

Association between Bone Mineral Density (BMD) and Carotid Artery Intima-Media Thickness (CIMT): A Cross Sectional Study

Hamidreza Talari, Batol Zamani, Mohammadreza Jafari*

Received: 11 March 2018 / Received in revised form: 20 July 2018, Accepted: 25 July 2018, Published online: 05 September 2018
© Biochemical Technology Society 2014-2018
© Sevas Educational Society 2008

Abstract

Background: Menopause, as a risk factor, increases the risk of cardiovascular and musculoskeletal diseases, particularly osteoporosis. It seems that common mechanisms are involved in the increased incidence of these conditions. In this study, the association between carotid artery intima-media thickness (CIMT) and bone mineral density (BMD) was examined in women after natural menopause. **Methods:** In this cross sectional study, 80 healthy postmenopausal women were examined in the osteoporotic (n=45) and health (n=45) groups based on BMD test results. Common carotid artery IMT was measured using B-mode ultrasound, and average CIMT was compared between the two groups. **Results:** The mean CIMT of both sides in this study was 0.69 ± 0.09 mm. This value was 0.63 ± 0.07 mm in healthy women and 0.75 ± 0.07 in osteoporotic women ($p < 0.001$). After adjusting for confounding factors, a significant relationship was found between CIMT and BMD test results ($p < 0.001$). **Conclusion:** Increased CIMT is independently associated with Low bone density in postmenopausal women.

Keywords: Bone Mineral Density (BMD), Intima-Media Thickness (IMT), Postmenopause, Osteoporosis.

Introduction

Osteoporosis and heart diseases are the main causes of mortality and morbidity in postmenopausal women (rezaei and et al., 2009; Si and et al., 2016). According to the International Osteoporosis Foundation's statistics, in 2000, more than 3.7 million bone fracture cases occurred following osteoporosis, of which, about 890 thousand cases were hip fractures, imposing 31 million euros on health systems (Lello and et al., 2015). Recent studies have shown that there is a close association between bone pathology and vascular diseases, so that vascular disorders are often associated with bone metabolism and angiogenesis disorders in bones. In this regard, vascular disorders and metabolic bone abnormalities are considered mutual underlying factors (Kim and et al., 2013; Tankó and et al., 2005).

Measurement of intima-media thickness in the distal common carotid artery (CIMT) using the ultrasonographic method is a noninvasive and reliable method used to detect subclinical atherosclerosis, through which the risk of cardiovascular diseases and stroke can be predicted (Cooney and et al., 2015; Rahman and et al., 2016; Zhang and et al., 2016; Pang and et al., 2016). Studies have confirmed the association between CIMT and some diseases and metabolic disorders such as subclinical hypothyroidism, nonalcoholic fatty liver disease, chronic kidney disease, and chronic obstructive pulmonary disease (Rahman and et al., 2016; Zhang and et al., 2016; Pang and et al., 2016; Köseoğlu and et al., 2016). In recent years, the association between CIMT and bone density has been examined. Some studies suggested that carotid artery atherosclerosis is associated with the lumbar spine bone mineral density in postmenopausal women. It was found that atherosclerotic plaque calcification in the carotid artery is associated with reduced bone mineral density (BMD) (Sumino and et al., 2008; Frost and et al., 2008). However, other studies have rejected such association (Özkaya and et al., 2011; Värril and et al., 2014). Racial differences may cause the difference in the results of the studies. Given that there is little evidence available about the association between CIMT and BMD, and no such study has been conducted on Iranians, the present study has examined the association between the mean carotid artery intima-media thickness and BMD measurement results in Kashan, Iran.

Materials and Methods

This case-control study included 80 postmenopausal women who had their last menstrual period at least two years ago. The study was

Hamidreza Talari and Mohammadreza Jafari*

Department of Radiology, Kashan University of Medical Sciences, Kashan, IR Iran.

Batol Zamani

Department of Autoimmune Diseases Research Center, Kashan University of Medical Sciences, Kashan, IR Iran

Department of Internal Medicine, Kashan University of Medical Sciences, Kashan, IR Iran.

*Email: jafari-md@outlook.com

conducted in Shahid Beheshti Hospital in Kashan, Iran. Based on a previous study in which the mean IMT was 0.114 ± 0.018 mm in osteoporotic patients and 0.091 ± 0.021 mm in normal patients, sample size was calculated as at least 16 in each group considering type I error of 5% and power of 92% and using the following formula. In this study, 40 patients were studied in each group (Mohammadi and et al., 2014).

