesterol is a major component of the myelin sheath that covers axons of brain neurons (reviewed in Fantini and Barrantes 2009) and is thought to modulate neurotransmitter release and binding to neurotransmitter receptors and therefore downstream events. A major neurotransmitter, serotonin, is important for the emotional well-being of humans and serotonin deficiencies are responsible for depression as well as aggression and suicide.

An association between serum cholesterol levels and serotonin has been established in several studies. People whose serum cholesterol levels are low also tend to have lower levels of serotonin in circulation (Steegmans et al. 1996). In a recent

study, it was seen that low serum cholesterol correlated with serotonin turnover in men. No such conclusive relationship could be demonstrated for women (Markianos et al. 2010). These scientists have postulated that lowered serotonin levels could be responsible for aggressive and violent behavior in men as a response to the evolutionary need to hunt and acquire food.

In a retrospective analysis of familial and personal suicide attempts, Bocchetta and colleagues have proposed a link between low cholesterol and suicidal behavior. A total of 783 patients who were undergoing lithium treatment were analyzed for reported personal or familial (first-order relative) suicide attempts. Based on one-time cholesterol measurements, the researchers found that lower levels of serum cholesterol in men were associated with attempted or completed suicide (Bocchetta et al. 2001), suggesting a neuromodulatory role for cholesterol.

In another study with panic disorder patients, the serum cholesterol levels in patients who attempted suicide were found to be lower than panic disorder patients who had not attempted suicide as well as normal control subjects. The mean total cholesterol levels as well as LDL levels were lower in panic disorder patients who had attempted suicide (Ozer et al. 2004). The study is hampered by limited sample size as well as a large age range of subjects. Extensive analyses will be required to further understand the association between low cholesterol and suicidal behavior.

In a study of 42 people who attempted suicide, a positive correlation was found between low serum cholesterol and low 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (Asellus et al. 2010). These patients were not under the influence of any other drug or therapy and had attempted suicide. The link between low serum cholesterol and depressed serotonergic responses has been suggested to explain these results. Although the cohort size was small with 42 individuals included, it is logically and practically difficult to add to these numbers of people who attempted suicide but missed the bus. Nonetheless, the work does show a correlation between low serum cholesterol and attenuated serotonergic response systems, which, perhaps is responsible for reckless suicidal behavior.

At the cellular level, a drastic reduction in the level of cholesterol is likely to affect the physiology of serotonin receptors (Paila et al. 2008). Paila and colleagues have used an inhibitor AY9944 in Chinese Hamster ovary fibroblast (CHO) cells to create a cellular model of the Smith-Lemli-Opitz syndrome. AY9944 inhibits the terminal step in the synthesis of cholesterol. In this model, signaling via the serotonin 1A ($5\text{-}HT_{1A}$) receptor was found to be reduced (Paila et al. 2008). The attenuation of signaling via this receptor was not explained by reduction in receptor expression or delivery to the plasma membrane. However, signaling via plasma membrane-resident 5-HT1A was reduced in the absence of cholesterol. Although these cells have abundant 7-dehydrocholesterol and 8-dehydrocholesterol, these sterols were not able to interact with 5-HT1A in the same manner as cholesterol and facilitate signaling via receptor-associated G-proteins (Paila et al. 2008). The overall membrane organization as measured by the fluidity of a non-specific fluorescent probe was unaffected in normal as well as SLOS cells used in this study. These results argue for a role of cholesterol in modulating serotonin signaling, albeit in a cell system that is non-neuronal.

In hippocampal tissue, oxidation of cholesterol reduced the binding of agonist as well as antagonist ligands to 5-HT1A receptor (Pucadyil et al. 2005). These results

indicate a physical interaction between cholesterol in the plane of the membrane and the neurotransmitter receptor. Taken together, these results suggest a mechanism for impairment of serotonin receptor dysfunction in situations of low cholesterol availability. Attenuated serotonin metabolism is a hallmark of depression and reduced availability of cholesterol may be a contributory factor.

