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Intra-operative grading of coronary artery atherosclerosis associated with homocysteine levels in postmenopausal women undergoing elective off-pump CABG surgery

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Abstract

Background:

Atherosclerosis is one of the common causes of morbidity and mortality, in postmenopausal women. Homocysteine, a sulfur-containing amino acid product of methionine metabolism, may play an important role in the development of cardiovascular diseases. This study was designed to evaluate the relationship between intra-operative grading of coronary artery atherosclerosis and homocysteine level in postmenopausal women who were candidates for off-pump coronary bypass graft surgery (CABG).

Materials and Methods:

In this cross-sectional study, 136 postmenopausal women (with the mean age of 54.9±4 years) were enrolled as candidates for elective off-pump CABG. For each patient the extent and severity of atherosclerosis was assessed by intra-operative grading (IOG) and Gensini score system. Total homocysteine was determined with ELISA method after 12 hours of fasting. The patients were classified into two groups (diffuse vs. discrete) based on intra-operative findings. Finally the relation between age, IOG, and Gensini score with homocysteine level was assessed by ANOVA, *T*-test, and Tukey HSD test.

Results:

There was a positive correlation between intra-operative grading and homocysteine level in both groups (P=0.005). The association between Gensini score and homocysteine was significant in higher levels of hyperhomocysteinemia (P<0.05). The homocysteine level also increased with age; therefore, patients were classified into two categories (<54 years and ≥54 years) by Levene test. Statistical analysis indicated no relationship between IOG, Gensini score, and homocysteine level in the patients who were younger than 54 years (P=0.3, P=0.2), but significant relation was detected between IOG, Gensini score, and homocysteine in the patients who were older than 54 years with diffuse or discrete lesions in coronary arteries (P=0.001, P=0.001).

Conclusion:

According to our findings, homocysteine level increases in post-menopausal women that can be an important risk factor for atherosclerosis and cardiovascular diseases.

INTRODUCTION

Atherosclerosis contributes to coronary artery disease (CAD), peripheral vascular events, and stroke. CAD is a common cause of morbidity and mortality worldwide. Hypertension and diabetes mellitus have been reported as the most important risk factors associated with the induction of atherosclerotic plaque in coronary and carotid arteries.[1–3] Menopause is a natural period of life with permanent cessation of menstruation and the end of reproductive period, which occurs at the age of 45-55 years. Mortality results from CAD are five to eight times higher in men than women during the years 25-55. In other words, hormone changes may induce unstable condition for cardiovascular events.[4–7] Homocysteine may play an important role in the development of CAD; therefore, changes of hormones in post-menopause duration increase level of homocysteine significantly.[8–10] This study was designed to evaluate the relationship between intra-operative grading of coronary artery atherosclerosis and hyperhomocysteinemia in menopausal patients who were candidates for elective off-pump coronary bypass graft surgery (CABG).

MATERIALS AND METHODS

The study was approved by the regional committee in our university. After receiving the written consent from patients, they participated voluntarily for off-pump CABG surgery in Afshar Cardiovascular Center of Yazd University of Medical Sciences from 25 August 2010 to 15 August 2011. All the operations were performed by a skilled surgical team. One hundred and thirty-six female patients (N=136) with Follicular Stimulating Hormone >40 IU/dl, estradiol <20 pg/mL, without any history of hormone replacement therapy during the last 3 months, no history of smoking, no diabetes, no history of consumption of drugs that increase or decrease homocysteine level, were candidates for elective off-pump CABG and enrolled in our study. For each patient, the extent and severity of atherosclerosis were assessed using intra-operative grading (IOG) and Gensini score system. Gensini score system was based on angiographic findings on percentage of occlusion of arteries and importance of function. (Gensini score = Stenosis score × Functional significant score). IOG method was based on severity of stenosis during surgery according to observational findings. The patients based on IOG were divided into two groups: Group A) patients with discrete stenosis (<1 cm), and group B) patients with diffuse stenosis (>2 cm). In all the patients, total homocysteine was determined with ELISA test after 12 hours of fasting. Finally, the relation between age, intra-operative grading, and Gensini score with homocysteine level was assessed with SPSS 17 software. We used ANOVA, T-test, and Tukey HSD test for quantitative and qualitative variables.

RESULTS

One hundred and thirty-six patients who were candidates for elective off-pump CABG surgery were enrolled in our study. The average age of the participants was 54.9±4 years. Severity and extent of the stenosis based on intra-operative grading divided our patients into diffuse or discrete groups; 65 cases of all patients (47.8%) had diffuse and 71 cases (52.2%) had discrete stenosis. The average age of the patients with diffuse and discrete stenosis was 55.7±4.8 years and 54.2±2.9 years, respectively. There was significant relationship between the age average and type of the stenosis (P=0.003). Total homocysteine was determined with ELISA method after 12 hours of fasting in all patients. Fasting level average of total homocysteine in patients with diffuse or discrete stenosis was 33±19.7 and 24.7±13.5, respectively. The difference in homocysteine level in both groups was significant (P=0.005). Gensini score was evaluated according to angiographic findings. The average of Gensini score in patients with diffuse or discrete stenosis was 53.6±48.8 and 31.4±18.6, respectively. Difference of Gensini score in both groups was significant (P=0.001) [Table 1]. Of all the patients, 34 cases had normal level of homocysteine, but 14, 34, and 54 cases had mild, moderate, and severe hyperhomocysteinemia, respectively. Gensini score average in patients with normal level of homocysteine was 29±17.1 and this score in patients with mild, moderate, and severe homocysteinemia turned out to be 29.11±17, 34.15±18.4, and 58.5±52, respectively. Therefore, there was a significant relationship between severe hyperhomocysteinemia and Gensini score (P<0.05). According to the existing significant relationship between age, homocysteine level, Gensini score, and