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

All postmenopausal women, referred to density measurement center of radiology department of Shahid Beheshti Hospital in Kashan for BMD measurement and underwent the lumbar spine (L2 to L4), femoral neck and total hip from the beginning of 2014, were divided into normal (T-score ≥ -1.0) or osteoporotic (T-score ≤ -2.5) groups. The measurements were done using dual energy X-ray absorptiometry (DXA) (Osteocore 2, France). Considering the gradual referral of patients, sample selection was done sequentially based on the BMD results. For this purpose, sampling was continued until the required sample size was reached.

The women undergoing hormone replacement therapy, those who received drugs affecting bone metabolism (such as corticosteroids, anticonvulsants or anticoagulants), patients with diseases affecting bone metabolism (such as thyroid disorders, absorption disorders, chronic liver or kidney disease, alcoholism), and those with any risk of malignancy and bone fractures were excluded from the study and replaced by other patients. After explaining the objectives and methodology of the study to the participants, written informed consent was obtained from all of them. Demographic and clinical information including age, age at menopause, weight, height, chronic disease, current medications, cigarette smoking, use of opium, and family history of cardiovascular disease were obtained through face-to-face interviews and entered into a checklist.

In order to the measure CIMT, both common carotid arteries were examined by a sonographer, who was unaware of the BMD results and the groups of subjects, using an ultrasonography device (Medison V20, South Korea) with a 7.5 to 13 MHz probe. A 1-cm segment of the distal part of the artery common carotid immediately before the bifurcation was studied, and CIMT in each side was digitally measured. CIMT values of both sides were recorded in the checklist.

Data were analyzed using SPSS 18. Quantitative results are reported as mean \pm SD, and qualitative results are reported as absolute and relative frequency. Kolmogorov-Smirnov test, Chi square, Fisher's exact test, independent t-test and logistic regression were used in the analysis. The p-value <0.05 was considered significant.

Results

Eighty postmenopausal women were studied in two groups of normal and osteoporotic subjects. The mean age of subjects was 50.65 ± 5.97 years, with minimum 41 years and maximum 71 years. Demographic and clinical characteristics of the study population are listed in Table 1.

The mean right side CIMT was 0.62 ± 0.07 mm in the normal women and 0.75 ± 0.07 mm in the osteoporotic women ($p < 0.001$). The mean left side CIMT was 0.63 ± 0.07 mm in the normal women and 0.75 ± 0.08 mm in the osteoporotic women ($p < 0.001$). The mean both sides CIMT was 0.65 ± 0.07 mm in the normal women and 0.75 ± 0.07 mm in the osteoporotic women ($p < 0.001$). After adjusting for the confounding factors, using the logistic regression, a statistical correlation was observed between the mean both sides CIMT and BMD results in postmenopausal women ($p < 0.001$).

Discussion

This study examined the association between carotid intima-media thickness (CIMT) and osteoporosis in 80 postmenopausal patients. Findings showed that CIMT is significantly higher in patients with osteoporosis than the control group. An association was also found between mean CIMT and BMD results.

Studies in this regard have yielded mixed results. The first study in this field was conducted by Uyama et al. (1997) in Japan, in which 30 postmenopausal women aged 67 to 85 years were examined. Findings showed a linear relationship between bone mineral density (BMD) and CIMT. Higher plaque scores were associated with lower bone density (Uyama and et al., 1997). Hmamouchi et al. (2009) studied 72 postmenopausal women with an average age of 59 years and examined the relationship between bone mineral density and femoral and carotid intima-media thickness. An association was observed between CIMT and BMD of femoral neck, trochanter and its trunk; however, no association was observed using lumbar spine BMD. Similarly, no association was observed between BMD in different areas

and femoral intima-media thickness (Hmamouchi and et al., 2009). In another study on 609 postmenopausal women with no history of heart disease, Tamaki et al. (2009) studied patients for 10 years. They found that higher CIMT was associated with an increase in the risk of osteoporosis and vertebral fractures during the first ten years after menopause (Tamaki and et al., 2009). Similar to the results of the present study and the studies mentioned above, Sumino et al. reported an association between CIMT and BMD in postmenopausal women (Sumino and et al., 2008). Fodor et al. (2011) investigated the association between common carotid intima-media thickness and BMD in 100 postmenopausal women with an average age of 64.5 years and reported an inverse relationship between CIMT with lumbar spine and the femoral head T- score (Mohammadi and et al., 2014). Similar results were reported by Kim et al. who examined the women with cerebral infarction; however, no relationship was observed between CIMT and bone density in men (Kim and et al., 2016). Similar findings have been reported by other studies (Mohammadi and et al., 2014; Muntean and et al., 2014; Muntean and et al., 2013).

