ISCHEMIC HEART DISEASE AND OBESITY: PLASMA LIPIDS, HOMOCYSTEINE AND HEMATOLOGICAL STUDIES

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ABSTRACT

Ischemic heart disease (IHD) or usually termed as myocardial ischemia is a group of clinical disorders/ syndromes that includes the chronic stable angina at one end and acute myocardial infarction on the other. Recent studies have taken a multidisciplinary and wider approach by investigating newer aspects for uncovering the mystery of the cause and cure of IHD. Obesity has been found profoundly involved as the causal factor for IHD. On the basis of a variety of studies and our own studies, we hypothesized that higher levels of plasma LDL-cholesterol (LDL-C), fibrinogen and homocysteine (Hcy) might be involved in disturbing the balance between the magnitude of injury and the capacity for repair, which may promote the progression of IHD with/ without obesity. There seems a significant role of Hcy, LDL-C, and fibrinogen beside other changes in lipid and hematological profile. Significant correlations for the association of plasma fibrinogen, LDL-C and Hcy further explain the role of these important factors in regulating the ischemic heart disease with/ without obesity and vice versa. Conclusively, this review study helps for acquiring better understanding of the pathophysiology of ischemic heart disease.

Key words: Ischemic heart disease (IHD), obesity, homocysteine (Hcy), lipids, fibrinogen, hematological changes, pathophysiology

INTRODUCTION

Ischemic heart disease (IHD) or usually termed as myocardial ischemia is a group of clinical disorders/ syndromes that includes the chronic stable angina at one end whereas acute myocardial infarction on the other. Within these two ends exists the intermediate syndromes, all related to oxygen demand and supply. There are several recent studies on the occurrence of IHD and its management (Mahendra *et al*., 2015; Całyniuk *et al*., 2016; Cioni *et al*., 2016; Hafez *et al*., 2016; Jepsen *et al*., 2016; Kunutsor *et al*., 2016; Woudberg *et al*., 2016; Mraz *et al*., 2017; Hejblum *et al*., 2018; Hodzic *et al*., 2018). There are excellent recent reviews on various aspects of IHD (Taqueti and Di Carli , 2018; Ahirwar and Mondal, 2019; Whayne and Saha, 2019).

The IHD comprises various aspects and has increased quite much dramatically in recent years particular after the appearance of updated report of the National Cholesterol Education Program (NCEP) in US (Hussain, 1993; Hussain, 1998c; Monte and Pascal, 2002). Although various aspects of the disorder have been studied, the major focus still is on LDL-C and possible ways to reduce its levels (Hussain, 1992b; Monte and Pascal, 2002).

Some important studies related to IHD in general are: the role of LDL-C and triglycerides in repairing the endothelial dependent vasodilation (Dart and Chin, 1999), interaction of LDL-C with nitric oxide signaling including receptor G protein coupling, nitric oxide synthase, and production of less potent dilator (Dart and Chin, 1999), association between serum lipid profile, CHD and cellular pathophysiology (Hussain, 1991a; Dart and Chin, 1999;), carp meet having significantly different effects on plasma lipids showing secondary prevention for ischemic heart disease (IHD) (Mraz *et al*., 2017), HDL functionality and subclass rather than just HDL-C levels suggesting as good indicator for cardiovascular disease (CVD) risk (Hussain, 1991c; Woudberg *et al*., 2016), remnant cholesterol instead of just LDL cholesterol associated with higher risk of IHD (Jepsen *et al*., 2016), HDL-C and LDL-C in the middle-aged male subjects associated with the occurrence of SCD (sudden cardiac death) (Kunutsor *et al*., 2016), major adverse cardiac events (MACE) mainly the postinfarctic angina pectoris and repeated infarction conditions having strong positive correlation with homocysteine being atherogenic marker (Hodzic *et al*., 2018), hyperfibrinogenemia increasing the risk for IHD (Mahendra *et al*., 2015), association between ischemic heart disease outcome and anti-Cit-fibrinogens (Hejblum *et al*., 2018), reduction in body mass/ BMI effecting blood levels of lipids leading to reduction of risk factors for IHD (Hussain, 1991b; Całyniuk *et al*., 2016), Hcy evaluation helpful as secondary prevention detecting the systemic atherosclerosis with acute coronary syndrome (Cioni *et al*., 2016),

and highly significant increase in fibrinogen levels in obese male and female subjects as stronger predictor for CVD risk (Hafez *et al.*, 2016).

