The Relation of Carotid Arteries' Intima-Media Thickness With Snoring and Obstructive Sleep Apnea in Type 2 Diabetes Patients

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Abstract- In recent decades, the relation of carotid artery intima-media thickness (IMT) as a marker of atherosclerosis with snoring and sleep disorders has been drawing attention. The aim of this study was to evaluate the relation of carotid arteries IMT with snoring in type 2 diabetic patients. This cross-sectional study was performed on type 2 diabetes patients referring to Mashhad University of Medical Sciences' clinics. The stop Bang, Epworth sleepiness scale, and Stanford questionnaires were used for evaluation of daily sleepiness and snoring. For assessment of carotid artery thickness, Madison X8 ultrasound with 10 MHz superficial probes was utilized. The data were entered into SPSS software, and then the ANOVA test with Turkey, chi-square comparison technique, and Kruskal Wallis with Mann-Whitney U technique was used. The level of significance was considered $P \leq 0.05$. In total 80 patients (37 snorers and 43 non-snorers) entered the study. The mean carotid artery IMT in the group of snoring patients (0.72±0.17) was significantly higher than non-snorers (0.56±0.17) ($P<0.001$). Frequency of daily based on Stanford and ESS questionnaires was 23.8% and 39.2%. The association of sleepiness and snoring was confirmed by Stanford and ESS questionnaires with $P=0.026$ and $P=0.007$. Patients with higher risk of apnea had higher thickness of the mean carotid artery IMT ($P<0.001$). The mean carotid artery IMT had a positive significant relation with age ($P=0.002$), serum creatinine level ($P<0.002$), blood cholesterol ($P=0.02$) and HbAIC level ($P=0.04$). Findings of this study provides evidence on the relation of carotid artery IMT in diabetic patients with snoring independent of other effective factors. Also, results showed that snoring is associated with increased daily sleepiness and patients with higher risk of apnea had higher thickness of the mean carotid artery IMT.

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Keywords: Intima-media thickness of carotid arteries; Snoring; Type 2 diabetes

Introduction

Type 2 diabetes is considered a silent disease which is demonstrated by a combination of insufficient insulin secretion and resistance to insulin. In the absence of insulin or its function, diabetes occurs and its immediate effects are hyperglycemia and renal excretion of glucose (1). The final result of deficiency in insulin secretion or its function is uncontrolled blood sugar levels (2). In chronic hyperglycemia, biomarkers (mostly inflammatory) such as leptin and other pro-inflammatory cytokines are secreted which causes disorders in oxidative processes. This causes impairment of the arteries' endothelial function and begins the process of atherosclerosis in all the arteries of type 2 diabetic patients (3). When the glucose serum levels are chronically high, the hexamine pathway in endothelial cells is activated which inhibits the function of nitric oxide synthesizing enzyme (NOS: nitric oxide synthase). In the physiological state, the nitric oxide resulting from the function of NOS enzyme has antiatherogenic effects on endothelial cells of arteries by inhibiting no. 2 and 9,

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of matrix metalloproteinase enzyme (MMP9, MMP2). Due to impairment of NOS enzyme function and disorders in nitric oxide production, its inhibitory effects on MMP9 and MMP2 is removed, and so the atherosclerosis process begins (4,5).

Increase in IMT of the carotid artery is considered as a reliable index in the detection of early stages of atherosclerosis (6). Therefore, besides the conventional risk factors of cardiovascular disease (such as dyslipidemia and hypertension) and the novel risk factors (Like adipokines), measurement of the carotid arteries' IMT can also be helpful in early diagnosis of this process (7).

One of the signs which its association with increased intima-media thickness has recently been studied is snoring when asleep. Snoring is a sound emitted from the upper airways and is indicative of its increased resistance against airflow (8).

As well as snoring is one of the early signs of obstructive sleep apnea syndrome (9), it is also considered to be associated with hypertension (10), cardiovascular diseases (11) type 2 diabetes (12) and metabolic syndrome (13). Also, some studies have focused on the effect of the energy resulting from the vibrations of snoring, and indicated that the energy being transmitted to the carotid's vascular endothelium increases the risk of damage to these vessels and atherosclerosis (14,15). Some studies (16-20) confirmed the association of snoring with increased carotid IMT others questioned this association (21,22).

