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The Effects of Plasma Homocysteine Concentration on Upper Arm-Ankle Pulse Wave Velocity

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혈장 호모시스테인 농도가 상완-발목 맥파 속도에 미치는 영향

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Abstract This study was conducted to investigate the effects of plasma homocysteine concentration on the brachial-ankle pulse wave velocity between the normal homocysteine group and the asymptomatic high homocysteine group. 435 subjects who visited the general health examination center from April 1 to October 31, 2016, as well as to compare the direct correlation of the brachial-ankle pulse wave velocity, which indirectly reflects the homocysteine test and arterial stiffness, as a predictor of future cardiovascular outcome. As a result of the study, age, waist circumference, BUN, and plasma creatinine were significantly higher, and HDL was significantly lower in the high homocysteine group (>15μmol/L) than in the normal homocysteine group (<15μmol/L) (p=0.05). In addition, homocysteinemia was associated with smoking and drinking (p<0.001) and was significantly higher in males (p<0.001). The right and left brachial-to-ankle pulse wave velocities were significantly higher in the high homocysteine group (right p<0.001, left p=0.003) before calibrating the relevant variables. There was no significant difference between right and left brachial-to-ankle pulse wave velocities after calibrating the relevant variables. Therefore, further studies on the independent association of lowering homocysteine concentration and prevention of cardiovascular disease and the relationship between homocysteine and renal function are needed.

요 약 본 연구는 2016년 4월 1일부터 2016년 10월 31일까지 종합병원 건강검진센터에 내원한 435명을 대상으로 혈장 호모시스테인 농도가 정상 호모시스테인 군과 무증상 고호모시스테인 군 간에 발목-상완 pulse wave velocity에 유의한 차이가 있는지를 비교해 심혈관 질환 발생의 향후 예측인자로서 호모시스테인 검사와 동맥의 경직도를 간접적으로 반영하는 상완-발목 pulse wave velocity의 직접적인 상호 연관성을 비교해보고자 시도되었다. 연구결과 고 호모시스테인혈증 군에서 정상 호모시스테인 군에 비해 연령, 허리둘레, BUN, 혈장 크레아티닌이 유의하게 높았고, HDL은 유의하게 낮았다. 또한, 고 호모시스테인혈증은 흡연 및 음주 여부와 관련이 있었으며, 남성에서 유의하게 많았다. 관련 변수를 보정하기 전에는 고 호모시스테인 군에서 우측 및 좌측 상완-발목 맥파 속도가 유의하게 높았으나 관련 변수를 보정한 후에는 두 군의 상완-발목 맥파 속도는 유의한 차이를 보이지 않았다. 따라서, 향후 국내 수검자를 대상으로 호모시스테인 농도를 낮추는 중재적 치료 후 심혈관질환 예방에 대한 독립적 연관성 및 호모시스테인과 신장 기능의 관련성에 대한 추가 연구가 필요하겠다.

Keywords : Homocysteine, brachial-ankle pulse wave velocity, creatinine, cardiovascular disease, arterial stiffness, plasma, concentration

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1. Introduction

Homocysteine has been emphasized as a predictor of various vascular diseases, including cerebrovascular and cardiovascular disease and thrombosis [1,2,3]. Homocysteine is a substance that is produced after S-adenosylmethionine turns into transmethylation and becomes a cysteine by cystathione synthase. In this metabolic process, vitamin B6 is involved as an important cofactor and is metabolized by the metabolic process, which is remethylated by vitamin B12 and cobalamin and is converted to methionine [4]. Increased homocysteine was associated with factors such as vitamin B6, insufficient folic acid intake and B12 absorption, as well as gender, age, smoking, plasma creatinine, and genetic factors [5,6,7,8,9]. Plasma homocysteine concentrations above 15 μmol/L have been reported to increase the risk of cardiovascular and cerebrovascular disease by 1.5 to 3 times [10]. The brachial-ankle pulse wave velocity (baPWV) is a noninvasive, economical, and highly reproducible method of assessing arterial stiffness using the difference in blood flow velocity between the upper arm and ankle; it is a useful test [11,12]. In a study of homocysteine and arterial stiffness as independent predictors of cardiovascular disease, central arterial pulse wave velocity was associated with mid-hyperhomocysteinemia but not with peripheral arterial pulse wave velocity [13]. In addition, when adjusted for cardiovascular risk factors including age, plasma homocysteine levels were not found to be significantly associated with central arterial pulse wave velocity [14]. In another study, hyperhomocysteinemia was significantly higher in patients with hypertension treated with plasma homocysteine 7.2 μmol/L than in those without hyperhomocysteinemia, and the response of blood pressure to stress was larger [15]. According to the present study, patients who underwent physical examinations on the basis of plasma homocysteine concentration of 15 μmol/L were classified into the normal homocysteine group and asymptomatic high homocysteine group by considering the results of previous studies [10]; we compared the actual correlation between brachial-ankle pulse wave velocity, which indirectly reflects the homocysteine test and the arterial stiffness, as a predictor of future cardiovascular events.