However, recent studies have taken a multidisciplinary and wider approach by investigating newer aspects for uncovering the mystery of the cause and cure of IHD. Obesity has been found profoundly involved in the causal source of IHD wherein the role of homocysteine, lipid profile (especially LDL-C) and hematological profile (specifically fibrinogen) might be very significant (Banz *et al.*, 2003; Dankner *et al.*, 2004 ; Skibińska *et al.*, 2004; Kazemi *et al.*, 2006; Ni *et al.*, 2007; Lin *et al.*, 2008; Semiz *et al.*, 2008; Tani *et al.*, 2009; Mirdamadi *et al.*, 2011; Zapolski *et al.*, 2011; Javaid *et al.*, 2012a,b; Hoţoleanu *et al.*, 2012; Rać *et al.*, 2012; Li *et al.*, 2013; Lin *et al.*, 2013; Mehlig *et al.*, 2013; Sadeghi *et al.*, 2013; Sohail *et al.*, 2013; Varbo *et al.*, 2013; Prajapati *et al.*, 2014; Mahendra *et al.*, 2015; Varbo *et al.*, 2015; Całyniuk *et al.*, 2016; Cioni *et al.*, 2016; Hafez *et al.*, 2016; Jepsen *et al.*, 2016; Kunutsor *et al.*, 2016; Woudberg *et al.*, 2016; Mraz *et al.*, 2017; Hejblum *et al.*, 2018; Hodzic *et al.*, 2018).

Furthermore, our previous reports on the role of homocysteine in ischemic stroke (Naz *et al.*, 2009), modifiable risk factors in ischemic disorders (Hussain, 1991b; Khan *et al.*, 2009; Khan and Hussain, 2008), renal ischemia (Yasmeen *et al.*, 2008), hypercholesteremia (Hussain, 1991a; Hussain, 1998b; Fatima *et al.*, 2007) and ischemic disorders in diabetes mellitus (Hussain *et al.*, 2007a,b) are in agreement with the present results. Some of our other studies (Hussain, 1991c, 1992a; Hussain and Zahir, 2012; Javaid *et al.*, 2012 a,b; Sohail *et al.*, 2013) also verify the present investigations. On the basis of a variety of studies and following previously described our clinical tests, methodologies and statistical analysis (Hussain, 1991d; Hussain, 2010; Zahir *et al.*, 2014), we hypothesized that higher levels of plasma LDL cholesterol, and plasma fibrinogen and homocysteine might be involved in disturbing the balance between the magnitude of injury and the capacity for repair, which may promote the progression of ischemic heart disease with/ without obesity (Javaid, 2015).

ISCHEMIC HEART DISEASE

Cardiovascular disease is linked with abdominal obesity, hypertension, low HDL-C and cholesterol related with RBC count, body weight, waist circumference, fibrinogen, glucose and a variety of other factors, and myocardial infarction was found associated significantly with low HDL-C (Longo-Mbenza *et al.*, 2007). The IHD in obese patients have been studied in various perspectives (Całyniuk *et al.*, 2016; Cioni *et al.*, 2016; Hafez *et al.*, 2016).

Two major types of polymorphisms were studied in patients with CAD, one manifesting in youth and comprising high prevalence of obesity and diabetes, whereas the other polymorphism appearing in old age MI with higher WBC count (Rać *et al.*, 2012). A new approach for treating obese CAD patients was demonstrated that increase in BMI decreases pravastatin-induced coronary atherosclerosis regression, whereas plaque volume positively correlates with BMI (the independent predictor of variation in plaque volume) and negatively with TC/HDL-C ratio and total WBC count (Tani *et al.*, 2009).

Diets used by vegetarians not only lower BMI but also decrease BMI related rise in atherogenic lipids, lipoproteins and ischemic heart disease. A study carried out in the adult population in Northern Nigeria indicates serum Hcy levels of the patients with myocardial infarction and control subjects were not significantly different, and BP and the LDL-C/HDL-C ratio associated with myocardial infarction (Glew *et al.*, 2004). The levels of TC, TG, and LDL were higher but HDL and Hcy were not significantly different in obese adolescents compared to normal adolescents, though one fourth of obese subjects had hyperhomocysteinemia. Hence, Hcy may be considered as a prominent risk factor in CAD in obese adolescents (Kouzehgaran *et al.*, 2015).