Based on the review of articles, there was no study specifically evaluating the relation of intima-media thickness with snoring in diabetic patients. Therefore, in this study, we aimed to evaluate the relation of intima-media thickness of carotid artery with snoring in type 2 diabetes patients.

Materials and Methods

This case-control study was done on type 2 diabetes patients referring to the Mashhad University's diabetes clinic. The studied population consists of type 2 diabetes patients who referred to the diabetes clinics of Mashhad University of Medical Sciences. The inclusion criteria included: 1) having type 2 diabetes, 2) age between 40-75 years, 3) be willing to take part in the study. Exclusion criteria were: 1) taking hypnotic and sedative medications, 2) history of cerebrovascular accidents and 3) history of left ventricular heart failure. Based on the articles and specialist's view, the minimum amount of change in intima thickness between the groups which is clinically valuable was considered 0.1 mm with 0.1 mm standard deviation (equal in groups).

The patient's personal data (including the recognized risk factors of atherosclerosis) and questionnaires evaluating sleepiness and sleep apnea (Epworth, Stanford, and Stop-Bang sleeping scale) were used in this study. The Epworth sleepiness scale was used for evaluating daily sleepiness. In this scale, eight different situations have been defined which the participant must state the probability of snoozing or sleeping in these eight situations. The Stop-Bang questionnaire includes eight questions about gender (male 1, female 0), history of repeated loud snoring in sleep, sleepiness during the day, sleep apnea, history of high blood pressure , age over 50 years, BMI higher than 35 kg/m^2 and neck circumference over 40 cm.

After collecting and preparation of the patient's data and test results, the statistical data were entered into the SPSS16 software, and then Mann-Whitney test, Kolmogorov-Smirnov, and chi-square comparison technique were used. Moreover, linear regression was done to consider the effects of confounding variables between the groups.

Results

In this study 80 type 2 diabetes patients with the age of 57±9.35-year-old participated of whom 35 (43.8%) were male, and 45(56/3%) were female. the baseline characteristics of the 80 study participants are given in (Table 1).

The frequency of snoring in the studied patients was 46.3% (37 cases), of whom 26 patients (70.3%) reported 1 to 3 nights, and 11 individuals reported 4 to 7 nights of snoring weekly. The frequency of sleepiness according to the ESS and Stanford questionnaires was reported 39.2 and 23.8 percent respectively. Results indicated the meaningful relation between sleepiness and snoring, according to ESS and Stanford questionnaires (P=0.025 and P=0.007) (Table 2).

The mean carotid IMT in the group of snoring patients (0.72±0.17) was significantly higher than non-snorers (0.56±0.17) (P<0.001).

High, average and low risk of sleep apnea existed in 26.3%, 26.3%, and 37.5%of patients, respectively. By applying hypothesis test, it is revealed that patients with higher risk of apnea had higher thickness of the mean carotid artery intima-media (P<0.001). The mean carotid artery IMT had a positive significant relation with age (P=0.002), serum creatinine level (P=<0.002), blood cholesterol (P=0.02) and HbAIC level (P=0.04) (Table

3).

Table 1. Demographic data of both groups

		Snorer	Non snorer	Test
Descriptive Variables	**Age (year old)**	58.18±8.40	56.02±10.08	*P*=0.305†
	Weight (Kg)	71.43±7.31	68.47±9.28	*P*=0.708†
	Neck circumstance (Cm)	39.34±4.96	38.84±4.40	*P*=0.650†
	BMI (Kg/m^2)	26.5±4.70	25.6±3.62	*P*=0.627#
	Diabetes duration (year)	8.1±8.72	8.43±7.16	*P*=0.887#
	Systolic blood pressure (mmHg)	128.1±13.5	128.6±19.8	*P*=0.887#
	Diastolic blood pressure (mmHg)	81.1±6.10	81.16±5.85	*P*=0.913#
	Hb1AC (%)	7.85±1.06	7.46±1.40	*P*=0.090#
	Serum Creatinine (mg)	1.36±0.82	1.03±0.36	*P*=0.887#
Quantitative variables				
Gender	**Male**	19 (51.4%)	16 (37.2%)	*P*=0.204
	Female	18 (48.6%)	27 (62.8)	
Smoking	**Yes**	3 (8.1%)	10 (23.3%)	*P*=0.078
	No	34 (91.9%)	33 (76.7%)	
Atherosclerosis family history	**Yes**	10 (27.8%)	12 (28.6%)	*P*=0.938
	No	26 (72.2%)	30 (71.4%)	