In contrast with the present and aforementioned studies, Özkaya et al. examined 90 postmenopausal women (45 women with natural menopause and 45 women with oophorectomy-induced menopause) and reported the lack of correlation between CIMT and BMD (Özkaya and et al., 2011). Värri et al. studied 290 postmenopausal women in Finland. They did not observe an association between mean results of common carotid artery CIMT and BMD; however, it was found that the maximum CIMT of both sides was correlated with BMD results (Värri and et al., 2014).

According to the present and other studies in hand, carotid intima-media thickness is independently correlated with bone mineral density in postmenopausal patients. No obvious cause has been suggested to biologically justify this relationship; however, several hypotheses have been proposed in this regard.

Hyperlipidemia is one of the known risk factors of atherosclerosis that can also be involved in the pathogenesis of osteoporosis. The relationship between hyperlipidemia and osteoporosis was studied in a laboratory setting. It was found that hyperlipidemia increased the number, size, and activity of osteoclasts in bone, in that increase in hyperlipidemia intensity was associated with higher intensity of osteoporosis (Tintut and et al., 2004). On the other hand, another study reported that hyperlipidemia can cause secondary hyperparathyroidism and, consequently, bone regeneration disorder (Pirih and et al., 2012).

Increased level of homocysteine is another known risk factor of cardiovascular diseases including atherosclerosis. In a cohort study, Van Meurs et al. suggested that people with increased levels of homocysteine are in the risk of osteoporosis-related fractures, and homocysteine is an independent and strong risk factor for osteoporosis (van Meurs and et al., 2004). This association was observed in other studies as well (Yılmaz and et al., 2009; Bahtiri and et al., 2015; Ebesunu and et al., 2014). However, the mechanism of homocysteine in the pathogenesis of osteoporosis is still unknown.

Vitamin K deficiency is another pathological route that can explain the association between BMD and CIMT. Gamma carboxyglutamate is a non-essential amino acid, which is produced through vitamin K. Proteins derived from this amino acid are involved in the regulation of processes that lead to calcification of bone tissue and vessel walls (Schurgers and et al., 2012). Studies have shown lower bone density in patients with vitamin K deficiency than those with normal levels of vitamin K (Kim and et al., 2015). Another study showed that patients with atherosclerosis and osteoporosis had lower serum levels of vitamin K than control subjects (Kim and et al., 2015). Determination of the exact role of vitamin K deficiency in the pathogenesis of atherosclerosis and reduced bone density requires further research. .

Infiltration of inflammatory cells into atherosclerotic arteries indicates the role of inflammatory system in the development of atherosclerotic plaques (Hansson, G. K. (2005; Sbarsi and et al., 2007). A causal relationship was found between inflammation and osteoporosis, and patients with immune system disorders such as AIDS, Hyper IgE syndrome, rheumatoid arthritis, hematologic disorders (particularly myeloma), and inflammatory bowel disease (IBD) were more susceptible to osteoporosis (Adamopoulos, 2013; Walker Harris & Brown, 2012; sowerwine and et al., 2012). Therefore, inflammation can be the pathophysiological interface between osteoporosis and atherosclerosis. Some conditions such as lipid oxidation, along with their direct impact on pathogenesis of osteoporosis can indirectly accelerate this process by stimulating the immune system (Graham and et al., 2010; Köseoğlu and et al., 2016).

Conclusion

Although the available evidence is not sufficient for finding the common biological pathways of osteoporosis and atherosclerosis, and assumptions have not been studied thoroughly, the association between carotid intima-media thickness and bone mineral density is well-established. Considering that CIMT measurements by ultrasound procedures do not expose patient to ionizing rays, this method can be used as an alternative to conventional methods of BMD measurement. CIMT measurements through ultrasound procedures can be used for screening patients prior to other osteoporosis diagnostic measures.

