

## **PATHOPHYSIOLOGY OF CORONARY HEART DISEASE**

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### **ABSTRACT**

It has been attempted in the present review to explore the important factors contributing in the development/occurrence of coronary heart disease (CHD). The main aspects discussed are: the risk factors leading to CHD, clinical studies and mechanisms of CHD, and obesity as one of the major risk factors in CHD. A number of factors can contribute in the development of CHD. Atherosclerosis is the most important cause of CHD and it may occur due to the inflammatory conditions. Pathogenesis of atherosclerosis involves mainly the inflammatory processes that may lead to CHD. Other risk factors of CHD are age, sex, familial causes, smoking, diabetes, hypertension, and hyperlipidemia. It has been attempted in the present review to explore the involvement of fibrinogen and other hematological parameters, homocysteine (Hcy), LDL-C and various other variables in the development of CHD. Hence it provides further understanding of the CHD. This review elucidates the prevention of risk factors, improvement in biomarker levels and control of CHD as a strategic plan for Saudi Vision 2030. Hence, it would provide a platform for conducting well organized studies in the prevalence of CHD, and would provide the pathophysiological understanding and control of CHD.

**Key-words:** Coronary heart disease (CHD), pathophysiology, lipid profile, obesity status, homocysteine, CRP, fibrinogen & hematological changes

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### **INTRODUCTION**

Coronary heart disease (CHD, coronary artery disease (CAD) or ischemic heart disease (IHD) manifests clinical disorders/ syndromes including chronic stable type of angina and the acute type (myocardial infarction). Mechanism to clinical practice in CHD has been reviewed recently (Shao *et al.*, 2020). Most interesting aspect in elucidating the development of CHD relates to the genetics of CHD (Agrawal *et al.*, 2020). Understanding the precise role of gene polymorphism and oxidative stress markers in CHD (Adam *et al.*, 2023) is quite a modern approach. Clinical studies have well revolutionized various clinical aspects of CHD considering the clinical approaches in the diagnosis, prognosis, and therapeutic/management Guidance (Li *et al.*, 2021). Oxygen is required for the intermediate syndromes. The CHD or CAD is characterized by either stenosis or occlusion of coronary arteries leading to myocardial ischemia or infarction respectively (Global Burden of Disease Study, 2013).

Several studies were carried out on the occurrence of CHD, and the mechanisms of occurrence (Mraz *et al.*, 2017; Violi *et al.*, 2017; Hodzic *et al.*, 2018). An excellent review article explains important perspectives of CHD (Taqueti and Di Carli, 2018). In spite of extensive studies in CHD, precise information for the exact cause and pathogenesis requires further studies to be conducted to relate the genetic factors with the clinical manifestations. Hereditary information of CHD along with genetic polymorphism studies, however, indicate the involvement of genetic architecture in the occurrence and progression of CHD. The CHD is increasing fast, although various aspects of the risk factors/ allied disorders have been studied, the major focus still is to search the possible relevant information to reduce its prevalence.

The WHO data shows 17.9 million people die due to cardiovascular disease (CVD) each year, and dyslipidemia is considered as the most important atherosclerotic risk factor leading to CVD progression and significantly associated with more than half of the cases with ischemic heart disease world over (Gupta *et al.*, 2017). Non-HDL-C has been given much importance than determining LDL-C since non-HDL-C determinations provide better picture of the association of CHD risk. Some significant approaches in CHD mechanism of disease occurrence are:

a) Association between serum lipid profile, CHD and cellular pathophysiology.