†Independent T test # U Mann-Whitney test

Table 2. Relation of Snoring and daily sleepiness

Daily sleepiness		Snorer (n=37)	Non-snorer (n=43)	Test
Stanford questionnaire	normal	24 (64.9%)	37 (86%)	*P*=0.026
	abnormal	13 (35.1%)	6 (14%)	
ESS questionnaire	Normal<7	16 (44.4%)	32 (74.4%)	*P*=0.007
	Abnormal>7	20 (55.6%)	11 (25.6%)	

Table 3. Spearman's correlation coefficient of measured variable and the mean carotid IMT

Variable		Mean ± SD	Spearman's correlation coefficient	*P*
Age		57±9.3	0.350	0.002
BMI		26±4.1	-0.046	0.686
Neck circumstance		39.1±4.6	0.147	0.213
Systolic blood pressure		128.3±17.1	0.131	0.250
Diastolic blood pressure		81.1±5.9	0.052	0.646
Cholesterol		220±57.7	0.264	0.020
HbA1C		7.6±1.2	0.238	0.036
Serum Creatinine		0.6±0.2	0.347	0.002
Variables [Frequency (%)]		**mean carotid IMT Mean ± SD**	**z Mann-Whitney**	***P***
Gender	**Male [35 (43.8)]**	0.66±0.1	0.935	0.350
	Female [45 (56.3)]	0.61±0.1		
Age	**≤55 [37(46.3)]**	0.57±0.17	3.01	0.003
	>55 [43(53.8)]	0.69±0.18		
Smoking	**Yes [13(16.5)]**	0.63±0.2	0.946	0.344
	No [67(83.7)]	0.61±0.1		
Atherosclerosis family history	**Yes [22(28.2)]**	0.63±0.2	0.028	0.977
	No [56(71.8)]	0.62±0.2		

For evaluating the relation of carotid IMT with snoring in diabetic patients, the multivariable regression model was used. Considering the results of the relation of snoring with the important variables being investigated, the confounding variables with a significance level below 0.2 which were related to snoring as well, were entered to the regression model and with the adjustment of these confounding variables (hemoglobin A1C, creatinine, and cholesterol) the relation between snoring and carotid artery intima-media thickness is studied. In Figure 1, the results of fitting the multivariate regression model for evaluating the association of carotid IMT and snoring in type 2 diabetic patients with adjustment of confounding variables, indicates the significant relation of snoring and mean carotid IMT with the adjustment of other confounding variables; mean carotid artery IMT is

increased 18.8% in snorer people. Although it is worth mentioning that among confounding variables, regression analysis has shown that hemoglobin A1C and creatinine have nothing to do with IMT at 5% significant level whereas cholesterol revealed a significant but little association with IMT. In the other word, increasing the cholesterol raises the IMT with the rate of 0.1%.

In terms of gender, finding showed that in both genders snoring was significantly related to the mean carotid artery IMT (Figure 2).

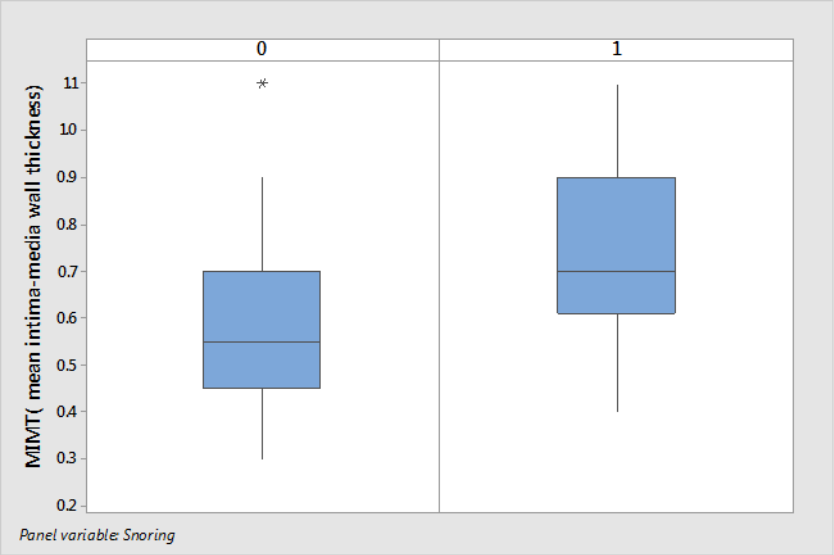

Figure 1. The multivariate regression model for evaluating the association of carotid IMT and snoring in type 2 diabetic patients (0: non-snorer, 1: snorer)