Volunteers exhibiting android obesity and at least one other risk factor for coronary artery disease were included in a study to aerobic or resistance training that revealed increase in plasma fibrinogen in both groups after their respective training regimen but no significant change in SBP (systolic blood pressure) and no change in plasma levels of TC, LDL-C, TC and glucose were found. Only aerobic training increased HDL-C (13%). More studies are needed to determine the effects of exercise on fibrinogen plasma levels (Banz *et al.*, 2003).

Young patients with heart disease showed significantly higher levels of TC, LDL and TG and significantly lower levels of HDL, and prominent common risk factors in young ACS (acute coronary syndrome) patients were positive family history, hyperhomocysteinaemia, and smoking (Prajapati *et al.*, 2014).

Plasma tHcy (total homocysteine) levels were not different significantly between patients with CAD, and controls, though increased levels of plasma fibrinogen and abdominal obesity were significantly associated with CAD (Gheye *et al.*, 1999). The Hcy levels in right and left carotid and right femoral arteries increased, whereas some of the prominent predictors of intima-media thickness (IMT) of carotid artery were age, Hcy, TG, waist circumference and waist/hip ratio, and the prominent predictors of atheroma were age and triglycerides (El-Gendi *et al.*, 2008).

The MI patients had hyperlipidemia in 86%, smoking in 89%, hypertension in 21%, obesity in 15%, and diabetes in 14% (Lewandowski *et al.*, 2003). Beside serum cholesterol, smoking, and hypertension, plasma

fibrinogen and homocysteine are considered as independent risk factors as well for CAD. It was revealed that increased plasma fibrinogen, abdominal obesity and non-significant change in homocysteine associated with CAD, and higher levels of TC, waist-to-thigh ratio and waist-to-hip ratio were the other determinants (Gheye *et al*., 1999). Significant correlation for HbA(1c) vs platelet count, pro-inflammatory state correlation with prothrombotic markers such as serum platelet count and fibrinogen and a variety of other alterations were found in patients with CAD and other disorders (Zapolski *et al*., 2011). It was investigated that Low lean mass index (LMI) but not body fat (BF) predicts all-cause mortality in Chinese CAD patients and hence, increasing LMI and reducing mortality rate has a close association (Huang *et al*., 2015).

LIPID AND RELATED PHYSIOLOGICAL STUDIES

Previous lipid studies carried out in our laboratory (Abbas *et al*., 1995; Khan *et al*., 1995; Hussain, 1998a; Hussain *et al*., 2007b,c; Sohail and Hussain, 2008) provided important insight about the significance of lipids in clinical disorders. Carp meet from two aquaculture systems had significantly different effects on plasma lipids showing secondary prevention for ischemic heart disease (IHD) (Mraz *et al*., 2017). Young patients with ACS showed significantly higher levels of TC, LDL and TG and significantly lower levels of HDL (Prajapati *et al*., 2014). The HDL functionality and subclass rather than just HDL-C levels have been suggested as good indicator for cardiovascular disease (CVD) risk (Woudberg *et al*., 2016).

Heart disease is linked with low HDL-C and cholesterol related with WC, and a variety of other factors, and myocardial infarction associated significantly ($p<0.05$) with low HDL-C (Longo-Mbenza *et al*., 2007). The patients with IHD without inflammation are associated causally with the elevated LDL-C (Varbo *et al*., 2013). The remnant cholesterol instead of just LDL cholesterol was found associated with higher risk of IHD (Jepsen *et al*., 2016).

Higher levels of TC associated with CAD (Gheye *et al*., 1999). Volunteers exhibiting android obesity and at least one other risk factor for coronary artery disease were included in a study to aerobic or resistance training that revealed no change in plasma levels of TC, LDL-C, and TC in both groups after their respective training regimen but only aerobic training increased HDL-C (13%) (Banz *et al*., 2003).

The CAD patients in Taiwan with low HDL-C, and normal weight or underweight were found to have higher mortality risk (Lin *et al*., 2013). Significantly higher concentration of TC and TG were found in patients with CHD compared to patients without CHD, and significant inverse relationship of WC with HDL-C were seen in CHD patients (Sadeghi *et al*., 2013). TG/HDL ratio in all categories of BMI has high predictive value associated with the first coronary artery event (Cordero *et al*., 2009). The young men with AMI are protected by HDL-C (Li *et al*., 2013). HDL-C and LDL-C in the middle-aged male subjects were found associated with the occurrence of SCD (sudden cardiac death) (Kunutso *et al*., 2016).

Volunteers exhibiting android obesity and at least one other risk factor for coronary artery disease were included in a study to aerobic or resistance training that revealed no significant change in SBP (systolic blood pressure) in both groups after their respective training regimen (Banz *et al*., 2003).