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- b) Formation of dilator with less potency via interactive synthesis of nitric oxide (NO), metabotropic receptor coupling, and NO signaling interacted with LDL-C.
- c) Repairment of the vasodilation related to endothelium with significant impact of triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C).
- d) The TC-LDLC-HDLC or the remnant form of cholesterol instead of just LDL-C having more association with the high risk of CHD.
- e) Considering the property of HDL as potential marker for CVD according to functionality/subclass instead of just high-density lipoprotein cholesterol (HDL-C) HDL-C serum levels.
- f) Preventing CHD secondarily via carp meat that has varied effects on serum lipids.
- g) Sudden cardiac death in middle age men occurring owing to LDL-C and HDL-C.
- h) Management for decreasing the body mass index (BMI) that resultantly influences the serum lipid levels and decreases the CHD risks.
- i) Understanding the precise role of gene polymorphism and oxidative stress markers in CHD
- j) Impact of anti-citrullinated-fibrinogen on CHD outcome.
- k) Heightened risk of hyperfibrinogenemia leading to the occurrence of CHD.
- l) The obese people showing significant elevated fibrinogen indicate the importance of fibrinogen as an important marker for the risks associated with CVD.
- m) Important involvement of the heightened levels of C-reactive protein (CRP) in the progressing CHD.
- n) Important role of Hcy in the detection of atherosclerosis along with acute-coronary-syndrome (ACS)
- o) The Hcy as an atherogenic indicator in a variety of cardiac events specially the angina pectoris occurring after myocardial infarction (MI) and other infarction manifestations.

The etiology and intricate care for CHD was investigated by employing various approaches. One important risk factor found quite clearly is obesity in association with hematological variations lipid levels, Hcy, CRP and various other factors (Zapolski *et al.*, 2011; Hoțoleanu *et al.*, 2012; Javaid *et al.*, 2012; Prajapati *et al.*, 2014; Hafez *et al.*, 2016; Mraz *et al.*, 2017; Hodzic *et al.*, 2018; Shao *et al.*, 2020).

Ischemic disorders (El-Gendi *et al.*, 2008; Cordero *et al.*, 2009; Taqueti and Di Carli, 2018; Shao *et al.*, 2020), role of modifiable risks (Khan and Hussain, 2008; Khan *et al.*, 2009), hypercholesteremic conditions (Hussain, 1991; Hussain, 1998; Dankner *et al.*, 2004; Fatima *et al.*, 2007; Longo-Mbenza *et al.*, 2007; El-Gendi *et al.*, 2008; Cordero *et al.*, 2009; obesity (Javaid, 2015) and other studies (Zapolski *et al.*, 2011; Taqueti and Di Carli, 2018; Shao *et al.*, 2020) are in agreement with the information in the present review of literature. Important involvement of the heightened levels of CRP in the progressing CHD has been indicated (Attia *et al.*, 2020; Serafi *et al.*, 2021). These studies reveal the pathophysiological role of fibrinogen, LDL-C, Hcy, CRP and a variety of other factors that may contribute to the progression of CHD.

## CORONARY HEART DISEASE

The CAD or CHD is one of the worldwide top disorders leading to death (GBDS, 2013; Shashu *et al.*, 2021). It was documented that the majority of deaths due to CVD are only resulting by CHD and it is becoming quite complicated since non-modifiable risk factors including smoking, diabetes, hypercholesterolemia, obesity, and hypertension are increasing tremendously with the change in environmental situations globally.

The CHD patients were dealt with two polymorphisms, oldage with elevated WBC count, & youth with diabetes and obesity (Rać *et al.*, 2012). An entirely new way of managing the patients with CHD depends on the basic concept that it is the BMI that takes part in the development of atherosclerosis, and even the plaque associates negatively with the WBC count and the ratio of TC and HDL-C, are in positively with the BMI. CHD in patients with obesity was studied following differing ways (Całyniuk *et al.*, 2016; Hafez *et al.*, 2016). The CVD in general links with increase in body weight and waist circumference, occurrence of central obesity, low HDL-C levels, RBC count related to cholesterol, hypertension, and involvement of other factors comprising glucose, fibrinogen etc, and on the other hand, low HDL-C indicated the myocardial infarction (MI) (Longo-Mbenza *et al.*, 2007).