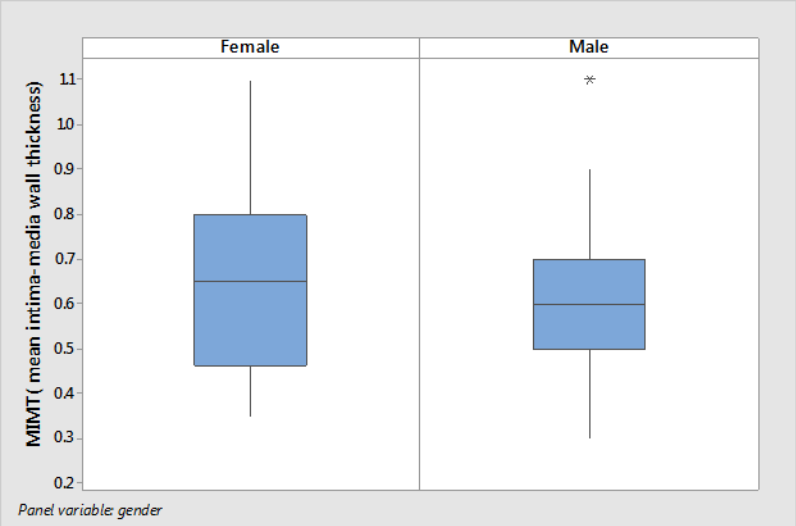

Figure 2. Comparison of the Mean IMT carotids based on gender

Discussion

The aim of this study was to evaluate carotid arteries' intima-media thickness in type 2 diabetic patients and its association with snoring in this group of patients.

In this study, the patients of the group with and without snoring were homogeneous regarding their age, weight and neck circumference. The results of this study indicated that the mean carotid artery IMT in snoring diabetic patients was significantly higher than non-snorers and this relation remained meaningful in spite of the adjustment of confounding variables (HbA1C, creatinine, and cholesterol).

Various studies have reported findings similar to our study, showing that there is a significant association between intima-media thickness of carotid artery and

snoring. Some of these studies have been conducted on the healthy general population and others on groups of patients with certain diseases. Of the studies performed in the healthy population are studies of Li *et al.,* (16), Lee *et al.,* (23), and Jacoby *et al*., (21) which all confirm the relation of carotid's intima-media thickness and snoring. Li *et al.,'s* study (16) showed that the mean intima-media thickness of the carotid artery is higher in all its sections (the common carotid artery, bifurcation of the carotid artery) in snoring patients compared to those who didn't snore, and after adjustment of age, gender, smoking, alcohol, BMI, fat profile, blood pressure and diabetes, regression analysis showed that the risk of increase in intima-media thickness of snoring patients is 1.7 times the patients who don't snore. A study by Lee *et al.,* (23) on the relation of carotid atherosclerosis with self-reported snoring in middle-aged and elderly adults, indicated that after adjustment of age and gender, snorers had a significantly higher carotid IM thickness in comparison to non–snorers, and OR for increased IM thickness (>0.823) was significantly higher in snorers compared to non–snorers (OR 1.31). Jacoby *et al.,* (21) also confirmed the results of our study.

Other studies evaluated the relation of snoring in patients with certain diseases. In Apaydin *et al.,'s* study (17) common carotid artery intima-media thickness (CCA-IMT) in habitual simple snoring (HSS) and obstructive sleep apnea syndrome (OSAS) patients were observed, and results showed a significant relation between CCA-IMT and OSAS, although there was no relation between the intensity of OSAS and artery thickness. Lee *et al.,'s* study (18) on the role of heavy snoring in atherosclerosis of the carotid artery showed that frequency of carotid artery atherosclerosis significantly increases with increasing intensity of snoring. According to our review of articles, study on the relation of carotid arteries' intima-media thickness and snoring in type 2 diabetic patients has not yet been carried out and this study is one of the first researches in this field of diabetic patients' disorders.