Cholesterol deficiencies are likely to manifest as changes in behavioral patterns as well. In a one-year follow-up of patients with unipolar or bipolar disorder, a positive correlation between low serum cholesterol and recurrence of manic episodes was noted (Fiedorowicz et al. 2010). The patients were assessed for serum cholesterol along with other parameters, as well as development of psychotic episodes. Patients with unipolar disorder were not affected but those with bipolar disorder experienced manic episodes in the year of follow-up. Depression was not seen in both kinds of patients. Although the difference in mean cholesterol levels of both groups of patients was slim, the persistent deficiency of cholesterol is likely to be influential in neurological responses and behavior. In this study, the prevalence of different fractions of cholesterol throughout the follow-up period was not monitored and perhaps better assessment of the cholesterol status of the patient at the time of occurrence of psychotic / manic events will shed more light on the role of cholesterol (Fiedorowicz et al. 2010). It would be interesting to know whether a sudden and transient reduction in serum cholesterol levels is a trigger or indicator of manic behavior. Since depressive symptoms were not associated with hypocholesterolemia, the study points to other neuromodulatory roles of cholesterol which remain to be investigated.

Dietary intake of cholesterol was shown to reduce dissociative behavior and aggression in a primate study (Kaplan et al. 1994). Cynomolgus monkeys were fed high-fat diets that were specifically low or high in cholesterol. Monkeys who received a low cholesterol diet showed aggressive behavior and tended to be socially alienated.

Serum cholesterol levels may play an important role in addiction as well as de-addiction from cocaine. In a study of thirty-eight cocaine abusers in hospital-based rehabilitation, it was seen that serum HDL levels were depressed in these patients, even in the recovery phase. Serum LDL, HDL cholesterol as well as neuroendocrine responses were assessed two weeks after discontinuation of cocaine abuse. Serum HDL cholesterol was reduced in all patients. The reduction in HDL also correlated with greater experience of a 'high' feeling and euphoria when the same patients were challenged with m-chlorophenylpiperazine (m-CPP). These responses are known to be attributed to altered serotonergic neuronal transmission. In agreement with prior studies, reduced HDL cholesterol was also seen in patients who had prior episodes of aggression (Buydens-Branchey et al. 2000).

The co-incidence of low serum cholesterol and occurrence of mixed manic episodes has also been reported by Cassidy and Carroll (2002). In a study of 174 subjects, patients suffering from bipolar disorder and mixed manic episodes were observed to have serum total cholesterol levels well below the reported national average values. Cholesterol levels were also lower in patients who suffered from pure manic disorders but a pronounced difference in levels of cholesterol was seen in patients who suffered from bipolar disorder. Although it is unclear from this study whether low cholesterol is the trigger for mixed manic episodes or whether the manic episode results in lowered cholesterol levels, the study suggests a link between these two health parameters (Cassidy and Carroll 2002).

Low levels of serum cholesterol have been seen in patients in whom Alzheimer's disease (AD) has been diagnosed. In a study with 138 patients with a confirmed diagnosis of Alzheimer's disease, serum cholesterol levels were found to be lower than normal people of similar average age. Within the AD cohort, the decrease in cholesterol levels correlated with increasing levels of dementia (Tully et al. 2003). Kim and colleagues, in a South Korean study of 291 individuals from a community as well as 79 AD patients, reported that people with AD showed lower levels of serum cholesterol. However, these researchers found no association between progressive dementia and reduction in level of serum cholesterol (Kim et al. 2002). The authors suggest that presence of lower serum cholesterol in AD patients may be a marker of the impaired cognitive state rather than a causative agent.

The molecular mechanisms that result in lowered serum cholesterol, however, appear to be different than just simple reduction in the synthesis of cholesterol resulting from aging. This is indicated by studies which show that treatment with statin drugs (HMGCoA reductase inhibitors) actually reduces the production of the amyloid peptide (deposition of this peptide in plaques on neurons is the primary cause of pathology in AD) and may actually show a neuroprotective therapeutic effect (Buxbaum et al. 2002; Friedhoff et al. 2001). Since a deliberate reduction in the total synthesis of cholesterol is not likely to be the triggering factor for the development of AD, there must be other transport related phenomena associated with cholesterol metabolism and its delivery to neurons.

