Original Article

Comorbid Conditions Responsible for the Higher Complications and Poorer Outcome in Cardiac and Vascular Surgery: Time to Reconsider Hyperhomocysteinemia and Its Repercussions

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Abstract

Background: Plasma homocysteine is a perceived risk factor for the cardiovascular diseases. Many studies confirmed its remarkably high level with severity of the disease. There are no studies to correlate plasma homocysteine level and outcome of surgery in patients suffering from cardiovascular diseases. **Objective:** The purpose of our clinical study is to analyze the correlation of plasma Homocysteine levels in patients undergoing coronary artery bypass grafting (CABG) and various peripheral vascular surgeries regarding various patient variables such as age, sex, and also the severity of disease and outcome of surgery. **Materials and Methods:** The plasma homocysteine levels of 200 patients undergoing CABG and various vascular surgeries, between January 2016 and January 2018 were analyzed. This was a prospective study, data about patient variables obtained from questionnaires handed out to the patients during the preoperative period. All peripheral arterial diseases patients were symptomatic and belong to Rutherford stage 3, 4, 5, and 6. The severity of disease was evaluated based on coronary angiogram (CAG), who was undergoing CABG and computed tomography (CT) angiograms for patients presenting with peripheral vascular disease (PVD) and peroperative findings. A total of 178 CAG and 100 CT peripheral angiograms assessed. Homocysteine levels were determined by CLIA method and levels of >13 mmol/L taken as hyperhomocysteinemia. All patients had surgical vascular intervention in the form of CABG, peripheral vascular bypass, and thromboembolectomy. The results and complications evaluated postoperatively. **Result:** Higher homocysteine levels associated with a higher number of triple vessel coronary disease and symptomatic PVD. They had greater severity of the disease. It is also associated with poorer target vessels with an increased morbidity and postoperative fatality. **Conclusion:** Homocysteine level is one of the independent risk factors for severity of CAD. It can have predictive value in CABG, peripheral vascular surgery, and poor postoperative outcome.

Keywords: Angiogram, bypass graft, coronary artery, homocysteine, risk factor

Introduction

Worldwide, coronary artery disease (CAD) and peripheral arterial diseases (PADs) are the major cause of mortality and morbidity.[1] There are many risk factors that contribute to CAD and PAD, such as dyslipidemia, smoking, hypertension, diabetes, and newer entity on the avenue considered independent risk factor is hyperhomocysteinemia.[2,3]

Many researchers have acknowledged the hyperhomocysteinemia is responsible for progressive atherosclerotic vascular disease, hypercoagulability of blood, activation of platelets, and clotting factors. Hyperhomocysteinemia evidently convinced that it is associated with premature vascular diseases irrespective of age and cause.[4]

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Plasma homocysteine levels are a strong predictor of mortality in patients with CAD and PAD. It is associated with an increased incidence of myocardial infarction, critical limb ischemia, and stroke.[5,6]

Free plasma homocysteine is responsible for the pathological effects on the organ vasculature. It affects the endothelial function, platelet function, and coagulation system. It induces

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endothelial dysfunction, enhance the growth of vascular smooth muscles, which contribute to the progression of severity of atherosclerotic pathophysiology and prothrombotic status of vessels made prone for *in situ* vessel thrombosis.[7,8] It also increases the platelet aggregation contributing aforementioned facts to enhance criticality of ischemia of organs. There are however few studies which try to test the severity of coronary artery disease (CAD), peripheral vascular disease (PAD), and its outcome after surgery in relation to the hyperhomocysteinemia levels. The aim of our study was to test the correlation of plasma homocysteine levels in patients with cardiovascular diseases, who were undergoing coronary artery bypass grafting (CABG) and various peripheral vascular bypass surgeries in Indian patients.