It is quite important to note that the vegetarian foods decrease the level of BMI as well as a variety of BMI dependent lipids associated to atherogenesis in CHD. The BP, LDL-C, TC, TG, the ratio of LDL-C and HDL-C in CHD were influenced, and in view of hyperhomocysteinemia, Hcy was found as a marker in obese subjects with CHD. Another study in obese subjects under aerobic exercise documents increase in HDL-C but no significant variation in glucose, systolic blood pressure, LDL-C, and TC (Prajapati *et al.*, 2014).

Heart disease revealed significant decreased HDL-C and increased TG, LDL-C, TC, with smoking and hyperhomocysteinemia (Prajapati *et al.*, 2014). Furthermore, elevated levels of Hcy, TG, waist / hip ratio and waist circumference were found as the evident predictors (El-Gendi *et al.*, 2008).

The patients with CHD accompanied the most prominent risk factors of smoking, hyperlipidemia, hypertension, obesity and diabetes. The important determinants besides smoking, hypertension, central obesity and cholesterol levels were documented as Hcy, and fibrinogen. Serum platelet count, and HbA1c vs the platelets and other significant changes were obtained in CHD (Zapolski *et al.*, 2011).

It is known that myocardial ischemia can trigger myocardial damage, life-threatening ventricular arrhythmias, and series of other damaging conditions. The reactive oxygen species (ROS) products may cause decrease in antioxidant activity, lethal ventricular arrhythmias, and tissue injury after reperfusion of the ischemic myocardium (Zapolski *et al.*, 2011). Ischemia-reperfusion or also called as ischemia-reperfusion injury (IRI), or reoxygenation injury is an intracellular inflammatory response due to tissue blood supply after ischemia. Reduction in cellular energy (ATP) content, as one of the mechanisms for IRI is reduction in cellular energy and destruction of cellular ion homeostasis with activation of hydrolases leading to decreased organ function after transplantation.

Oxygen dependent cells in heart, brain and other organs are damaged by IRI and anaerobic glycolysis alone in place of mitochondrial oxidative phosphorylation cannot fulfil the energy requirements. Hence, decrease in pH of the cell occurs with release of H<sup>+</sup> from the lysosomes and increase in the flow rate of cytosolic Na<sup>+</sup> and Ca<sup>2+</sup> that destroys cellular ion homeostasis. ROS has potential significance in pathophysiology of myocardial infarction (MI) (Ojha *et al.*, 2012), and it has been investigated that post-ischemia ROS production and decrease in antioxidant task cause tissue dysfunction and ventricular arrhythmias.

Accumulation of free radicals, membrane lipid peroxidation as well as DNA damage have been found mainly related to CHD and other atherosclerotic disorders (Violi *et al.*, 2017) It is further known that control of cellular detoxification of various exogenous toxins is carried out by Glutathione-S-transferases (GSTs) that perform anti-oxidation activity, protection for cells against oxidative stress and related DNA damage. Kidney function dysfunction occurs with increased risk for CVD, and risk of CVD is increased partly to higher prevalence of older age, diabetes, hypertension, oxidative stress, and dyslipidemia. Serum creatinine is also an indicator of insulin functionality and hence diabetes mellitus is associated with CAD. Serum creatinine was found associated with pre-inflammatory markers such as Lp(a), apoAI and hsCRP, and independent relation with CAD. Elevated levels of leptin (Karbowska and Kochan, 2012) and resistin (Reilly *et al.*, 2005) were shown to be associated with increased BMI. This shows that these adipokines might have diagnostic importance in CHD with/ without obesity and will hence be determined in the present proposal.

