INT. J. BIOL. BIOTECH., 16 (1): 49-58, 2019.

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

Aisha Javaid[1], Sumera Sohail[1], Taseer Ahmed Khan[1], Huma Zahir[2] and Zahir Hussain[3*]

[1]*Department of Physiology, University of Karachi, Karachi, Pakistan*
[2]*Biomedical, Computational and Theoretical Research (BCTR) Lab, DHA, Karachi, Pakistan*
[3]*Department of Physiology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia*
[*]**Corresponding author email: zahussai@yahoo.ca**

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 (Hoţoleanu *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.

REFERENCES

Ahirwar, R. and P.R. Mondal (2019). Prevalence of obesity in India: A systematic review. *Diabetes Metab Syndr*., 13(1): 318-321.

Abbas, K., N. Khan, S. Inam, S. Masood, and Z. Hussain (1995). Influence of estradiol valerate on plasma phospholipids in Uromastix hardwickii. *First National Conference on Pharmacology and Therapeutics*, Faculty of Pharmacy, University of Karachi. p. 34.

Banz, W.J., M.A. Maher, W.G. Thompson, D.R. Bassett, W. Moore, M. Ashraf, D.J. Keefer and M.B. Zemel (2003). Effects of resistance versus aerobic training on coronary artery disease risk factors. *Exp Biol Med.* (Maywood)., 228(4): 434-40.

Borowska, M., M. Dworacka, H. Winiarska and E. Krzyżagórska (2017). Homocysteine as a non-classical risk factor for atherosclerosis in relation to pharmacotherapy of type 2 diabetes mellitus. *Acta Biochim Pol.*, 64(4): 603-607.

Całyniuk, B., E. Grochowska-Niedworok, M. Muc-Wierzgoń, E. Nowakowska-Zajdel, M. Osowski (2016). The effectiveness of the low energy diet in overweight and obese adults. *Rocz Panstw Zakl Hig*., 67(2): 137-46.

Cioni, G., R. Marcucci, A. M. Gori, S. Valente, C. Giglioli, G.F. Gensini, R. Abbate and M. Boddi (2016). Increased homocysteine and lipoprotein(a) levels highlight systemic atherosclerotic burden in patients with a history of acute coronary syndromes. *J Vasc Surg*., 64(1):163-70.

Cordero, A., E. Andrés, B. Ordoñez, M. León, M. Laclaustra, A. Grima, E. Luengo, J. Moreno, M. Bes, I. Pascual, F. Civeira, M. Pocoví, E. Alegría and J.A. Casasnovas (2009). Metabolic Syndrome Active Subjects Study Investigators.Usefulness of triglycerides-to-high-density lipoprotein cholesterol ratio for predicting the first coronary event in men. *Am J Cardiol.*, 104(10): 1393-7.

Cummings, D.M., D.E. King, A.G. Mainous and M.E. Geesey (2006). Combining serum biomarkers: the association of C-reactive protein, insulin sensitivity, and homocysteine with cardiovascular disease history in the general US population. *Eur J Cardiovasc Prev Rehabil*., 13(2): 180-5.

Dankner, R., A. Chetrit, F. Lubin and B.A. Sela (2004). Life-style habits and homocysteine levels in an elderly population. *Aging Clin Exp Res*., 16(6):437-42.

Dart, A.M. and J.P. Chin-Dusting (1999). Lipids and the endothelium. *Cardiovasc Res*., 43(2): 308-22.

El-Gendi, S.S., M. Bakeet, E.A. El-Hamed, F.K. Ibrahim and R. Ahmed (2008). The value of lipoprotein (a), homocysteine, and Doppler of carotid and femoral arteries in assessment of atherosclerosis in asymptomatic cardiovascular risk patients. *J Cardiol*., 52(3): 202-11.

Ezgü, F., L. Tümer, F. Ozbay, A. Hasanoglu, G. Biberoğlu and C. Aybay (2009). Homocysteine, fibrinogen and anti-ox-LDL antibody levels as markers of atherosclerosis in prepubertal obese children. *J Pediatr Endocrinol Metab*., 22(10): 915-20.

Fatima, S., N.I. Khan, G. Yasmeen, B. Hajir and Z. Hussain (2007). Antiatherogenic effects of Nigella Sativa (Kalonji) in rabbits with experimentally induced hypercholesterolemia. *Int.J.Biol.Biotech.*, 4(4): 437-441.