Cardiovascular disease is linked with hypertension, and a variety of other factors (Longo-Mbenza *et al*., 2007). Hypertensives with two or more risk factors had significantly higher WBC count compared to those hypertensives with no apparent risk factors (Capuano *et al*., 1998). Volunteers exhibiting android obesity and at least one other risk factor for coronary artery disease were included in a study to aerobic or resistance training that revealed no change in plasma levels glucose after their respective training regimen (Banz *et al*., 2003). Smoking was one of the prominent common risk factors in young heart disease patients (Prajapati *et al*., 2014).

HOMOCYSTEINE

Major adverse cardiac events (MACE) mainly the postinfarctic angina pectoris and repeated infarction conditions were found having strong positive correlation with homocysteine being atherogenic marker (Hodzic *et al*., 2018). Mean values of Hcy obtained were 10.5 +/- 5.5 micromol/L L (11.4 +/- 6.1 and 9.3 +/- 4.5 respectively for males and females) (Dankner *et al*., 2004). Hcy was found 10% higher in sedentary subjects, 17% higher in male subjects, and 1% higher for each year increase in age (Dankner *et al*., 2004). Elder people need to keep themselves physically active that help decreasing the Hcy levels (Dankner *et al*., 2004).

It was suggested that the hyperhomocysteinemia is a risk factor for CHD, and the patients with CAD showed significantly higher plasma tHcy compared to controls (17.1 ± 5.3 versus 14.2 ± 3.8; P= 0.004) (Mirdamadi *et al*., 2011). Plasma level of Hcy has significant association with the incidence and progression of CAD (Skibińska *et al*., 2004). Hyperhomocysteinemia relates as an independent risk factor with CAD, and with no other risk factors and Hcy and number of coronary artery involvements are correlated linearly (Kazemi *et al*., 2006). Furthermore, homocysteinemia was found an important independent risk factor of CAD similar to that of dyslipidemia in the Chinese population at high risk of CAD (Ni *et al*., 2007).

It is known that increased plasma Hcy is a prominent risk factor for CVD, and there are a variety of ways to bring the Hcy level toward normal range by modifying the life style risk factors including regular physical activity, appropriate diet for controlling CVD, hypertension, obesity and diabetes (Dankner *et al*., 2004). Hyperhomocysteinaemia was one of the prominent common risk factors in young ACS patients (Prajapati *et al*., 2014).

It was noted that that it was not BMI but WHR a strong independent predictor correlating with plasma level of tHcy in male patients with CAD (Lin *et al*., 2008). Hcy and cardiovascular disease has an established association, and trying to assess the association of multiple markers present to any extent in patients as predictors of CVD will be more helpful in the management of complications (Cummings *et al*., 2006). Hcy was 10% higher in those who did not use B vitamin-supplements (Dankner *et al*., 2004). Deficiency of vitamins B6, B12 or folic acid along with mild hyperhomocysteinemia are the highly prevalent risk factors for patients with CAD especially acute myocardial infarction (AMI) and Hcy levels were significantly lower in the subjects using B vitamin supplements (p = 0.004) and those who are physically active (p = 0.002) (Dankner *et al*., 2004). The Hcy levels were not found to be associated with smoking (Dankner *et al*., 2004).

The IHD was found associated with serum tHcy independently of other risk factors except diabetes in a Mediterranean cohort (Vrentzos *et al*., 2004). Hcy serves as a predictor for any future coronary complication in men and women, and hence, relationship of Hcy levels with BMI, relative weight (RW), obesity and cardiovascular risk factors was investigated (Semiz *et al*., 2008). However, it did not show correlation with serum lipid levels, BMI, BP (systolic and diastolic), glucose, and RW (Semiz *et al*., 2008).

Homocysteine level differentiates patients with classically diagnosed heart disease without clinical symptoms but with similar levels of serum lipids, BMI and BP, and Hcy levels were observed as lower than 10 mmol/l in 53.3% controls and 27.7% of patients diagnosed as CHD whereas 29.7% patients with CHD and 5% controls had above 15 mmol/l of Hcy levels (Jarosz and Nowicka, 2008). High total Hcy is a risk factor of CHD. However, association between plasma Hcy and CAD is changed by certain polymorphism while not by others (Mehlig *et al*., 2013).