Thereby we present a pathophysiologic explanation for the association observed between snoring and increase in intima-media thickness of the carotid artery. One of the early signs of obstructive sleep apnea syndrome is snoring (9) which is considered as an accompanying factor of hypertension (10), cardiovascular diseases, and other chronic conditions which the presence of these disorders is associated with changes in vascular structure and increase of carotid IM thickness. Besides this association, there are studies indicating that the energy from the vibration resulting from snoring is transferred to the carotid's vascular endothelium, increasing the susceptibility and risk of atherosclerosis in these arteries. In a study by Lee *et al.,* (14) the relation of CCA-IMT with snoring in OSA patients was evaluated which showed that CCA-TMA is significantly related to snoring sound energy in the D -20 HZ and 652-1500 Hz range. It seems that the background sounds due to snoring may be related to the increased thickness of the carotid artery. Also, it seems the background sounds being created due to snoring may be associated with vascular remodeling in the carotid artery (21).

This study showed that mean carotid artery IMT increased with age. A study was conducted by Kim *et al*., (22) on the relation of snoring with subclinical changes in atherosclerosis of the carotid during a period of four years and findings showed the average, and maximum IMT increased over time, and in dot comparison on time, both the average and max IMT in habitual/occasional snorers was significantly higher than non-snorers and also the baseline. It appears that snoring accelerates the subclinical atherosclerotic changes over time. Also, Polak *et al.,'s* study in 2011 which investigated the carotid IMT changes in diabetic patients during a 12 month period, indicated that over the time thickness increases although in case of intensive control of diabetes, the pace of increase in thickness is reduced (24). Su *et al.,'s* study in 2012 showed that in the general population IMT increases with age (25). It appears that changes in vascular structure and increased cardiovascular risk factors in the old aged is associated with carotid's intima-media thickness, Although, the changes observed in carotid IMT may be merely due to the physiologic body changes which create various ranges of normal amounts in different ages (26).

In this study, the average carotid artery intima-media thickness in snoring and non-snoring male diabetic patients had no significant difference. A study by Kim *et al.,* (19) on CCA-IMT in non-apneic female snorers showed that IMT significantly increased with higher degrees of snoring solely in females, and had no difference in snoring or non–snoring males. Another study by Kim *et al.,* (22) showed that at the beginning the average and max. IMT in the three snorer groups had no difference in males, whereas in habitual/occasional female snorers the average and max. IMT was significantly higher than non-snorers.

Daily sleepiness in snorers was significantly higher than non-snoring patients. Consistent with the results of this study, Svensson *et al.,'s* study in 2008 which reported that sleepiness and daily fatigue are related to habitual snoring, independent of the other risk factors (27). Sleep-related breathing disorders (SRBD) such as snoring is one

of the most important multi-factorial causes of daily sleepiness which in the presence of daily sleepiness is effective in increase of cardiovascular accidents (28).

Based on STOP bang questionnaire, patients with higher risk of apnea had higher thickness of the mean carotid artery IMT. The association of increased carotid IMT with obstructive sleep area has been frequently evaluated in the past. Similar to the results of our study was Minoguchi *et al*.,'s study (2005) which showed that carotid IMT in obstructive sleep apnea patients was significantly higher than the obese control group patients (29).

The mean carotids artery IMT was significantly related to increasing in HbAIC and cholesterol levels. Polak *et al.,'s* Study also showed a significant relation between Hb AIC serum level and IMT of the carotid (24). The hbaic level is associated with long-term control of diabetes. In this regard , these results are consistent with the results of a study performed in 2003 which showed that intensive control of diabetes was associated with reduced pace of carotid IMT increase, and the average increase in thickness in the group who were conventionally intensively treated was 0.046 mm and 0.032 mm respectively (*P*=0.001) (30).

This study showed correlation between increased carotid IMT and snoring in diabetic type II patients. We also found that the group of diabetic snorers experienced more daytime sleepiness and those with higher STOP-BANG score showed thicker carotid IMTs.

This is a cross-sectional study, and therefore there is a high risk of systematic or random error in this type of study. Future studies especially with cohort design and focus on time to event is suggested. In the growing mass of non-communicable diseases in today's world, finding preventable variables such as snoring can help in controlling complications of these diseases.

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