severity and extent of stenosis based on intra-operative grading, the patients were divided into two age groups; group 1: Women younger than 54 years (*n*=74), and group 2: Women as old or older than 54 years (*n*=62). Of all the patients younger than 54 years, 32 cases suffered from diffuse stenosis and 42 cases had discrete stenosis. Average of fasting level of homocysteine was 21.3±14.6 and 24.1±11.9 in patients with diffuse and discrete stenosis, respectively. However, out of all patients younger than 54 years, 33 cases and 29 cases had diffuse and discrete stenosis, respectively, and the average of fasting level of homocysteine was 44.4±17.3 and 25.5±15.6, respectively. Gensini score average in diffuse and discrete stenosis groups in patients younger than 54 years was 37.5±22.6 and 31.5±20.7, respectively (*P*=0.2), and this score in patients older than 54 years was 69.3±61.3 and 31.3±15.4, respectively. Therefore, there were significant differences in Gensini score and average level of homocysteine between discrete and diffuse in older than 54 years (*P*=0.001, *P*=0.001). The difference, however, was not significant in patients younger than 54 years [Tables 2 and 3].

DISCUSSION

High level of total homocysteine has been found to be an independent risk factor in atherosclerotic process in coronary arteries.[1,2] Postmenopausal period includes increasing prevalence of cardiovascular events and atherosclerosis ratio to premenopause duration.[4,5] It is believed that induction of hormone changes during postmenopausal condition is the most important cause of cardiovascular disease. Low level of homocysteine during high consumption of oestrogen in women who utilize oral contraceptive pill indicating that oestrogen has significant role in homocysteine metabolism.[7–10]

Average level of homocysteine in the participants of our study was 28.7±17. In our study, incidence of homocysteinemia was 75% in postmenopausal women. However, in another Iranian study carried out by Bandarian *et al*., the incidence of homocysteinemia in all ages was 50%.[11] This difference may be due to the effects of age and menopause. According to the results, the severity and extent of coronary artery stenosis based on intra-operative findings assisted us to divide our subjects into diffuse and discrete groups. An increase in homocysteine level was significant in both groups; in other words, there was a significant relationship between homocysteine and atherosclerosis. In our study, there were positive relationship between age and homocysteine level with intra-operative findings, respectively (*P*=0.03, *P*=0.005). A study which was conducted by Refahi *et al*., on hyperhomocysteinemia and severity of atherosclerosis lesion was inconsistent with our findings because of the presence of men and pre-and postmenopausal women in their study.[12]

In a study carried out by Rasuli *et al*., it was reported that patients with homocysteine level higher than 12 micromol/L vs. lower than 12 micromol/L show average increase in coronary calcium progression of 35% and 17% per year, respectively. They reported that neither cholesterol value, sex, and age nor presence of risk factor predicted coronary calcium. In other words, hyperhomocysteinemia strongly predicts progression of coronary atherosclerosis.[13] In our study, there was no significant relationship between Gensini score and level of homocysteine in mild-to-moderate severity; however, there was a significant relationship in severe hyperhomocysteinemia. Mild hyperhomocysteinemia seems not to be related to the risk of unstable CAD in postmenopausal women. The trend towards higher plasma and total homocysteine with increasing degree of coronary atherosclerosis may be a marker of the disease. These findings are in line with our study.[14] Our study indicated that in patients under 54 years, there was not any statistical relationship between increase of homocysteine and Gensini score with intra-operative findings, respectively (*P*=0.3, *P*=0.2). However, in patients older than 54 years, the relationship was significant (*P*=0.001, *P*=0.001). These results suggest that age and onset of menopause have a significant role on cardiovascular events. In a study carried out by Christodoulakos *et al*., it was reported that total homocysteine level increased in women who were above 60 years. Duration of menopause increased homocysteine level significantly after 180 months.[15] In our study, duration of menopause increased homocysteine level significantly after 60 months. According to the findings, we conclude that homocysteine level increases during postmenopause and it can be a strong risk factor of severity and extent of atherosclerosis; therefore, hyperhomocysteinemia in postmenopausal women provides endothelial and vascular dysfunction and cardiovascular diseases. Finally, we recommended evaluation of the patients with unexplained diffuse stenosis and risk factors such as hyperhomocysteinemia.

Footnotes

Source of Support: Nil

Conflict of Interest: None declared.

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Figures and Tables

Table 1

Variables	Diffuse stenosis (n=65)	Discrete stenosis (n=71)	P value
Age (year)	55.7±4.8	54.2±2.9	0.03
Homocysteine level	33±19.7	24.7±13.5	0.005
Gensini score	53.6±48.8	31.4±18.6	0.001

Relationship between intra-operative findings with age, homocysteine level, and Gensini score

Table 1

Variables	Diffuse stenosis (n=65)	Discrete stenosis (n=71)	P value
Age (year)	55.7±4.8	54.2±2.9	0.03
Homocysteine level	33±19.7	24.7±13.5	0.005
Gensini score	53.6±48.8	31.4±18.6	0.001

Table 2

Variables	Diffuse stenosis (n=32)	Discrete stenosis (n=42)	P value
Homocysteine level	21.3±14.6	24.1±11.9	0.3
Gensini score	37.5±22.6	31.5±20.7	0.2

(n=74)

Intra-operative findings in patients younger than 54 years

Table 3

Variables	Diffuse stenosis (n=33)	Discrete stenosis (n=29)	P value
Homocysteine level	44.4±17.3	25.5±15.6	0.001
Gensini score	69.3±61.3	31.3±15.4	0.001

(n=62)

Intra-operative findings in patients older than 54 years