2. Study Method

2.1 Study Subjects

Among the 552 patients who visited the general health examination center from April 1, 2016 to October 31, 2016, 118 people who were diagnosed with diabetes, hypertension, thyroid disease, kidney failure, and heart disease were excluded from the study; a total of 435 people participated[16,17,18, 19,20](Fig. 1).

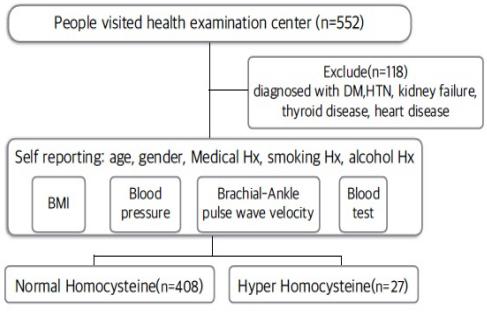

Fig. 1. study flow diagram

2.2 Research Tools

2.2.1 Preparing Questionnaire and Measuring the Body

The subjects were asked to write a self-filling questionnaire consisting of six categories: age, gender, medical history, smoking history, drinking history, and medication history. They were also changed into a checkup gown and had their height, weight, and blood pressure measured. Their body mass index (BMI) was measured automatically using a ZEUS 9.9 body composition analyzer (JAWON Medical Co., Ltd.,

Seoul, South Korea), and blood pressure was stabilized for at least 15 minutes to record the average value. Medical history was examined for hospitalization and surgical outcome, and smoking history was categorized into three groups: smokers who were in the current smoking group on the day of the examination, ex-smokers who quit smoking for more than 3 months, and non-smokers. The history of drinking was classified as three groups: one where men consumed more than 210g per week, another where women consumed more than 140g per week, and a final group for nondrinkers who consumed less than that.

2.2.2 Brachial-Ankle Pulse Wave Velocity

Brachial-ankle pulse wave velocities were measured by using a VP-1000 (Omron Healthcare global, Kyoto, Japan); after resting for more than 15 minutes, the cuffs were wound on both their upper arms and ankles to measure baPWV (brachial-ankle pulse wave velocity). The cuff is equipped with a sensor to sense the pressure of the pulse wave. The time difference (Δ Tba) is measured through the pulse waves of both upper arms and ankles from the cuff. The distance from the heart to both upper arms and the distance between both ankles was automatically measured to the standard value by the following formula set on the device based on the subject's height and weight. This is a calculation based on the measured height and weight from large amounts of data [21].

baPWV = La-Lb/ΔTba (Unit : cm/sec)

La = 0.8129 × Height (cm) - 2.0734

Lb = 0.2195 × Height (cm) + 12.328

(baPWV: brachial-ankle pulse wave velocity, La: aortic valve entrance - ankle length, Lb: aortic valve entrance - length of upper arm, ΔTba: time difference in pulse wave arrival times of both the upper arm and ankle)

2.2.3 Blood Test

Blood samples were taken from patients who had been hospitalized and fasting more than 8 hours after 24:00 on the day before the test, and homocysteine was measured by IMX homocysteine assay (Abbott, USA) using fluorescence polarization immunoassay (FPIA); the normal range was 5~15 μmol/L.