A patient diagnosed with stable angina class functional II suffered from moderate hyperhomocysteinemia due to polymorphism (Hoțoleanu *et al*., 2012). In patients having same degree of CAD, those having hyperhomocysteinaemia had a decreased burden of general risk factors while compared with those having normal levels of tHcy (Pizzolo *et al*., 2006). Another study shows hyperhomocystinemia (> 12 micromol/L) in Mexican people but without CA (coronary atherosclerosis) that needs further studies to clarify in this population (Montaño-Loza *et al*., 2004). Another report investigates non-significant change in homocysteine associated with CAD (Gheye *et al*., 1999).

HEMATOLOGICAL STUDIES

Previous clinical and experimental studies in our lab (Hussain, 1990, 2007; Hussain *et al*., 2007c) were helpful for carrying out such studies in human patients with IHD. It was revealed that hyperfibrinogenemia increases the risk for IHD (Mahendra *et al*., 2015). Increased levels of plasma fibrinogen was significantly associated with CAD (Gheye *et al*., 1999). Plasma fibrinogen level (435.45 mg/dl +/- 115.25 mg/dl) was higher as an independent risk factor in the peripheral arterial occlusive disease (PAOD) group patients than in the control group (360.96 mg/dl +/- 93.52 mg/dl; P = 0.001), and hence, inhibiting platelet aggregation and reducing plasma fibrinogen level in the PAOD patients is a choice for the clinician (Wang *et al*., 2005). A population of men and women showing increased fibrinogen concentration and even hyperfibrinogenemia in CAD, and concomitant impaired activity of the fibrinolytic system were considered as significant cardiovascular risk predictor (Stein *et al*., 1997). Furthermore, Association between ischemic heart disease outcome and anti-Cit-fibrinogens was investigated (Hejblum *et al*., 2018).

Increased level of plasma fibrinogen is considered as independent risk factor for CAD (Gheye *et al*., 1999). Plasma levels of fibrinogen because of suspected unstable CAD (unstable angina pectoris or non-Q-wave MI) were determined and it was important to note that beside diagnosing the unstable CAD, obesity and smoking contributed independently in elevating the plasma fibrinogen. However, fibrinogen was high in non-Q-wave MI regardless of obesity and smoking that interpreted that myocardial necrosis was the major cause and obesity and smoking additionally effected the metabolism of fibrinogen and exaggerated the event, and clearly the increased level of fibrinogen in unstable CAD contributed in causing the hypercoagulability for the progression of the lesions in CAD (Swahn *et al*., 1989).

Volunteers exhibiting android obesity and at least one other risk factor for coronary artery disease were included in a study to aerobic or resistance training that revealed increase in plasma fibrinogen (P < 0.02) in both groups after their respective training regimen More studies are needed to determine the effects of exercise on

fibrinogen plasma levels (Banz *et al*., 2003). It was suggested that cardiac disease is linked with RBC count, fibrinogen and a variety of other factors (Longo-Mbenza *et al*., 2007). Significant correlation for HbA(1c) vs platelet count (r = 0.263; p = 0.0112), pro-inflammatory state correlation with prothrombotic markers such as serum platelet count and fibrinogen and a variety of other alterations were found in patients with CAD and other disorders (Zapolski *et al*., 2011).

Polymorphisms in the genes encoding for three separate chains of fibrinogen have been documented and polymorphism of fibrinogen beta-chain gene having significantly higher frequency in young survivors of myocardial infarction (MI) than in controls (40.4% vs 29.5%, p<0.01) is associated with an increased plasma fibrinogen in MI patients carrying the mutant allele compared to patients without mutant allele (3.87 vs 3.55 g/L, p=0.05) in young survivors of myocardial infarction (MI) (Lewandowski *et al*., 2003).

The WBC count is considered as a risk factor in cardiovascular disease by the decreased insulin sensitivity that is a link between WBC count and cardiovascular disease especially CAD, and hence insulin resistance syndrome (IRS) could be partly due to elevated WBC count (Piédrola *et al*., 2001). There is an association between neutrophil to lymphocyte ratio (NLR) and coronary artery ectasia (CAE) and in isolated form it has no significant stenosis but comprises more evident inflammatory symptoms (significantly increased NLR compared to the patients having normal coronary artery pathology (3.39 ± 1.36 vs. 2.25 ± 0.58; p<0.001) (Işık *et al*., 2013).

OBESITY

Our lab and other studies on obesity in various perspectives (Hussain, 1992c; Hasan *et al*., 2011; Rehman *et al*., 2013, 2014, 2016; Sohail *et al*., 2017) provided a platform to study its association with IHD and underlying changes. No correlation of Hcy was found with BMI and RW (relative weight) in obese subjects (Semiz *et al*., 2008). The Hcy levels were not found associated with BMI (Dankner *et al*., 2004).