Gheye, S., A.V. Lakshmi, T.P. Krishna and K. Krishnaswamy (1999). Fibrinogen and homocysteine levels in coronary artery disease. *Indian Heart J.*, 51(5): 499-502.

Glew, R.H., H. Okolie, M. Crossey, O. Suberu, M. Trujillo, M. Pereyra and D.J. Vanderjagt (2004). Serum lipid profiles and homocysteine levels in adults with stroke or myocardial infarction in the town of Gombe in northern Nigeria. *J Health Popul Nutr*., 22(4):341-7.

Hafez, M., S. El-Masry, N. Musa, M. Fathy, M. Hassan, N. Hassan, M. El Husseiny and M. Tareef (2016). Relationship between visceral obesity and plasma fibrinogen in obese children. *J Pediatr Endocrinol Meta*b., 29(3):289-96.

Hasan, R., M. Ahmad, A. Javaid and Z. Hussain (2011). The altered plasma electrolytes concentrations induced by weight reducing herbal drug (Mehzileen) in common rabbits. *Int. J. Biol. Biotech*., 8 (4): 575-578.

Hejblum, B.P., J. Cui, L.J. Lahey, A. Cagan, J.A. Sparks, J. Sokolove, T. Ca and K.P. Liao (2018). Association Between Anti-Citrullinated Fibrinogen Antibodies and Coronary Artery Disease in Rheumatoid Arthritis. *Arthritis Care Res* (Hoboken)., 70(7):1113-1117.

Hodzic, E. (2018). Potential Anti-Inflammatory Treatment of Ischemic Heart Disease. *Med Arch.*, 72(2):94-98.

Hoţoleanu, C. and E. Chouky (2012). Hyperhomocysteinemia and methylenetetrahydrofolate reductase polymorphism in a patient with coronary artery disease and repetitive miscarriages. *Rom J Intern Med.*, 50(4):313-6.

Huang, B.T., Y. Peng, W. Liu, C. Zhang, F.Y. Huang, P.J. Wang, Z.L. Zuo, Y.B. Liao, H. Chai, K.S. Huang, D.J. Huang and M. Chen (2015). Lean mass index, body fat and survival in Chinese patients with coronary artery disease. *QJM*, 108(8):641-7.

Huang, X.M., Y.Y. Zhang, Z.S. Yu, W.H. Zhu, J.F. Fu, J. He and G.P. Jiang (2005). Early arterial atherosclerosis and level of plasma homocysteine in simply obese children. *Zhonghua Er Ke Za Zhi.*, 43(3):192-5.

Hussain, Z. (2010). *Menstrual Cycle and Epilepsy: Premenstrual Reproductive Study. Germany* (Printed in USA & UK). (ISBN (International Standard Book No.): 978-3-639-28200-9; GNL (German National Library-Thomson Reuters-ISI Copyright Library). Pages: 239 (Book).

Hussain, Z. (2007). Hematobiochemical changes in a kindling model of epilepsy. *Int. J. Biol Biotech*. 4 (2-3) :205-211.

Hussain, Z. (1998a). Angina pectoris-Clinical and therapeutic considerations. *The Med Intern,* 1(3): 2

Hussain, Z. (1998b). Diagnosis and treatment of ischemic heart disease. *The Med Intern*, 1(3): 7

Hussain, Z. (1998c). Coronary artery disease-clinical and therapeutic consideration. *The Med Intern*, 1(1): 3-4

Hussain, Z. (1993) Angina pectoris. *Med Rev*, 5 (8):2-4.

Hussain, Z. (1992a). Clinical study of angina pectoris. *Med Rev*, 4(1):1-3.

Hussain, Z. (1992b). Clinical presentation and treatment measures of congestive heart failure. *Med Rev*, 4(4):3-5.

Hussain, Z. (1992c). Recognizing the complexities of obesity. *Med Rev*, 4 (10): 2-4.

Hussain, Z. (1991a). Clinico-biological study of coronary artery disease. *Pak Med J.*, 14 (5): 35-38.

Hussain, Z. (1991b). Ischemic heart disease-Recent perspectives. *Med Rev*, 3 (10): 1-3.