2.2.4 Data Analysis

All subjects were divided into two groups: high homocysteinemia (>15 μmol/L) and normal homocysteinemia (≤15 μmol/L) based on 15 μmol/L homocysteine concentration. A t-test was used for the mean and a chi-square test was used for smoking, drinking, and gender. At this time, the brachial-ankle pulse wave velocity showed a significant positive correlation ($r=0.978$, $P< 0.001$) in the left and right arm ankle pulse wave velocities; therefore, the mean value was used. Age, BMI, waist circumference, percentage of body fat, systolic and diastolic blood pressure, total cholesterol, triglyceride, low density lipoprotein, high density lipoprotein, BUN, creatinine, fasting blood sugar, and hemoglobin A1c, which can affect upper arm-ankle pulse wave velocity, were used for a Pearson's correlation analysis, and an ANOCOVA was used to correct the related variable. In addition, for the simple comparison, a Pearson's correlation analysis was performed for homocysteine concentration and brachial-ankle pulse wave velocity with or without hyperhomocysteinemia; the correlation coefficient was measured after correcting the related variables affecting the brachial-ankle pulse wave velocity. The statistical program used was SPSS 12.0 for Windows and the statistical significance was set at $p<0.05$.

3. Results

3.1 General Characteristics of Patients with or Without High Homocystinemia

Table 1 shows the general characteristics of each group when the whole subject was divided into two groups: the high homocysteinemia group and the

normal homocysteine group. 408 patients (93.8%) were in the normal homocysteine group and 27 patients (6.2%) were in the high homocysteinemia group. There was a significant correlation between high homocysteinemia and when age, waist circumference, high plasma creatinine was higher, and high density was lower, lipoprotein levels were lower in patients. Smoking and drinking were also significantly associated ($p<0.05$) (Table 1).

3.2 The Relationship Between Brachial–Ankle Pulse Wave Velocity and Other Variables

In the normal homocysteine group age, waist circumstance, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, low density lipoprotein, BUN, creatinine, blood glucose, and hemoglobin A1c showed a significant correlation with the brachial-ankle pulse wave velocity; in the normal homocysteinemia group age, systolic blood pressure, BUN, creatinine, blood glucose, and hemoglobin A1c showed a significant correlation with the brachial-ankle pulse wave velocity ($p<0.05$) (Table 2).

3.3 The Relationship Between Brachial and Ankle Pulse Wave Velocities of Two Groups After Variable Correction Affecting Upper Arm–Ankle Pulse Wave Velocity

Before adjustment for the variables of gender, age, smoking, drinking, waist circumference, blood pressure, total cholesterol, triglyceride, low density lipoprotein,

Table 1. Characteristics of the population according to hyperhomocysteinemia status

Variables		Normal Homocysteine (n=408)	Hyper Homocysteine (n=27)	p value
Age (years)		51.9±11.5	61.1±10.6	<0.001
Body mass index (kg/m2)		24.7±3.4	25.1±2.5	0.503
Waist Circumference (cm)		78.62±9.2	83.7±6.7	0.005
Percentage of body fat (%)		27.8±5.9	25.7±5.7	0.069
Systolic BP‡ (mmHg)		125.9±13.7	131.2±15.9	0.058
Diastolic BP‡ (mmHg)		76.9±9.6	80.2±10.9	0.087
Total cholesterol (mg/dL)		188.2±34.9	190.2±30.9	0.764
Triglyceride (mg/dL)		130.1±93.4	158.4±68.9	0.122
LDL§cholesterol(mg/dL)		115.9±29.9	123.6±26.5	0.196
HDL ‖ cholesterol (mg/dL)		53.5±11.1	46.9±8.9	0.002
BUN¶(mg/dL)		14.7±3.9	17.3±5.4	0.001
Creatinine (mg/dL)		0.8±0.2	1.1±0.3	<0.001
Glucose (mg/dL)		103.1±26.8	100.5±17.6	0.623
Hemoglobin A1c (%)		6.1±1.1	6.2±0.9	0.742
baPWV**(cm/s)		1442.4±293.2	1632.6±420.9	0.002
Smoking, n (%)*	Smoker	3(0.7)	16(59.3)	<0.001
	Ex-smoker	48(5.4)	4(14.8)	
	Non-smoker	357(87.5)	7(59.3)	
Alcohol Hx, n (%)*	Yes	22(5.4)	27(100)	<0.001
	No	386(94.6)	0(0)	
Gender, n (%)*	Male	192 (47.1)	22 (81.5)	<0.001
	Female	216 (52.9)	5 (18.5)	

‡BP: Blood pressure, §LDL: Low density lipoprotein ‖HDL: High density lipoprotein, BUN: Blood urea nitrogen, **baPWV: Brachial-ankle pulse wave velocity