Authors' Contribution:

Development of the original idea: Hamidreza Talari. Study concept and design: Batol Zamani. Data collection: Mohammadreza Jafari & Hamidreza Talari. Analysis and interpretation of data: Mohammadreza Jafari. Preparation of the manuscript: Hamidreza Talari, Batol Zamani & Mohammadreza Jafari. Revision of the manuscript: Mohammadreza Jafari.

Conflict of interest

There is no conflict of interest between the authors.

Acknowledgements

The authors are grateful from personnel of radiology ward of Kashan's Shahid Beheshti Hospital.

References

- Adamopoulos, I. E., & Pflanz, S. (2013). The emerging role of Interleukin 27 in inflammatory arthritis and bone destruction. *Cytokine & growth factor reviews*, 24(2), 115-121.
- Bahtiri, E., Islami, H., Rexhepi, S., Qorraj-Bytyqi, H., Thaçi, K., Thaçi, S., ... & Hoxha, R. (2015). Relationship of homocysteine levels with lumbar spine and femur neck BMD in postmenopausal women. *Acta Reumatol Port*, 40(4), 355-362.
- Cooney, M., Cooney, M. T., Maher, V., Khan, B., Leong, T., & Graham, I. (2015). Improvement in the estimation of cardiovascular risk by carotid intima-medial thickness: a report from the Dublin Cardiohealth station study. *Preventive medicine reports*, 2, 725-729.
- Ebesunun, M. O., Umahoin, K. O., Alonge, T. O., & Adebusoye, L. A. (2014). Plasma homocysteine, B vitamins and bone mineral density in osteoporosis: a possible risk for bone fracture. *African journal of medicine and medical sciences*, 43(1), 41-47.
- Frost, M. L., Grella, R., Millasseau, S. C., Jiang, B. Y., Hampson, G., Fogelman, I., & Chowienczyk, P. J. (2008). Relationship of calcification of atherosclerotic plaque and arterial stiffness to bone mineral density and osteoprotegerin in postmenopausal women referred for osteoporosis screening. *Calcified tissue international*, 83(2), 112-120.
- Graham, L. S., Tintut, Y., Parhami, F., Kitchen, C. M., Ivanov, Y., Tetradis, S., & Effros, R. B. (2010). Bone density and hyperlipidemia: The T-lymphocyte connection. *Journal of Bone and Mineral Research*, 25(11), 2460-2469.
- Hansson, G. K. (2005). Inflammation, atherosclerosis, and coronary artery disease. *New England Journal of Medicine*, 352(16), 1685-1695.
- Hmamouchi, I., Allali, F., Khazzani, H., Bennani, L., Mansouri, L. E., Ichchou, L., ... & Hajjaj-Hassouni, N. (2009). Low bone mineral density is related to atherosclerosis in postmenopausal Moroccan women. *BMC public health*, 9(1), 388.
- Jie, K. S. G., Bots, M. L., Vermeer, C., Witteman, J. C., & Grobbee, D. E. (1995). Vitamin K intake and osteocalcin levels in women with and without aortic atherosclerosis: a population-based study. *Atherosclerosis*, 116(1), 117-123.
- Kim, B. J., Ahn, S. H., Bae, S. J., Kim, E. H., Kim, T. H., Lee, S. H., ... & Kim, G. S. (2013). Association between metabolic syndrome and bone loss at various skeletal sites in postmenopausal women: a 3-year retrospective longitudinal study. *Osteoporosis International*, 24(8), 2243-2252.
- Kim, M. S., Kim, E. S., & Sohn, C. M. (2015). Dietary intake of vitamin K in relation to bone mineral density in Korea adults: The Korea National Health and Nutrition Examination Survey (2010–2011). *Journal of clinical biochemistry and nutrition*, 57(3), 223-227.
- Kim, S. N., Lee, H. S., Nam, H. S., Lee, H. R., Kim, J. M., Han, S. W., ... & Park, J. H. (2016). Carotid Intima-Media Thickness is Inversely Related to Bone Density in Female but not in Male Patients with Acute Stroke. *Journal of Neuroimaging*, 26(1), 83-88.
- Köseoğlu, C., Kurmuş, Ö., Ertem, A. G., Çolak, B., Bilen, E., İpek, G., ... & Bozkurt, E. (2016). Association between carotid intima-media thickness and presence of coronary artery disease in chronic obstructive pulmonary disease patients. *Anatolian journal of cardiology*, 16(8), 601.
- Lello, S., Sorge, R., Surico, N., & OMERO Study Group. (2015). Osteoporosis's Menopausal Epidemiological Risk Observation (OMERO) study. *Gynecological Endocrinology*, 31(12), 992-998.
- Mohammadi, A., Shateri, K., Behzadi, F., Maleki-Miandoab, T., Lesha, E., Ghasemi-rad, M., & Rosta, Y. (2014). Relationship between intima-media thickness and bone mineral density in postmenopausal women: a cross-sectional study. *International journal of clinical and experimental medicine*, 7(12), 5535.
- Mohammadi, A., Shateri, K., Behzadi, F., Maleki-Miandoab, T., Lesha, E., Ghasemi-rad, M., & Rosta, Y. (2014). Relationship between intima-media thickness and bone mineral density in postmenopausal women: a cross-sectional study. *International journal of clinical and experimental medicine*, 7(12), 5535.