### CHD-CLINICAL STUDIES TO MECHANISMS OF DISEASE

Evaluation of novel lipid indices using the most modern techniques for predicting the incidence of CVD and especially the CAD risk factors has revolutionized the recent approaches of understanding the mechanism of CHD (Jafari *et al.*, 2023). Experimental studies on the involvement of cholesterol metabolism, blood cholesterol, smoking and diabetes (Hussain *et al.*, 2007) and cholesterol and electrolyte variations (Sohail and Hussain, 2008) added important aspects related to involvement of lipid metabolism in medical disorders.

Influence of carp meat on lipid metabolism as preventive approach in CHD was quite successful (Mraz *et al.*, 2017). Functionality of HDL-C instead of measuring HDL-C was considered as a better marker for CHD and other CVD (Woudberg *et al.*, 2016), and the decreased concentration of HDL-C and increased concentration of LDL-C, TC and TG (Prajapati *et al.*, 2014) were revealed.

The remnant cholesterol rather than LDL-C associated with increased risks of CHD (Jepsen *et al.*, 2016), whereas the subjects of CHD with no inflammatory findings manifested higher LDL-C. Another report indicates the low levels of HDL-C as the better indicator for CHD (Longo-Mbenza *et al.*, 2007).

The resistance/aerobic training did not show high variation in LDL-C and TC, though the patients with CHD revealed higher levels of TC. Young patients had an association with sudden cardiac death (SCD) (Kunutsor *et al.*, 2017). The ratio of TG/HDL had high value in the initial event of CHD (Cordero *et al.*, 2009). It was shown that mortality risk was more in CHD patients having low HDL-C, and even the normal weight (NW) and underweight (UW) patients with low levels of HDL-C had increased mortality. The TC and TG levels were found in high levels in CHD patients (Sadeghi *et al.*, 2013). The CVD associates with hypertension (Longo-Mbenza *et al.*, 2007) and those hypertensive patients having two or more than two risk factors revealed significant high WBC count, and the smoking was noted as an important risk factor (Prajapati *et al.*, 2014).

The Hcy was found as an important factor in the atherogenesis in conditions comprising angina and repeated infarctions (Hodzic *et al.*, 2018; Habib *et al.*, 2023). The Hcy was noted as high in concentration in sedentary people, increasing with age and higher in males than females (Dankner *et al.*, 2004). Another study finds association of the progression of CHD with hyperhomocysteinemia (Mirdamadi *et al.*, 2011). Management of the heightened Hcy levels is possible by using the right diet, exercise, changing various lifestyle behaviors, and controlling obesity, diabetes, hypertension and other risk factors (Dankner *et al.*, 2004). The Hcy serves as a

predictor and the prognostic marker for atherosclerotic CVD, and its high concentrations have prognostic association with the progression to CHD processes (Habib *et al.*, 2023).

The Hcy was found in high concentration in those who were smoking, and those not using the vitamin-B supplements, and low in those who were using vitamin B. Patients with CHD manifested hyperhomocysteinemia with the deficiency of vitamin B6 and B12/or folic acid (Dankner *et al.*, 2004). The Hcy independently associates with CHD and found as a marker for predicting for CHD via BMI, obesity level and risks of CVD (Semiz *et al.*, 2008).

It is also important to note that though the Hcy is an important risk factor for CVD and especially CHD, its relation with CHD is altered by some polymorphisms (Mehlig *et al.*, 2013). In view of polymorphisms, some patients diagnosed as having the stable angina may have moderate hyperhomocysteinemic condition (Hoşoğlu *et al.*, 2012). Hyperhomocysteinemia was also seen without atherosclerosis that requires further studies for the clarification of the role of Hcy in CHD (Montaño-Loza *et al.*, 2004). The hematological aspects and endothelial mechanisms (Hussain *et al.*, 2007) emphasize to have more CHD studies. Role of hyperfibrinogenemia serving as risk for CHD (Mahendra *et al.*, 2015) was previously managed by reducing the fibrinogen levels (Wang *et al.*, 2005), and anti-Cit-fibrinogens was found associated with CHD (Hejblum *et al.*, 2018).