Table 2. The Relationship between brachial-ankle pulse wave velocity and other variables

Variables	Normal Homocysteine		Hyper Homocysteine	
	r	*p*	*r*	*p*
Age (years)	0.632	<0.001	0.548	0.003
Body mass index (kg/m2)	0.058	0.246	0.161	0.423
Waist Circumference (cm)	0.188	<0.001	0.373	0.055
Percentage of body fat (%)	0.081	0.101	0.264	0.183
Systolic BP† (mmHg)	0.574	<0.001	0.468	0.014
Diastolic BP† (mmHg)	0.436	<0.001	0.237	0.234
Total cholesterol (mg/dL)	0.119	0.016	0.041	0.840
Triglyceride (mg/dL)	0.185	<0.001	0.086	0.671
LDL‡ cholesterol(mg/dL)	0.099	0.045	0.002	0.994
HDL§cholesterol(mg/dL)	-0.087	0.081	-0.089	0.659
BUN‖ (mg/dL)	0.203	<0.001	0.530	0.004
Creatinine (mg/dL)	0.105	0.034	0.419	0.037
Glucose (mg/dL)	0.182	<0.001	0.738	<0.001
Hemoglobin A1c (%)	0.170	0.001	0.653	<0.001

† BP: Blood pressure, ‡ LDL : Low density lipoprotein, §HDL: High density lipoprotein, ‖ BUN: Blood urea nitrogen.

BUN, plasma creatinine, blood glucose, and hemoglominA1c in the asymptomatic hyperhomocysteinemia group, the superior-ankle pulse wave velocity was significantly higher than the normal homocysteine group (p=0.05). There was no statistically significant difference in the ankle pulse wave velocity between the asymptomatic hyperhomocysteinemia group and the normal homocysteine group after adjustment for the variable (Table 3).

3.4 The Correlation Between Plasma Homocysteine Concentration and Brachial-Ankle Pulse Wave Velocity

The plasma homocysteine concentration has significant correlation in the right brachial-ankle pulse wave velocity (r=0.230, p<0.001) and in the left brachial-ankle pulse wave velocity (r=0.208, p<0.001) with or without high homocysteinemia. After adjustment for variables such as gender, age, smoking, drinking, waist circumference, blood pressure, total cholesterol, triglyceride, low density lipoprotein, BUN, plasma creatinine, blood glucose, and hemoglobin A1c, there was no significant correlation in plasma homocysteine concentration, right-brachial pulse wave velocity (r=0.043, p=0.383), and left-brachial pulse wave velocity (r=0.027, p=0.574) (Table 4).

Table 3. Mean brachial-ankle pulse wave velocity difference and ankle-brachial index difference between the two groups before and after multivariate adjustment

	Unadjusted analysis			Multivariate-adjusted analysis		
	Normal Hcyt†	Hyper Hcyt†	P	Normal Hcyt†	Hyper Hcyt†	P
RbaPWV‡	1435.4±299.9	1639.0±420.5	0.001	1446.9±11.1	1465.5±64.6	0.785
LbaPWV§	1449.4±290.0	1626.2±424.4	0.003	1457.6±11.0	1501.9±63.6	0.508

† Hcyt: Homocysteine, ‡ RbaPWV:Rightbrachial-anklepulsewavevelocity(cm/sec)
§LbaPWV: Left brachial-ankle pulse wave velocity(cm/sec)

Table 4. Relationship between serum homocysteine level and brachial-ankle pulse wave velocity

	Pearson correlation coefficient (r)	P-value	Partial correlation coefficient	P-value
RbaPWV† (cm/s)	0.230	<0.001	0.043	0.383
LbaPWV‡ (cm/s)	0.208	<0.001	0.027	0.574

† RbaPWV: Right brachial-ankle pulse wave velocity(cm/sec)
‡ LbaPWV:Leftbrachial-anklepulsewavevelocity(cm/sec)

4. Discussion and Conclusion

In this study, the hyperhomocysteinemia group had higher brachial-ankle pulse wave velocity than the normal homocysteine group ($p<0.001$), but after correcting the variables affecting brachiocephalic pulse wave velocity there was no significant difference. This is consistent with previous studies that compared the association between homocysteine concentration and brachial-ankle pulse wave velocity [14,22]. In addition, in the general characteristics, the high homocysteine group showed a significant difference ($p<0.001$) in age, BUN, and creatinine compared to the normal homocysteine group, which is partially related to the decrease in renal function due to age increase [23]. In addition, smoking and drinking were also significantly associated with hyperhomocysteinemia ($p<0.001$), which is consistent with the results of Varela-Moreiras G et al. [24].