Hussain, Z. (1991c). Diagnosis and treatment of congestive heart failure. *Med Rev*, 3(5): 11-12.

Hussain, Z. (1991d*). Clinical, electroencephalographic and hormonal study in menstruation related seizures*. PhD Thesis, Department of Physiology, University of Karachi. Pages: 236.

Hussain, Z. (1991e). Recent developments in the management of rheumatic heart disease. *Med Rev*, 3 (1):1-3.

Hussain, Z. (1991f). Clinical and therapeutic aspects of angina pectoris. Med Rev, 3 (12): 4-6.

Hussain, Z. (1990). Hematological changes associated with infection. Cardiology and Hematology. *Med Rev*, 2 (4): 1-3.

Hussain, Z., K.Z. Hasan, H. Aziz and M.A. Qureshi (2007a). Clinical and neurological study of women with precatamenial epilepsy. *JCPSP*, 17 (4):211-214.

Hussain, Z., S. Sohail and A. Ashraf. (2007 b). Blood cholesterol concentration in smoking and non-smoking patients with diabetes mellitus. *Human Health*, 3(7 & 8): 5-8.

Hussain Z, S. Sohail and A. Ashraf (2007 c). Endothelial dysfunction, cytokines and diabetes mellitus. *Human Health, 3(7 & 8): 3-4.*

Hussain, Z. and H. Zahir (2012). Sodium channels, neurosteroid receptors and physiochemical and ischemic changes in a kindling model of epilepsy in rat. *Annual Symposium* JPMC, Karachi.

Işık, T., E. Ayhan, H. Uyarel, I.H. Tanboğa, M. Kurt, M. Uluganyan, M. Ergelen and A. Eksik (2013). Association of neutrophil to lymphocyte ratio with presence of isolated coronary artery ectasia. *Turk Kardiyol Dern Ars*., 41(2):123-30.

Jarosz, A. and G. Nowicka (2008). C-reactive protein and homocysteine as risk factors of atherosclerosis. *Przegl Lek*., 65(6):268-72.

Javaid, A. (2015*). LDL cholesterol, hematological profile and other physiological studies in patients with ischemic heart disease*. PhD Thesis, Department of Physiology, University of Karachi, P: 76.

Javaid, A., R. Hasan, A. Zohra and Z. Hussain (2012a). A comparative study of the antihypertensive agents on serum liver enzymes ALT, AST and ALP of hypertensive and cardiac patients. *J Basic Appl Sci.*, l:8:468-472.

Javaid, A., Z. Hussain, R. Hasan and A.E. Ali (2012b). Homocysteine variations in patients with ischemic heart disease. *Int J Biol Biotech*., 9(3): 263-266.

Jepsen, A.M., A. Langsted, A. Varbo, L.E. Bang, P.R. Kamstrup and B.G. Nordestgaard (2016). Increased Remnant Cholesterol Explains Part of Residual Risk of All-Cause Mortality in 5414 Patients with Ischemic Heart Disease. *Clin Chem.*, 62(4):593-604.

Kazemi, M.B., K. Eshraghian, G.R. Omrani, K.B. Lankarani and E. Hosseini (2006). Homocysteine level and coronary artery disease. *Angiology*, 57(1):9-14.

Khan, N., K. Abbas, S. Masood, S. Inam and Z. Hussain (1995). Effect of estradiol valerate on plasma cholesterol in *Uromastix hardwickii. First National Conference on pharmacology and therapeutics*. Faculty of Pharmacy. University of Karachi. p.43.

Khan, N.I. and Z. Hussain (2008). Pathophysiology of ischemic disorders: 1- LDL cholesterol and Ischemic stroke. *Int J Biol Biotech*., 5 (1-2): 1-16.

Khan, N.I., L. Naz, S. Mushtaq, L. Rukh, S. Ali and Z. Hussain (2009). Ischemic stroke: Prevalence of modifiable risk factors in male and female patients in Pakistan. *Pak J Pharmaceut* Sci., 22(1): 62-67.

Klempel, M.C., C.M. Kroeger, S. Bhutani, J.F. Trepanowski and K.A. Varady (2012). Intermittent fasting combined with calorie restriction is effective for weight loss and cardio-protection in obese women. *Nutr J.*, 11:98.