Materials and Methods

Material

Ours was a prospective single-center study of 200 patients that took place in cardiovascular and thoracic surgery department, from January 2016 to January 2018. All 200 patients underwent CABG and various peripheral vascular operations. For the CABG, left internal mammary artery(LIMA) and reversed great saphenous vein (RSVG) used. The Dacron, PTFE and reversed great saphenous vein (RSVG) grafts used for peripheral vascular bypass surgery based on location of PAD. Patients with kidney disease in any form, vascular embolism <15 days excluded from the study. The study authorized by the Ethics Committee. All patients gave us their informed written consent. Patient's detailed history taken on admission regarding presenting complaints, associated risk factors.

Method

Homocysteine levels of all the patients analyzed in the preoperative period. Homocysteine levels were estimated by CLIA method and levels of >13 mmol/L taken as hyperhomocysteinemia. Hyperhomocysteinemia divided into four groups on the basis of plasma homocysteine level.

The followings are:

- Normal - <13 mmol/L
- Mild - 13.1 mmol/L–30 mmol/L
- Moderate - 30.1 mmol/L–50 mmol/L
- Severe - above 50.1 mmol/L.

Patient's Coronary angiogram and computed tomography peripheral angiogram was evaluated. Peroperative findings of the coronary vessels, all peripheral vessels condition and character assessed during surgery.

Postoperative recovery was assessed by the vital data, ventilator requirement, the number of intensive care unit (ICU) days, and the need for postoperative inotropic support. Postoperative morbidity and mortality analyzed in detail.

Statistical analysis

The statistical software used for statistical analysis is SPSS 20 (IBM corp, SPSS Statistics, Armonk, Newyork). $P < 0.05$ was considered statistically significant.

Results

In the study, 200 patients were included. Of these, 100 patients underwent CABG, other 100 patients underwent various peripheral vascular surgeries, and three underwent concomitant CABG and aortobifemoral grafting (ABFG).

The age group of patients varied from 25 to 83 years. The homocysteine levels varied with age. The highest homocysteine levels were found in the age group of 51–70 years [Figure 1].

In our study, there was a greater preponderance of hyperhomocysteinemia in men compared to women in each age group, but it was not significant ($P = 0.377$) [Figure 2].

Smoking was associated with increased homocysteine levels in the study with statistically significant ($P = 0.007$) [Figure 3].

One hundred and twenty patients were hypertensive and 122 patients were diabetic. The association of hyperhomocysteinemia with hypertension and diabetes mellitus was not statistically significant [Figure 4].