Homocysteine is a metabolic product in which methionine is activated by ATP and S-adenosylmethionine (SAM) through the transmethylation process. This transmethylation process is accompanied by the synthesis of creatinine and phosphatidylcholine and is accompanied by the methylation of DNA, RNA, and many neuromediators. The homocysteine is metabolized to cystathionine or remethylated, and it is converted back to methionine; in this remethylation process, vitamin B_{12} (Cobalamin) acts as an important cofactor and in the metabolism of cystathionine vitamin B6 acts as a major cofactor [25].

In a number of observational studies, homocysteine has been implicated in vascular endothelial cells, platelets, and coagulation factors leading to peripheral vascular disease, cardiovascular disease, thrombus formation, and cognitive impairment of arterial and venous blood [26, 27, 28]. However, Djuric et al. [29] recently questioned whether hyperhomocysteinemia is a sufficient predictor of thrombotic cardiovascular disease, as well as the failure to identify the causal relationship between homocysteine to cardiovascular events in randomized, controlled trials that lowered homocysteine concentrations. Huang et al. [30] reviewed the results of the studies published between 1932 and 2007 and found that the mechanism by which homocysteine is involved in the development of cardiovascular disease is unclear, pointing out that further research is needed.

According to Potter et al. [31], homocysteine concentration was not related to the thickness of the vessel wall when all serologic markers related to renal dysfunction were corrected. Homocysteine was not a predictor of independent cardiovascular disease and may be more meaningful as an indicator of impaired kidney function. In addition, Bayo et al. [32] Reported that homocysteine levels did not recover to normal after 18 months of folic acid administration in patients with renal disease. In this study, BUN and plasma creatinine were significantly higher in the asymptomatic hyperhomocysteinemia group than in the normal homocysteine group. There were also positive correlations in the normal homocysteine group and the high homocysteine group ($p<0.001$). However, after adjusting for related variables, the results showed that the brachial-ankle pulse wave velocity did not show a significant increase in the high homocysteinemia group.

In the future, it may be necessary to study the factors that are not taken into account in using the

plasma homocysteine concentrations measured by the asymptomatic health examiner as an indirect utilization of cardiovascular disease. In the future, interventional changes of hyperhomocysteinemia should be more important to reduce the incidence of actual cardiovascular disease and to prevent negative changes of the cardiovascular system. They should also be more important as an indicator of the damaged or impaired renal function for domestic patients; additional studies are needed.

References

[1] Arnesen E, Refsum H, Bonaa KH, Ueland PM, Forde OH, Nordrehaug JE, ″Serum total homocystein and coronary heart disease″, *Int J Epidemol*, Vol.24 pp. 704-709, 1995.
DOI: https://doi.org/10.1093/ije/24.4.704

[2] Boushey CJ, Ber esford SA, Omenn GS, Motulsky AG, ″A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intake″, *JAMA*, Vol. 274 pp. 1049-1057, 1995.
DOI: https://doi.org/10.1001/jama.1995.03530130055028

[3] Fowler B, ″Homocystein--an independent risk factor for cardiovascular and thrombotic diseases″, *Ther Umsch,* Vol.*62* pp, 641-646, 2005.
DOI: https://doi.org/10.1024/0040-5930.62.9.641

[4] Philippe Durand, Michel Prost, Nadine Loreau, Suzanne Lussier-Cacan, Denis Blache, ″Impaired Homocysteine Metabolism and Atherothrombotic Disease″, *Lab Invest*, Vol.81 pp, 645-672, 2001.
DOI: https://doi.org/10.1038/labinvest.3780275

[5] Hu CP, Shao JM., Yan JT, Fan Q, Liu ZJ, Tian C, Wu HL, Li XP, Wang DW, ″Study on the distribution of serum homocysteine and on multi-stepwise regression analysis of the associated factors in the population of community areas in Wuhan″ *Zhonghua Liu Xing Bing Xue Za Zhi*, Vol.25 pp, 945-948, 2004.