Kouzehgaran, S., R. Vakili, M. Nematy, M. Safarian, M. Ghayour-Mobarhan and M. Khajedaluee (2015). Comparison of Novel Coronary Artery Disease Risk Factors between Obese and Normal Adolescent. *Iran J Med Sci.*, 40(4):322-7.

Kumar, K.J., K. Saldanha, K. Sushma, D.S. Murthy and P. Vishwanath (2017). A Prospective Study of Homocysteine and its relation to Body Mass Index and Lipid Profile in School. *Children. Indian Pediatr*., 54(11):935-937.

Kunutsor, S.K., F. Zaccardi, J. Karppi, S. Kurl and J.A. Laukkanen (2017). Is High Serum LDL/HDL Cholesterol Ratio an Emerging Risk Factor for Sudden Cardiac Death? Findings from the KIHD Study. *J Atheroscler Thromb*., 24(6):600-608.

Lavie, C.J., R.V. Milani, S.M. Artham, D.A. Patel and H.O. Ventura (2009). The obesity paradox, weight loss, and coronary disease. *Am J Med*., 122(12):1106-14.

Lewandowski, K., P. Kwaśnikowski, W. Elikowski and K. Zawilska (2003). Myocardial infarction in patients aged less than 40 years. Frequency of BclI polymorphism in the fibrinogen beta-chain gene and plasma fibrinogen. *Kardiol Pol.*, 59(9):205-12.

Li, Z., Y. Tao, J. Huang, Q. Wang, D.H. Zhang and X.Y. Wu (2013). The characteristics of high density lipoprotein cholesterol and the relationship between high density lipoprotein cholesterol and the severity of coronary artery lesions in young men with acute myocardial infarction. *Zhonghua Yi Xue Za Zhi.*, 93(19):1458-62.

Lin, G.M., Y.H. Li, C.L. Lin, J.H. Wang and C.L. Han (2013). Low high-density lipoprotein cholesterol and low/normal body mass index are associated with increased mortality in coronary artery disease patients in Taiwan. *Circ J*., 77(8): 2079-87.

Lin, Y.H., K.Y. Pao, W.S. Yang, V.C. Wu, Y.J. Chen, Y.L. Lin, W.S. Tsai, I.J. Tsai, C.S. Gau and J.J. Hwang (2008). Waist-to-hip ratio correlates with homocysteine levels in male patients with coronary artery disease. *Clin Chem Lab Med*., 46(1):125-30.

Longo-Mbenza, B., H.F. Mambune, J.B. Kasiam, E.K. Vita, S.M. Fuele, J.N. Nsenga, L. Mabwa and V. Nzuzi (2007). Relationship between waist circumference and cholesterol in Central Africans with congestive heart failure. *West Afr J Med.*, 26(3):183-90.

Mahendra, J.V., S.D. Kumar, T.S. Anuradha, P. Talikoti, R.S. Nagaraj and V. Vishali 2015). Plasma Fibrinogen in Type 2 Diabetic Patients with Metabolic Syndrome and its relation with Ischemic Heart Disease (IHD) and Retinopathy. *J Clin Diagn Res*., 9(1): BC18-21.

Mehlig, K., K. Leander, U. de Faire, F. Nyberg, C. Berg, A. Rosengren, L. Björck, H. Zetterberg, K. Blennow, G. Tognon, K. Torén, E. Strandhagen, L. Lissner and D. Thelle (2013). The association between plasma homocysteine and coronary heart disease is modified by the MTHFR 677C.T *polymorphism. Heart*, 99(23):1761-5.

Mirdamadi, A., H. Farzamnia, P. Varzandeh, N. Almasi and M. Arasteh (2011). Association between serum homocysteine concentration with coronary artery disease in Iranian patients. *ARYA Atheroscler*., 7(2):63-7.

Montaño-Loza, A., J. Meza-Junco, V. Valles, L. Castillo-Martínez and A. Orea-Tejeda (2004). Plasma homocysteine concentrations in Mexican patients with ischemic heart disease. *Rev Invest Clin*., 56(5):580-5.

Monte, M. and J.I. Pascal (2002). The importance of lipid evaluation and management in the prevention and treatment of acute myocardial infarction. *Prev Cardiol*., 5(3):131-137.