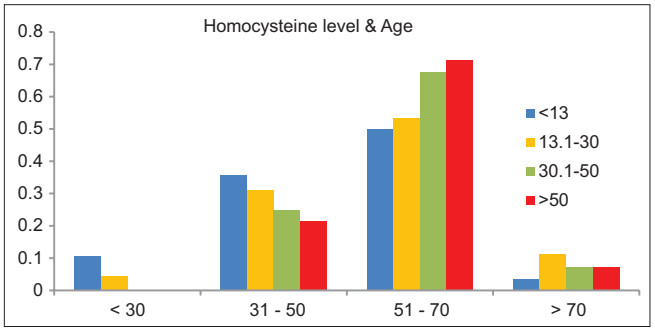

Figure 1: Plasma homocysteine as per age groups

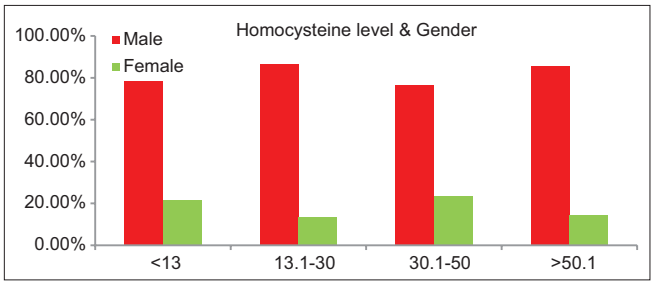

Figure 2: Plasma homocysteine and gender

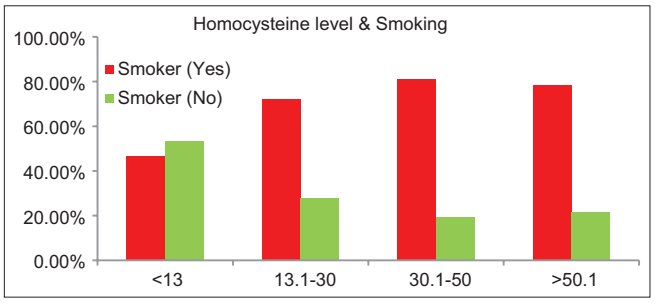

Figure 3: Plasma homocysteine in smokers

Among the patients with CAD, who underwent CABG, two patients had single vessel disease with left main coronary artery (LMCA) involvement. Fifteen patients had double vessel disease of which two had LMCA disease. Eighty-three patients had triple vessel disease with 28 having LMCA disease [Figure 5].

One hundred patients from CAD group and three patients from PAD group who had CAD underwent CABG. Left internal mammary artery (LIMA) and reversed great saphenous vein (RSVG) grafts used for CABG. Twenty-five (12.5%) had aortoiliac occlusive disease underwent ABFG using Dacron bifurcating graft. Three (1.5%) cases had femorofemoral jump grafting using ringed PTFE graft for iliac artery occlusive disease. Thirty (15%) patients underwent femoropopliteal bypass using PTFE, Dacron and reversed great saphenous vein (RSVG) grafts for femoro-popliteal occlusive diseases. Forty-two (21%) cases undergone successful thromboembolectomy for thromboembolism using Fogarty artery embolectomy and Fogarty adherent clot removal catheter [Table 1].

Out of the 103 CABG patients, 68 patients had grafting of LIMA to the left anterior descending artery.

Eighteen patients needed right coronary artery endarterectomy on the table during CABG. All of these patients had hyperhomocysteinemia [Figure 6].

In our study, we found a significant association of hyperhomocysteinemia with increased requirement of inotropic support and increased postoperative ICU stay [Figure 7].

The pattern of PAD in accordance with Rutherford classification is as follows: in Stage III 51 cases (51%), Stage IV 42 cases (42%), Stage V five cases (5%), and Stage VI two cases (2%) [Table 2].

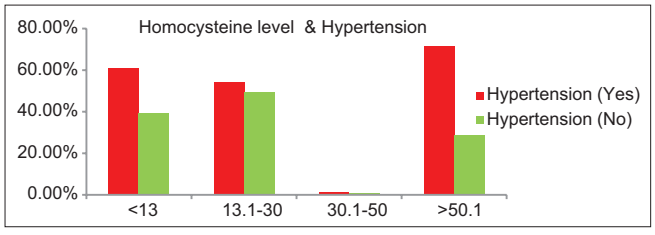

Figure 4: Plasma homocysteine level and hypertension

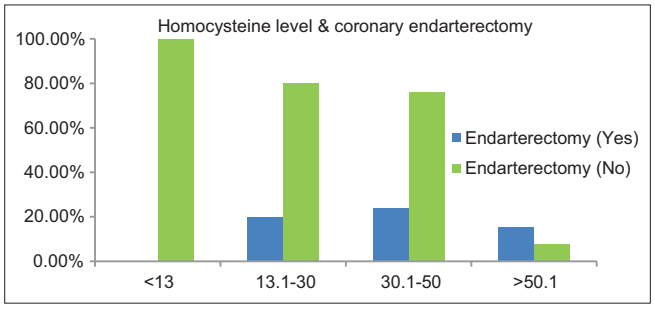

Figure 6: Plasma homocysteine and coronary artery endarterectomy

Three patients with peripheral vascular disease were found to have concurrent CAD with left main CAD and required concomitant CABG with peripheral arterial bypass on a priority basis. All three patients had hyperhomocysteinemia [Figure 8].