[6] Dong Kuk Lee, Hyun Kook Choi, Jung Cheon Son, Yoo Ji Chung, Bom Taeck Kim, Kwang Min Kim, ″Serum Homocysteine and Its Relevant Factors among Health Screeners in a University Hospital″, *J Korean Acad Fam Med*, Vol.26 pp, 671-679, 2005.

[7] Berciano J, ″From the genetics to the prevention of stroke″, *Rev Neurol*, Vol.29 pp, 836-847, 1999.

[8] McCully KS, ″Homocysteine, vitamins, and vascular disease prevention″, *Am J Clin Nutr*, Vol.86, pp, 1563S-1568S, 2007.
DOI: https://doi.org/10.1093/ajcn/86.5.1563s

[9] Jacobsen DW, ″Homocysteine and vitamins in cardiovascular disease″, *Clin Chem*, Vol.44 pp, 1833-1843, 1998.

[10] Conri C, Constans J, Parrot F, Skopinski S, Cipriano C, ″Homocysteinemia: role in vascular disease″, *Presse Med*, Vol.29 pp, 737-741, 2008.

[11] Hlimonenko I, Meigas K, Viigimaa M, Temitski K, ″Assessment of Pulse Wave Velocity and Augmentation Indexin different arteriesin patients with severe coronary heart disease″, Conf Proc IEEE Eng Med BioSoc, pp, 1703-1706, 2007.
DOI: https://doi.org/10.1109/iembs.2007.4352637

[12] Safar H, Mourad JJ, Safar M, Blacher J, ″Aortic pulse wave velocity, an independent marker of cardiovascular risk″, *Arch Mal Coeur Vaiss*, Vol.95 pp, 1215-1218, 2002.

[13] Pannier BM, Avolio AP, Hoeks A, Mancia G, Takazawa K, ″Methods and devices for measuring arterial compliance in humans″, *Am J Hypertens*, Vol.15 pp, 743-753, 2002.
DOI: https://doi.org/10.1016/s0895-7061(02)02962-x

[14] Mayer O, Filipovsk J, Dolejsov M, Cfkov R, Simon J, Bolek L, ″Mild hyperhomocysteinaemia is associated with increased aortic stiffness in general population″, *J Hum Hypertens*, Vol.20 pp. 267-271, 2006.
DOI: https://doi.org/10.1038/sj.jhh.1001983

[15] Nakhai-Pour HR, Grobbee DE, Bots ML, Muller M, Van der Schouw YT, ″Circulating homocysteine and large arterial stiffness and thickness in a population-based sample of middle-aged and elderly men″, *J Hum Hypertens*, Vol.21 pp, 942-948, 2007.
DOI: https://doi.org/10.1038/sj.jhh.1002247

[16] Tao Huang, JingJing Ren,Jinyan Huang, Duo Li, "Association of homocysteine with type 2 diabetes: a meta-analysis implementing Mendelian randomization approach", BMC Genomics, Vol.14, 867, 2014.
DOI: https://doi.org/10.1186/1471-2164-14-867

[17] Yang B Fan S, Zhi X, He J, Ma P, Yu L, Zheng Q, Sun G, ″Interactions of homocysteine and conventional predisposing factors on hypertension in Chinese adult s″, J Clin Hypertens (Greenwich). Vol.19 pp, 1162-1170, 20017.
DOI: https://doi.org/10.1111/jch.13075

[18] Sundström J, Sullivan L, D'Agostino RB, Jacques PF, Selhub J, Rosenberg IH, Wilson PW, Levy D, Vasan RS, ″Plasma homocysteine, hypertension incidence, and blood pressure tracking: the Framingham Heart Study″, *J Hypertension*, Vol.42 pp, 1110-1105, 2003.
DOI: https://doi.org/10.1161/01.hyp.0000101690.58391.13

[19] Yande Zhou, Yufang Chen, Xueqin Cao, Chunfeng Liu, Ying Xie, ″Association between plasma homocysteine status and hypothyroidism: a meta-analysis ″, Int J Clin Exp Med, Vol7(11) pp, 4544–4553, 2014.

