CARDIOVASCULAR diseases (CVD) are and will be the leading cause of death in human beings in the world. Its progression, development and attack are directly linked to elevated levels of cholesterol in the blood. This is because, when cholesterol is simply dumped into the bloodstream, it forms unusable globs (a thick, hard deposit) that choke the blood vessels restricting supply of blood to the vital organs. Over time, this build up causes atherosclerosis (hardening of the arteries) which leads to heart diseases.

Cholesterol is a waxy substance, chemically a lipid/fat that flows through our body via our bloodstream and gets deposited frequently because lipids are oil-based and blood is water-based, and oil and water don’t mix well. Thus, high cholesterol is going to be a serious health problem in human beings. It is estimated that half of all men and a third of all women will get it at some time in their lives.

To get around the problem of high cholesterol (hypercholesterolaemia), our body packages cholesterol into minuscule protein-covered particles called lipoproteins (lipid + protein) that mix easily with blood and circulate to all cells that require it for vital function. The question is if it is required for vital functions, how is it connected to heart disease and is it possible to optimize/reduce cholesterol levels in humans?

Cholesterol is fat and chemically a lipid that is used for synthesis of steroid hormones. It performs four main functions in our body: (a) allows the body to make Vitamin D and hormones; (b) makes up the bile acids that digest food in the intestine; (c) serve as reserve source of energy and (d) makes outer coating of cells and being a constituent of membranes helps strengthen the epidermis. Without cholesterol none of these functions will take place and existence of human beings would be impossible. Thus, cholesterol itself isn’t bad but too much cholesterol can be harmful. Just the right amount of it is essential.

Two main types of lipoproteins that are involved in heart ailment (see box Types of Cholesterol in Human Body) are low-density lipoproteins (LDL) and high-density lipoproteins (HDL). The difference between the two is in the ratio of protein to lipid. Particles with more fat and less protein (LDL) have a lower density than their high-protein, low-fat counterparts (HDL).

In most people, 60 to 70 per cent of cholesterol is carried in LDL particles. These LDL particles ferry cholesterol to different parts of the body. If one has too much LDL in the bloodstream, it deposits
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the cholesterol into the arteries, which can cause blockages that lead to heart attacks. That’s why LDL is referred as the “bad” cholesterol.

HDL on the other hand has more protein and fewer lipids. Instead of transporting cholesterol around the body, it acts like a vacuum cleaner sucking up excess cholesterol from cells and taking it back to the liver, which either uses it to make bile or recycles it. This action explains why high levels of HDL, also referred as “good” cholesterol, are associated with low risk for heart disease.

Because LDL cholesterol is a major risk factor for heart disease, it is the main focus of cholesterol-lowering treatments. The ideal limit of LDL is 100-129 mg/dl of blood for healthy human beings while less than 100 mg/dl is strongly desired for people who are at risk of heart disease. However, lower the LDL cholesterol level, the better it is because there is no evidence that low LDL cholesterol levels are harmful. However, cholesterol level abysmally low as 15 mg/dl is a dream that can be achieved probably when a person is as healthy as a horse.

Recently, scientists have identified a 40-year-old lady, a mother of two kids, having normal human physiology and who is as healthy as a horse. Using every tool in modern medical diagnostics – from brain scans to 24-hour blood-pressure monitors – doctors examined her to make sure that the two highly unusual genetic mutations which she carries are responsible for an incredibly low level of cholesterol in her blood. While the target for LDL cholesterol in blood is less than 100 milligrams per deciliter, her level is just 14 mg/dL!

Genetic studies on her enabled scientists to uncover one of the most promising compounds for controlling cholesterol since the first statin drug was approved in 1987. She has inherited two mutations, one from her father and the other from her mother, that has erased the function of a gene called PCSK9. This mutation effectively eliminates all possible traces of the PCSK 9 protein in her blood that has a fundamental role in controlling levels of LDL cholesterol.

Scientists from Canada and France together identified this gene from people having higher cholesterol and named it as “proprotein convertase subtilisin/kexin type 9” or PCSK9. According to medical estimates, people with this mutation have nearly 90% reduced risk of heart disease.

Statin, used to lower cholesterol, has side-effects such as muscle pain and forgetfulness. Many patients cannot tolerate the side effects and for many others, the drugs do not control cholesterol properly.

The search for better treatments for heart disease gained impetus after scientists published the draft sequence of the human genome in 2001. In an effort to identify the genetic basis of common ailments such as heart disease and diabetes, scientists used a strategy based on detailed physiological profiles, or phenotypes, of a large population by dividing them according to physiological traits, such as extremely high or low cholesterol levels, and then looked into the extreme groups for variations of candidate genes known to be related to the trait.

The team measured blood pressure, body mass index, heart physiology and body-fat distribution, along with other factors related to cholesterol metabolism such as triglycerides, HDL cholesterol and LDL cholesterol. They were then divided into two groups, one with the highest and one with the lowest cholesterol levels. Then their DNA was sequenced for three
genes known to be the key to metabolism of HDL cholesterol. A medically important gene – PCSK9 – was found to be involved in the process.

The discovery of PCSK9 has become an “iconic example” of translational medicine that has made “super-fast” progress to the clinic in the genomics era. Preliminary clinical trials have shown that drugs that inhibit the PCSK9 protein – used with or without statins – produce dramatic reductions in LDL cholesterol (more than 70% in some patients). Later, it was reported that people who had two (severe) mutations in PCSK9 had 28% less LDL cholesterol and a 47% reduced risk of developing heart disease than people without the mutations. People with the less severe mutation in the gene had a 15% reduction in LDL and a 47% reduced risk of heart disease.

An intriguing question is how does the gene exert such profound effects on LDL cholesterol levels? PCSK9 protein normally circulates in the bloodstream along with LDL cholesterol. Usually, LDLs are captured by its receptors which are present on the surface of liver cells and removed from the blood. However, when PCSK9 is present in the bloodstream, it competes with LDLs to bind to the same receptors on the liver cells. After competitively binding to the receptor, PCSK9 is escorted into the interior of the cell, where it is eventually degraded.

Thus, when there is a lot of PCSK9 (in case of hypercholesterolaemia) all the LDL receptors are either blocked by this protein and so fewer receptors remain to trap and remove bad cholesterol (LDL) from the blood. On the contrary, when there is little or no PCSK9, there are more free LDL receptors, which in turn remove more LDL cholesterol and blood LDL remains very low. Thus, absence of PCSK9 achieved by the mutation is a desirable phenomenon for better human health.

Although drugs against PCSK9 are heralded as the next generation statins, success in controlling LDL is still out of grasp. It is a pharmacological challenge to find a small molecule that would interrupt PCSK9 interaction with the LDL receptor and at the same time could be packaged in a pill. However, use of monoclonal antibodies, one of the most successful approaches of biological medicine, to attack and destroy PCSK9 has shown promise in phase II clinical-trial.

Patients with high LDL cholesterol levels injected with an anti-PCSK9 monoclonal antibody along with a high-dose statin saw their LDL cholesterol levels fall by 73% in comparison to patients taking high-dose statins alone who showed a decrease of just 17%.

It is envisaged that discovery of PCSK9 will be the harbinger of a new medicine for cardio-vascular disease in human beings in the near future.

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