Hyperhomocysteinemia was associated with significant preoperative gangrene in patients of PAD requiring intervention in the form of amputation during the vascular procedure ($P = 0.001$) [Figure 9].

In the PAD subgroup, 58 of the 100 required bypass grafting and the rest were managed with thromboembolectomy using Fogarty arterial embolectomy catheter and Fogarty adherent clot removal catheter of the affected vessels [Figure 10].

In the vascular subgroup of patients, postoperative gangrene occurred in five patients, and all five had hyperhomocysteinemia. Underwent amputation of affected part in the same hospital stay in <15 days [Figure 11].

The outcome of procedure in PAD was significantly associated with the homocysteine levels of the patient. Patients had a better recovery when with lower homocysteine levels. Whereas, those patients with hyperhomocysteinemia had poorer outcomes [Figure 12].

Discussion

Homocysteine is an amino acid, generated by catabolism of methionine. Homocysteine dependent on various vitamins as the cofactor for its degradation, any deficiency of such vitamin enhances the level of homocysteine in the individual. It is found to be increased with elderly people, renal dysfunction patients, and smokers. Hyperhomocysteinemia induces endothelial dysfunction with its endothelial proliferation, enhance endothelial prothrombotic status attracting platelet

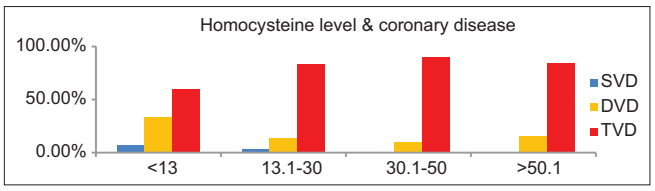

Figure 5: Plasma homocysteine and coronary artery disease

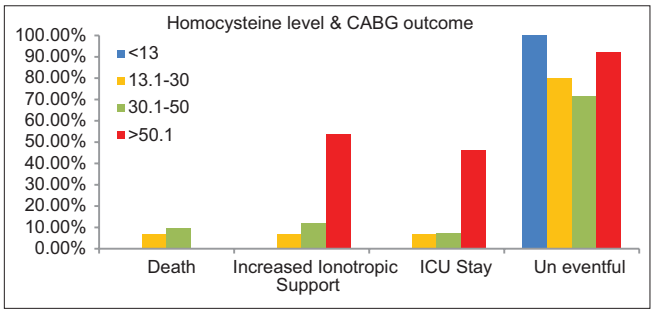

Figure 7: Plasma homocysteine and coronary artery bypass grafting outcome

Table 1: Diagnosis and surgery done

Cause	Surgery	Graft	*n* (%)
CAD	CABG	LIMA/RGSV	103 (51.50)
AIOC	ABFG	Dacron bifurcating graft	25 (12.50)
IAOD	Femorofemoral jump graft	Ringed PTFE Graft	3 (1.50)
FPOD	Femoropopliteal bypass	PTFE/Dacron graft	30 (15.00)
Thromboembolism	Thromboembolectomy		42 (21.00)

CAD: Coronary artery disease, FPOD: Femoropopliteal occlusive disease, CABG: Coronary artery bypass grafting, ABFG: Aortobifemoral grafting, LIMA: Left internal mammary artery, PTFE: Polytetrafluoroethylene, RSVG: Reversed great saphenous vein, AIOD: Aorto-iliac occlusive disease, IAOD: Iliac artery occlusive disease

Table 2: Rutherford classification for peripheral arterial disease

Class	Number of patients (%)
III	51 (51.00)
IV	42 (42.00)
V	5 (5.00)
VI	2 (2.00)

aggregation, and promoting coagulation cascade so contributing to progressive atherosclerosis and *in situ* thrombosis.[9]

Hyperhomocysteinemia is modifiable, independent known risk factor for CAD and PAD. It increases the incidence of multiple myocardial infarction and peripheral limb ischemia.[9,10] Uniformly, it involves all vasculature of the body. It consistently involves coronary artery, peripheral vasculature, and cerebrovascular vessel.[11] It is also found to be associated evidently with an increased incidence of venous thrombosis.[12]