Mraz, J., T. Zajic, P. Kozak, J. Pickova, P. Kacer, V. Adamek, I. Kralova Lesna, V. Lanska V and V. Adamkova (2017). Intake of carp meat from two aquaculture production systems aimed at secondary prevention of ischemic heart disease - a follow-up study. Physiol Res., 66 (Supplementum 1): S129-S137.

Naz, L., Z. Hussain and T. Husain (2009). Risk factors and biochemical variations in patients with ischemic stroke. *Int J. Biol Biotech*., 6 (1-2): 83-87.

Ni, M., X.H. Zhang, S.L. Jiang and Y. Zhang (2007). Homocysteinemia as an independent risk factor in the Chinese population at a high risk of coronary artery disease. *Am J Cardiol.,* 100(3):455-8.

Piédrola, G., E. Novo, F. Escobar and R. García-Robles (2001). White blood cell count and insulin resistance in patients with coronary artery disease.Ann Endocrinol (Paris)., 62 (1 Pt 1):7-10.

Pizzolo, F., S. Friso, O. Olivieri, N. Martinelli, C. Bozzini, P. Guarini, E. Trabetti, G. Faccini, R. Corrocher and D. Girelli (2006). Homocysteine, traditional risk factors and impaired renal function in coronary artery disease. *Eur J Clin Invest.,* 36(10):698-704.

Prajapati, J., S. Jain, K. Virpariya, J. Rawal, H. Joshi, K. Sharma, B. Roy and A. Thakkar (2014). Novel atherosclerotic risk factors and angiographic profile of young Gujarati patients with acute coronary syndrome. *J Assoc Physicians India,* 62(7):584-8.

Rać, M.E., J. Suchy, G. Kurzawski, A. Kurlapska, K. Safranow, M. Rać, D. Sagasz-Tysiewicz, A. Krzystolik, W. Poncyljusz, K. Jakubowska, M. Olszewska, B. Krupa and D. Chlubek (2012). Polymorphism of the CD36 Gene and Cardiovascular Risk Factors in Patients with Coronary Artery Disease Manifested at a Young Age. *Biochem Genet.,* 50(1-2):103-11.

Rehman, R., Z. Hussian and N. Faraz (2013). Effect of body mass index on reproductive outcome after intra cytoplasmic sperm injection. 3rd BUMDC (Bahria University Medical & Dental College) symposium, Karachi.

Rehman, R., Z. Hussian and N. Faraz (2012). Effect of estradiol levels on pregnancy outcome in obese women. *Journal of Ayub Medical College*, Abbottabad: JAMC, 24(3-4):3-5.

Rehman, R., Z. Hussain and S.S. Fatima (2013). Effect of weight status on pregnancy outcome in intra cytoplasmic sperm injection. *International Journal of Reproductive Biomedicine*, 11(9): 717–724.

Rehman, R., Z. Hussain, S.S. Fatima, F. Alam and H. Gul (2016). Impact of obesity on infertility. Research Day, Department of Medicine, Aga Khan University, Karachi.

Rehman, R., Z. Hussain, S.S. Fatima, F. Alam and H. Gul (2015). Effect of body mass index on implantation after intracytoplasmic sperm injection. 6th Annual Research Day, Conference, DUHS, Karachi, Pakistan.

Sadeghi, M., Z. Pourmoghaddas, A. Hekmatnia, H. Sanei, B. Tavakoli, A. Tchernof, H. Roohafza and N. Sarrafzadegan (2013). Abdominal fat distribution and serum lipids in patients with and without coronary heart disease. *Arch Iran Med.,* 2013;16(3):149-53.

Semiz, S., S. Rota, O. Ozdemir, A. Ozdemir and B. Kaptanoğlu (2008). Are C-reactive protein and homocysteine cardiovascular risk factors in obese children and adolescents? Pediatr Int., 50(4):419-23.

Skibińska, E., R. Sawicki, A. Lewczuk, J. Prokop, W. Musiał, I. Kowalski and B. Mroczko 92004). Homocysteine and progression of coronary artery disease. *Kardiol Pol.,* 60(3):197-205.

Sohail, S. and Z. Hussain (2013). Pathophysiology of ischemic disorders- Ischemia, adipocytokines and diabetes mellitus. (2013). *Int. J. Biol. and Biotech.,* 10 (2): 155-166.