The elevated fibrinogen plasma levels have been revealed as risk for CHD. The clonal hematopoiesis, and other hematological analysis show the associations of these factors with CHD (Honigberg *et al.*, 2021). Plasma fibrinogen was noted to increase in response both to smoking and obesity factors independently beside proper diagnosis of unstable CHD, though the rise in fibrinogen levels were found in Q-wave CHD with/ without smoking and obesity that pointed out the development of necrosis whereas obesity and smoking additionally affected and raised the level of fibrinogen (Honigberg *et al.*, 2021).

The CHD was revealed to be associated with fibrinogen, RBC count and various other variables (Longo-Mbenza *et al.*, 2007) whereas fibrinogen rise was noted after exercise in those having at least one risk factor of CHD that showed association of fibrinogen with platelet count (Zapolski *et al.*, 2011). While studying the gene polymorphisms, fibrinogen chain gene has significantly more frequency in young CHD patients who survive and white blood cell count has high impact in CHD and other CVD as it associates with the decline in insulin sensitivity/resistance and association of neutrophil to lymphocyte ratio and CHD involvement.

## OBESITY AND PATHOPHYSIOLOGY OF CHD

Studies on obesity in various perspectives and risk factors for diabetic neuropathy (Sohail *et al.*, 2017) provided interesting information about the alterations occurring in CHD. There are several studies providing alterations occurring in view of obesity in CHD. Semiz *et al.* (2008) did not find a firm relation of BP, lipids and glucose levels with Hcy in obese people, though the fibrinogen levels during fasting were elevated. The Hcy levels associated with obesity and overweight status (Kumar *et al.*, 2017).

Cardiovascular disorders associated with central obesity (Hussain, 1998b) and a variety of variables/risk factors (Longo-Mbenza *et al.*, 2007; Lowenstern *et al.*, 2023). Obesity has enormous influence on the clinical outcome of CHD (Lowenstern *et al.*, 2023). Increased levels of abdominal obesity were significantly associated with CAD.

Diabetes and obesity in youth follows the main polymorphism (Rać *et al.*, 2012), and hence a new approach for the management of CHD patients emerged manifesting elevated obesity associating with atherosclerosis with the high correlation of BMI with plaque volume. Another approach is to fast on alternate day that helps decreasing body weight and CHD risk. A study investigated the influence of such fasting and additionally using the liquid food reduces the body weight leading to decrease in CHD risks (Klempel *et al.*, 2012).

The weight loss program improves the behavior, life quality, inflammatory conditions lipid levels and obesity. The long-term studies investigated that elevated level of CHD risks owing to obesity were not due to HDL-C but due to elevated BP and LDL-C to certain extent (Całyniuk *et al.*, 2016), and decreasing BMI influences the lipid levels and leads to less level of CHD risks (Całyniuk *et al.*, 2016). Obesity causes the arterial atherosclerosis due to increased levels of Hcy. Hence determining the Hcy is highly helpful for managing the atherosclerosis (Cioni *et al.*, 2016).

## CONCLUSION

There are a number of factors that can contribute in the development of CHD (Bytyçi *et al.*, 2021). Atherosclerosis is the most important cause of CHD and it may occur due to the inflammatory conditions (Libby, 2012). Pathogenesis of atherosclerosis involves mainly the inflammatory processes that may lead to CHD (Libby, 2012). Other risk factors of CHD are age, sex, familial causes, smoking, diabetes, hypertension, and hyperlipidemia.

The present review attempts to explore the extent of the involvement of fibrinogen and other hematological parameters, Hcy, LDL-C and various other variables in the development of CHD. Hence it provides further understanding of the CHD. It elucidates the prevention of risk factors, improvement in biomarker levels and control of CHD as a strategic plan for Saudi Vision 2030. Hence, it would provide a platform for conducting well organized studies in the prevalence and control of CHD, and would provide the pathophysiological understanding and control of CHD.

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