- Muntean, L. M., Simon, S. P., Albu, A., Poanta, L., Rednic, S., & Fodor, D. (2013). SAT0360 Low bone mass is associated with carotid intima-media thickness and atherosclerotic plaque in postmenopausal women referred for osteoporosis screening. *Annals of the Rheumatic Diseases*, 71, 593.
- Muntean, L., Simon, S. P., Popp, R., Albu, A., & Fodor, D. (2014). Bone mineral density, carotid artery intima-media thickness, and Klotho gene polymorphism in postmenopausal women. *Open Medicine*, 9(2), 315-324.
- Özkaya, E., Çakir, E., Okuyan, E., Çakir, C., Üstün, G., & Küçüközkan, T. (2011). Comparison of the effects of surgical and natural menopause on carotid intima media thickness, osteoporosis, and homocysteine levels. *Menopause*, 18(1), 73-76.
- Özkaya, E., Çakir, E., Okuyan, E., Çakir, C., Üstün, G., & Küçüközkan, T. (2011). Comparison of the effects of surgical and natural menopause on carotid intima media thickness, osteoporosis, and homocysteine levels. *Menopause*, 18(1), 73-76.
- Pang, Y., Sang, Y., Ballew, S. H., Grams, M. E., Heiss, G., Coresh, J., & Matsushita, K. (2016). Carotid intima-media thickness and incident ESRD: The Atherosclerosis Risk in Communities (ARIC) study. *Clinical Journal of the American Society of Nephrology*, CJN-11951115.
- Pirih, F., Lu, J., Ye, F., Bezouglaia, O., Atti, E., Ascenzi, M. G., ... & Tintut, Y. (2012). Adverse effects of hyperlipidemia on bone regeneration and strength. *Journal of bone and mineral research*, 27(2), 309-318.
- Rahman, F., Haque, F. S., Biswas, S. K., Begum, R., Hossain, S., Sharmin, S., ... & Nahar, K. (2016). Evaluation of Carotid Intima-Media Thickness in Sub-clinical Hypothyroid Patients. *Bangladesh Journal of Nuclear Medicine*, 19(2), 123-127.
- Redlich, K., & Smolen, J. S. (2012). Inflammatory bone loss: pathogenesis and therapeutic intervention. *Nature reviews Drug discovery*, 11(3), 234.
- Rezaei, K., Zand, S., & Baghcheghi, N. (2009). Comparison Of Biochemical Values Obtained By Venipuncture And Saline Lock After Intermittent Adminis-Tration Of Fluids And Drugs.
- Sbarsi, I., Falcone, C., Boiocchi, C., Campo, I., Zorzetto, M., De Silvestri, A., & Cuccia, M. (2007). Inflammation and atherosclerosis: the role of TNF and TNF receptors polymorphisms in coronary artery disease. *International Journal of Immunopathology and Pharmacology*, 20(1), 145-154.
- Schurgers, L. J., Joosen, I. A., Laufer, E. M., Chatrou, M. L., Herfs, M., Winkens, M. H., ... & Jahnke-Dechent, W. (2012). Vitamin K-antagonists accelerate atherosclerotic calcification and induce a vulnerable plaque phenotype. *PLoS one*, 7(8), e43229.
- Si, L., Winzenberg, T. M., Chen, M., Jiang, Q., Neil, A., & Palmer, A. J. (2016). Screening for osteoporosis in Chinese postmenopausal women: a health economic modelling study. *Osteoporosis International*, 27(7), 2259-2269.
- Sowerwine, K. J., Holland, S. M., & Freeman, A. F. (2012). Hyper-IgE syndrome update. *Annals of the New York Academy of Sciences*, 1250(1), 25-32.