In 1969, McCully made the correlation between high homocysteine and vascular disease. It is proved hyperhomocysteinemia induces atherosclerosis.[13] In 1976, Wilcken and Wilcken showed that hyperhomocysteinemia associated with CAD, PAD, and proved that it is linked with the heightened proportion of morbidities and mortality.[14]

Although some studies conducted in India did not show increased homocysteine levels among patients with CAD. It may not be reliable as they studied in a minuscule group of patients.[15,16] Our study showed profound association of hyperhomocysteinemia with increased severity of CAD and PAD.

Our study indicates that the prevalence of hyperhomocysteinemia in preoperative patients is astoundingly high involving, 85% of our study population. This is coherent with the findings of other western studies. Despite that, independent comorbid condition like hyperhomocysteinemia and its detrimental effects is disregarded while treating the patients presenting with cardiovascular disease.

Our study revealed increased homocysteine levels, seemingly associated with smoking which is the most common practice in rural society. This is consistent with the finding in other studies.[17,18] Smoking itself directly responsible for hyperhomocysteinemia or not remained to seen with further concrete researches.

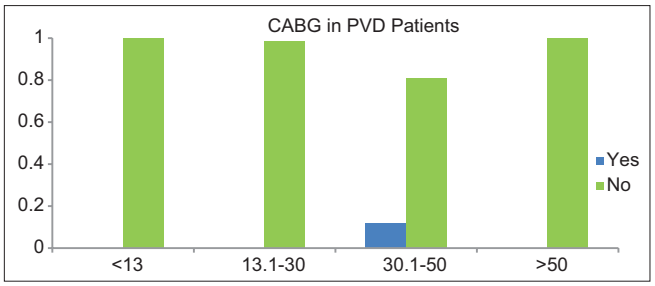

Figure 8: Incidence of concomitant coronary artery bypass grafting and peripheral vascular disease surgery

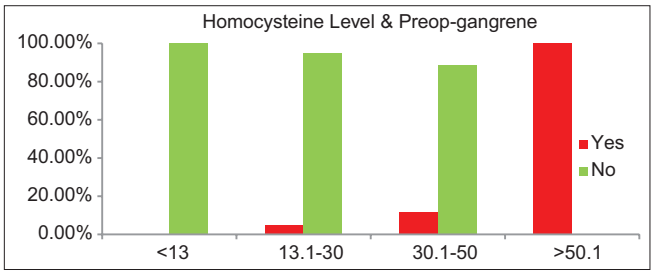

Figure 9: Plasma homocysteine level and incidence of preoperative gangrene

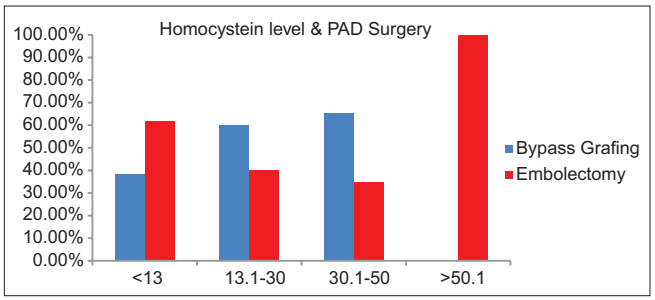

Figure 10: Plasma homocysteine and peripheral arterial disease surgery

In this study, we found increased severity of coronary artery and peripheral vascular artery diseases. These findings were substantiated with peroperative findings. The patient had multiple vessel involvement, numerous short distance skip lesion, and overall diffuse narrowing of distal vessels. There was a raised incidence of endarterectomy in both coronary as well as peripheral vasculature. Peroperatively, such patients required unusually more number of grafts than predicted. Typically in peripheral vascular surgery needed not only merely multiple bypasses but also multiple endarterectomy