No correlation of Hcy was found with serum lipid levels, glucose and BP (systolic and diastolic) in obese subjects (Semiz *et al*., 2008). Another report revealed that fasting levels of fibrinogen in obese children were significantly increased than those in the controls subjects (Ezgü *et al*., 2009). Significantly higher levels of serum homocysteine in a recent report were obtained in overweight as well as obese children while compared with normal children (Kumar *et al*., 2017). It was investigated in another recent study that pro-atherogenic homocysteine levels may be modified by abdominal obesity (Borowska *et al*., 2017).

ISCHEMIC HEART DISEASE AND OBESITY

Cardiovascular disease and other disorders are linked with abdominal obesity, body weight, glucose and a variety of other factors (Hussain, 1998b; Longo-Mbenza *et al*., 2007; Rehman *et al*., 2013). Increased levels of abdominal obesity was significantly associated with CAD (Gheye *et al*., 1999). Two major types of polymorphisms were studies in patients with CAD, one of these is manifested in youth and comprising high prevalence of obesity and diabetes (Rać *et al*., 2012). A new approach for treating obese CAD patients was demonstrated that increase in BMI decreases pravastatin-induced coronary atherosclerosis regression, whereas plaque volume positively correlates with BMI (the independent predictor of variation in plaque volume) (Tani *et al*., 2009).

Alternate day fasting (ADF) for the obese people is quite appropriate for losing body weight and decreasing the risk of CAD (Varady *et al*., 2009). Intermittent fasting (IF) with calorie restriction (CR) and use of liquid meals is an important approach to help obese women lose their weight and lower the CHD risk (reduction in body weight (P = 0.04),and TC and LDL-C (P = 0.04) were greater; and decrease in glucose, heart rate, and Hcy levels occurred (P < 0.05) (Klempel *et al*., 2012).

Though the concept of obesity paradox for using baseline BMI or baseline percent fat criteria is considered essential, purposeful weight loss with cardiac rehabilitation and exercise training (CRET) program for obese/overweight cardiac patients is considered as non-significant way for decreasing mortality, and it shows clear improvements in obesity indices, plasma lipids, inflammation, exercise capacity, quality of life and other behavioral improvements (Lavie *et al*., 2009).

Follow up study of about 22 years showed that increased IHD risk developing due to obesity was mediated partly via increased LDL-C and BP (especially systolic BP) and possibly through increased non-fasting glucose, but not through decreased HDL-C as found by genetic analysis (Varbo *et al*., 2015). Reducing the body mass/ BMI effects blood levels of lipids and reduces the risk factors for IHD (Całyniuk *et al*., 2016)

Level of Hcy in early arterial atherosclerotic found in simply obese children reveals obesity induced early arterial atherosclerosis due to hyperhomocysteinemia (Huang *et al*., 2005). For the secondary prevention, evaluation of Hcy helps detecting the systemic atherosclerosis with acute coronary syndrome (Cioni *et al*., 2016). A new approach for treating obese CAD patients was demonstrated that increase in BMI decreases pravastatin-induced coronary atherosclerosis regression, whereas plaque volume correlates negatively with total WBC count (Tani *et al*.,

2009). Moreover, highly significant increase in fibrinogen levels were found in obese male and female subjects and were considered stronger predictor for CVD risk (Hafez *et al*., 2016).

CONCLUSIONS

Ischemic heart disease occurs usually due to atherosclerosis of coronary arteries that is considered as the most common cause of death world over. Age, sex, hyperlipidemia, hypertension, smoking, diabetes and familial causes are the major risk factors of ischemic heart disease. These might be the main risk factors of coronary heart disease, but there are CHD patients with no identifiable risk factors. Hence, there is need of further work to be carried out to establish sound pathophysiological backgrounds for ischemic heart disease.

The impact and role of plasma homocysteine, lipid profile and hematological and general physiological aspects in causing ischemic heart disease have been discussed in this review. There is a significant role of Hcy, LDL-C, and fibrinogen beside other changes in lipid and hematological profile. Significant correlations for the association of plasma fibrinogen, LDL-C and Hcy further explain the role of these important factors in regulating the ischemic heart disease and vice versa. Conclusively, the current literature in IHD helps in acquiring better understanding of the pathophysiology of ischemic heart disease.

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