[20] Hou Zhenjiang, Mu Zhaoxin, Zhang Jingyu, Fan Hong, Hou Jianzhang, ″The Correlation of Blood Lipid Profile and its Ratio, Cystatin C and Homocysteine of Thyroid Dysfunction″, American Journal of Clinical and Experimental Medicine, Vol.5(4) pp, 108-114, 20017.
DOI: https://doi.org/10.11648/j.ajcem.20170504.12

[21] Tayama J, Munakata M, Yoshinaga K, Toyota T, ″Higher plasma homocysteine concentration is associated with more advanced systemic arterial stiffness and greater blood pressure response to stress in hypertensive patients″, *Hypertens Res*, Vol.29 pp, 403-409, 2006.

DOI: https://doi.org/10.1291/hypres.29.403

[22] Matsui Y, Kario K, Ishikawa J, Eguchi K, Hoshide S, Shimada K, ″Reproducibility of arterial stiffness indices (pulse wave velocity and augmentation index) simultaneously assessed by automated pulse wave analysis and their associated risk factors in essential hypertensive patients″, *Hypertens Res,* Vol.27, pp, 851-857, 2004.
DOI: https://doi.org/10.1291/hypres.27.851

[23] De Bree A, Mennen LI, Zureik M, Ducros V, Guilland JC, Nicolas JP, Emery-Fillon N, Blacher J, Hercberg S, Galan P, ″Homocysteine is not associated with arterial thickness and stiffness in healthy middle-aged French volunteers″ *Int J Cardiol*, Vol.113 pp, 332-340, 2006.
DOI: https://doi.org/10.1016/j.ijcard.2005.11.045

[24] Norlund L, Grubb A, Fex G, Leksell H, Nilsson JE, Schenck H, Hultberg B, ″The increase of plasma homocysteine concentrations with age is partly due to the deterioration of renal function as determined by plasma cystatin C″ *Clin Chem Lab Med*, Vol.36 pp, 175-178, 1998.

[25] Varela-Moreiras G, Escudero JM, Alonso-Aperte E, ″Homocysteine related vitamins and lifestyles in the elderly people: The SENECA study″ *Nutr Hosp*, Vol.23 pp, 363-370, 2007.

[26] Durand P, Prost M, Loreau N, Lussier-Cacan S, Blache D, ″Impaired homocysteine metabolism and atherothrombotic disease″ *Lab Invest*, Vol.81 pp, 645-672, 2001.
DOI: https://doi.org/10.1038/labinvest.3780275

[27] EL Mayer, DW Jacobsen, and K Robinson, ″Homocysteine and coronary atherosclerosis″ *J Am Coll Cardiol*, Vol.27 pp, 517-527, 1996.
DOI: https://doi.org/10.1016/0735-1097(95)00508-0

[28] Cattaneo M, ″Hyperhomocysteinemia: a risk factor for arterial and venous thrombotic disease″ *Int J Clin Lab Res*, Vol.27 pp, 139-144, 1997.
DOI: https://doi.org/10.1007/bf02912449

[29] Chin AV, Robinson DJ, O'Connell H, Hamilton F, Bruce I, Coen R, Walsh B, Coakley D, Molloy A, Scott J, Lawlor BA, Cunningham CJ, ″Vascular biomarkers of cognitive performance in a community-based elderly population: the Dublin Healthy Ageing study″ Age Ageing, Vol.37 pp, 559-564, 2008.
DOI: https://doi.org/10.1093/ageing/afn144

[29] Djuric D, Jakovljevic V, Rasic-Markovic A, Djuric A, Stanojlovic O, ″Homocysteine, folic acid and coronary artery disease: possible impact on prognosis and therap y″, *Indian J Chest Dis Allied Sci*, Vol.50 pp, 39-48, 2008.

[30] Huang T, Yuan G, Zhang Z, Zou Z, Li D, ″Cardiovascular pathogenesis in hyperhomocysteinemia″ *Asia Pac J Clin Nutr*, Vol.17 pp, 8-16, 2008.

[31] Potter K., Hankey GJ., Green DJ., Eikelboom JW., Arnolda LF., Homocysteine or renal impairment: which is the real cardiovascular risk factor? *Arterioscler Thromb Vasc Biol*. Vol.28 pp,1158-1164, 2008.
DOI: https://doi.org/10.1161/atvbaha.108.162743

[32] Bayo MP, Lpez MJ, Ortega AO, Peinado CA, Granados JJ, de la Serrana HL, Martnez MC, “Resistance of hyperhomocysteinemia in renal patients to treatment with supra-physiological doses of parenteral folic acid ″ *Nutr Hosp*, Vol.23 pp, 268-276, 2008.

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