Sohail, S. and Z. Hussain (2008). Electrolyte and cholesterol variations in patients with diabetes mellitus. 35th All Pak Sc Conf, Genomics for Health and Prosperity, University of Karachi.

Sohail, S., Z. Hussain, Quratul ain and S.J. Ashraf. (2013). Blood cholesterol and leptin levels in male smoking and non-smoking patients with diabetes mellitus. *Int. J. Biol. Research,* 1(1): 13-16.

Sohail, S., A. Qadir, A. Ashraf, S.J. Ashraf, A.S. Serafi and Z. Hussain (2017). Prevalence of risk factors promoting diabetic neuropathy. International Journal of Biology Research, 2017; 5(1)1-5.

Stein, D., M. Heins, F.C. Schoebel, K. Pels, T.W. Jax, H. Stiegler, H. Reinauer, B.E. Strauer and M. Leschke(1997). Activation of the fibrinolytic system in patients with coronary artery disease and hyperfibrinogenemia. *Thromb Haemost.,* 77(5):970-4.

Swahn, E., H. von Schenck H and L. Wallentin (1989). Plasma fibrinogen in unstable coronary artery disease. *Scand. J Clin Lab Invest*., 49(1):49-54.

Tani, S., K. Nagao, T. Anazawa, H. Kawamata, S. Furuya, H. Takahashi, K. Iida, M. Matsumoto, T. Washio, N. Kumabe and A. Hirayama (2009). Association of body mass index with coronary plaque regression: 6-month prospective study. *J Atheroscler Thromb.,* 16(3):275-82.

Taqueti V.R. and M.F. Di Carli (2018). Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. *J Am Coll Cardiol.,* 72(21):2625-2641.

Varady, K.A., S. Bhutani, E.C. Church and M.C. Klempel (2009). Short-term modified alternate-day fasting: a novel dietary strategy for weight loss and cardioprotection in obese adults. *Am J Clin Nutr.,* 90(5):1138-43.

Varbo, A., G.D. Benn M, Smith, N.J. Timpson, A. Tybjaerg-Hansen and B.G. Nordestgaard (2015). Remnant cholesterol, low-density lipoprotein cholesterol, and blood pressure as mediators from obesity to ischemic heart disease. *Circ Res.,* 116(4):665-73.

Varbo, A., M. Benn, A. Tybjærg-Hansen and B.G. Nordestgaard (2013). Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. *Circulation,* 128(12):1298-309.

Vrentzos, G., J.A. Papadakis, N. Malliaraki, E.A. Zacharis, K. Katsogridakis, A.N. Margioris, P.E. Vardas and E.S. Ganotakis (2004). Association of serum total homocysteine with the extent of ischemic heart disease in a Mediterranean cohort. *Angiology*, 55(5):517-24.

Wang, J., X.Y. Li, Y. He and B. Ni (2005). Study on the relationship of plasma fibrinogen, platelet aggregation rate and peripheral arterial occlusive disease. *Zhonghua Liu Xing Bing Xue Za Zhi., 26*(1):1-4.

Yasmeen, G., Z. Hussain and M.L. Bharwani (2008). Gender differences in the progression of acute renal failure. *Int J Biol Biotech*., 5 (3-4): 215-218.

Whayne, T.F. Jr, and S.P. Saha (2019). Genetic Risk, Adherence to a Healthy Lifestyle, and Ischemic Heart *Disease.Curr Cardiol Rep.,* 10; 21(1):1.

Woudberg, N.J., J.H. Goedecke and S. Lecour (2016). Protection from Cardiovascular Disease Due to Increased High-Density Lipoprotein Cholesterol in African Black Populations: Myth or Reality? *Ethn Dis*., 26(4): 553-560.

Zahir, H., A. Javaid, R. Rehman and Z. Hussain (2014). Statistical concepts in biology and health sciences. *J Ayub Med Coll* Abbottabad, 26 (1): 95-7.

Zapolski, T., P. Waciński, B. Kondracki, E. Rychta, M.J. Buraczyńska and A. Wysokiński (2011). Uric acid as a link between renal dysfunction and both pro-inflammatory and prothrombotic state in patients with metabolic syndrome and coronary artery disease. *Kardiol Pol.,* 69(4): 319-26.

(*Accepted for publication December 2018*)