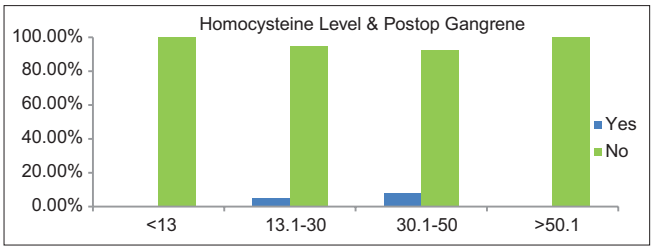

Figure 11: Incidence of postoperative gangrene

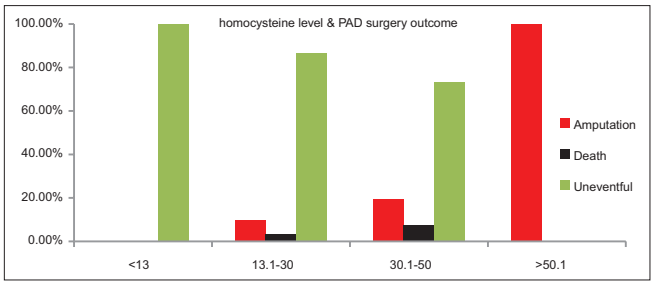

Figure 12: Plasma homocysteine and peripheral arterial disease surgery outcome

and patch plasty for better distal runoff. The same proved in other studies.[19]

In our study, we found a considerable association of hyperhomocysteinemia with an increased demand of inotropic support, intra-aortic balloon pump support, increased ICU stay for post-CABG patients. Post peripheral vascular surgery associated with an increased proportion of re-thrombosis of graft needing reexploration and embolectomy. There was also a high rate of amputation in patients, who had a high level of homocysteine. Dictum is higher the homocysteine; more is the associated morbidities and mortality.

Recently completed large randomized controlled trials, supplementation of folic acid, vitamin B6, and vitamin B12 has been revealed to decrease homocysteine levels over a period.[20] However, that treating patients with hyperhomocysteinemia with supplementation of vitamin B has failed to decrease cardiovascular morbidity and mortality, perhaps as disease is already set in and immutable.[21]

The investigations that have been promulgated so far regarding the effects of raised Homocysteine levels, on vessels and their atherothrombotic predisposition has demonstrated with increased CAD, PAD in hyperhomocysteinemia. This is legitimate in our research as well.

Homocysteine levels can foresee the severity of cardiovascular disease and poor outcome of the treatment whatsoever way. It has been established that curtailing the considerably elevated circulating homocysteine, greatly reduces cardiovascular risk.[22] Supplementation of folic acid has been shown to decrease homocysteine levels.[23] However, further researches are recommended to confirm the role of various nutritional supplementations and other forms intervention if any for decreasing the homocysteine levels. It is also time to study long-term benefits of such treatment for either interruption of progression or revoking the changes it has contributed to organ vasculature.

Conclusion

Hyperhomocysteinemia is an independent risk factor taken seriously such as diabetes. Homocysteine level can predict morbidity and mortality risk in patients who are undergoing cardiovascular surgery.

The identification of hyperhomocysteinemia in such patients may allow the surgeon to modify and plan his procedure, for the better outcome.

It requires aggressive management with anticoagulants and nutritional supplementation in view of the increased risk of thromboembolic events due to underlying diffuse vasculature disease and prothrombotic endothelium. It is an innate character of patients with hyperhomocysteinemia.

Routine supplementation of folic acid and other vitamin has to be evaluated further in such cases to look out for long-term benefits in reversing the underlying pathology.

There is a demand for further studies regarding precautions and protective strategies to be undertaken in patients with hyperhomocysteinemia suffering from cardiovascular disease and undergoing vascular surgical intervention.

Limitations

Our study is a single center study with a limited number of patients. The conclusions of our study need to be validated with further trials. In patients undergoing emergency cases, homocysteine evaluation avoided.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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