CHOLESTEROL AND AIDS

Hypocholesterolemia has been noted in patients seropositive for human immunodeficiency virus (HIV). In a study of 94 patients, serum cholesterol and triglyceride levels were assessed along with other parameters in patients who were seropositive and seronegative for HIV (Shor-Posner et al. 1993). Shor-Posner and colleagues found that patients with low total cholesterol (below 150 mg/dl) were seropositive (indicating greater viral load and active virus multiplication in the system) as compared to patients with higher total cholesterol levels who were seronegative, though they were infected with HIV (Shor-Posner et al. 1993). Cholesterol may therefore be required as part of an antiviral mechanism that might possibly slow down virus progression, if not prevent infection.

In a recent study with HIV-positive patients, Miguez and colleagues have reported a startling connection between cholesterol levels and HIV virulence (Miguez et al. 2010). These researchers compared the cholesterol levels of 165 HIV-positive people at the beginning of highly active antiretroviral therapy (HAART) and after 24 weeks. Patients were classified as hypocholesterolemic if their total serum cholesterol levels were below 150 mg/dl. These patients showed detectable viral loads as compared to patients who had higher levels of serum cholesterol. The CD4+ cell counts in the hypocholesterolemic patients were lower than those with higher cholesterol levels implying that the immune response was modulated by hypocholesterolemia. The viral load in hypocholesterolemic patients was seen despite HAART, indicating that cholesterol may be included as a therapeutic molecule in such patients. Thymic output was reduced in patients with low cholesterol levels resulting in very low (<200) CD4+-cell counts in these patients.

CONCLUSION

Cholesterol is an important molecule in human physiology and plays an important role in all processes wherein cellular membrane composition and topography are crucial. Cholesterol is both synthesized in the human body and is acquired from food sources. Excess intake of dietary cholesterol resulting in excessive accumulation of LDL-cholesterol in the vascular system has been identified as the causative factor for cardiovascular disease (Daniels et al. 2009; Ferrieres 2009), leading to the perception that keeping cholesterol levels low has to be a priority in health and wellness management. However, exceedingly low levels of cholesterol also have other detrimental effects on human physiology. Cholesterol is an important modulator of neurotransmitter receptors like serotonin, which are involved in maintaining a healthy neurophysiological state (Paila et al. 2008; Pucadyil et al. 2005). Cholesterol in the form of lipoproteins also helps to fight bacterial infections by neutralizing bacterial toxins and LPS, a function that may be severely compromised in hypocholesterolemic patients suffering from sepsis (Wilson et al. 2003).

Cholesterol is certainly involved in the etiology of cardiovascular disease. LDL-bound cholesterol is capable of acting as the seed molecule for the formation of atherogenic plaques and can be a significant health hazard, moderate to extreme reductions in the levels of total serum cholesterol also represent health hazards.

Mechanisms that result in reduction of total serum cholesterol also seem to have a bearing on the health outcomes. For example patients suffering from SLOS, although lacking in inherent cholesterol synthesis, do not always suffer from depression resulting from serotonergic neuronal dysfunction. Many physiological deficiencies of the SLOS defect can be overcome with dietary intake of cholesterol. However, in other situations like sepsis and critical injury or surgical trauma, cholesterol synthesis alone may not bring up the serum cholesterol to optimal levels in some patients (Vyroubal et al. 2008; Wilson et al. 2003).

Cholesterol is perhaps a unique membrane component that is involved in possibly every membrane turnover event such as exocyotosis and secretion (Gondre-Lewis et al. 2006), neurotransmitter modulation (Paila et al. 2008; Pucadyil et al. 2005) and endocytosis (Sabharanjak and Mayor 2004; Sabharanjak et al. 2002), viral metabolism and cardiovascular health (Miguez et al. 2010).

Research suggests that management of 'optimal' cholesterol levels should be the choice to make rather than aiming for very low levels of cholesterol in circulation.

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