- Sumino, H., Ichikawa, S., Kasama, S., Takahashi, T., Sakamoto, H., Kumakura, H., ... & Kurabayashi, M. (2008). Relationship between carotid atherosclerosis and lumbar spine bone mineral density in postmenopausal women. *Hypertension Research*, 31(6), 1191.
- Tamaki, J., Iki, M., Hirano, Y., Sato, Y., Kajita, E., Kagamimori, S., ... & Yoneshima, H. (2009). Low bone mass is associated with carotid atherosclerosis in postmenopausal women: the Japanese Population-based Osteoporosis (JPOS) Cohort Study. *Osteoporosis International*, 20(1), 53-60.
- Tankó, L. B., Christiansen, C., Cox, D. A., Geiger, M. J., McNabb, M. A., & Cummings, S. R. (2005). Relationship between osteoporosis and cardiovascular disease in postmenopausal women. *Journal of Bone and Mineral Research*, 20(11), 1912-1920.
- Tintut, Y., Morony, S., & Demer, L. L. (2004). Hyperlipidemia promotes osteoclastic potential of bone marrow cells ex vivo. *Arteriosclerosis, thrombosis, and vascular biology*, 24(2), e6-e10.
- Uyama, O., Yoshimoto, Y., Yamamoto, Y., & Kawai, A. (1997). Bone changes and carotid atherosclerosis in postmenopausal women. *Stroke*, 28(9), 1730-1732.
- van Meurs, J. B., Dhonukshe-Rutten, R. A., Pluijm, S. M., van der Klift, M., de Jonge, R., Lindemans, J., ... & Breteler, M. M. (2004). Homocysteine levels and the risk of osteoporotic fracture. *New England Journal of Medicine*, 350(20), 2033-2041.
- Värrö, M., Tuomainen, T. P., Honkanen, R., Rikkinen, T., Niskanen, L., Kröger, H., & Tuppurainen, M. T. (2014). Carotid intima-media thickness and calcification in relation to bone mineral density in postmenopausal women—The OSTPRE-BBA study. *Maturitas*, 78(4), 304-309.
- Värrö, M., Tuomainen, TP, Honkanen, R., Rikkinen, T., Niskanen, L., Kröger, H., & Tuppurainen, MT (2014). Carotid intima-media thickness and calcification in bone mineralization in postmenopausal women — The OSTPRE-BBA study. *Maturitas* , 78 (4), 304-309.
- Walker Harris, V., & Brown, T. T. (2012). Bone loss in the HIV-infected patient: evidence, clinical implications, and treatment strategies. *Journal of Infectious Diseases*, 205(suppl_3), S391-S398.
- Yılmaz, N., & Eren, E. (2009). Homocysteine oxidative stress and relation to bone mineral density in post-menopausal osteoporosis. *Aging clinical and experimental research*, 21(4-5), 353-357.
- Zhang, L., Guo, K., Lu, J., Zhao, F., Yu, H., Han, J., ... & Jia, W. (2016). Nonalcoholic Fatty Liver Disease is Associated with Increased Carotid Intima-Media Thickness in Type 1 Diabetic Patients. *Scientific reports*, 6, 2680

Table 1. Baseline Characteristics

Characteristics	Group		P value
	Normal	Osteoporotic	
Age ^a	50.07±5.46	51.22±6.46	0.39
Age at menopause	46.82±5.33	48.05±6.42	0.36
Weight	72.8±11.81	67.05±9.8	0.02
Height	1.64±0.05	1.65±0.05	0.52
Family History			
No	31 (77.5)	35 (87.5)	0.38
Yes	9 (22.5)	5 (12.5)	
Smoking			
No	34 (85.0)	32 (80.0)	0.56
Yes	6 (15.0)	8 (20.0)	
Hypertension			
No	30 (75.0)	34 (85.0)	0.26
Yes	10 (25.0)	6 (15.0)	
Diabetes			
No	37 (92.5)	36 (90.0)	0.69
Yes	3 (7.5)	4 (10.0)	
Hyperlipidemia			
No	33 (82.5)	31 (77.5)	0.58
Yes	7 (17.5)	9 (22.5)	