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RESEARCH

AN EVALUATION OF METABOLIC SYNDROME AND ITS COMPONENTS IN ALZHEIMER'S DISEASE: DOES GENDER MAKE A DIFFERENCE?

ABSTRACT

Introduction: Recent studies have indicated that vascular risk factors and metabolic syndrome may contribute to the process of Alzheimer's disease. The aim of this study was to evaluate the metabolic syndrome and its components in etiopathogenesis of Alzheimer's disease and the possible influences of these factors and gender.

Materials and Method: Fifty-one patients were included in the study. Global deterioration scale and Standardized Mini-Mental Test (SMMT) were applied to all patients. Forty-two individuals with no cognitive complaint and normal results for SMMT were included as the control group. NCEP-ATP III criteria were used for the diagnosis of metabolic syndrome.

Findings: Fifty-one patients (18 male, 33 female) and 42 controls (25 male, 17 female) were matched for age (73.47±6.49 and 73.04±4.61, respectively). The frequencies of metabolic syndrome (p=0.013) and its components [high waist circumference (p=0.001), hyperglycemia (p=0.05) and hypertriglyceridemia (p=0.040)] were significantly higher in female patients when compared to the male patients.

Conclusion: Our results support a relation between Alzheimer's disease and metabolic syndrome and its components of high waist circumference, hyperglycemia and hypertriglyceridemia in women and suggest that different physiopathological mechanisms with respect to gender may be effective in this neurodegenerative process. Furthermore metabolic factors in women may contribute more prominently to the disease pathogenesis.

Key Words: Metabolic Syndrome X/complications; Metabolic Syndrome X/epidemiology; Alzheimer Disease; Dementia; Risk Factors.

ARAŞTIRMA

METABOLİK SENDROM VE KOMPONENTLERİNİN ALZHEİMER HASTALIĞINDA DEĞERLENDİRİLMESİ: CİNSİYET FARK YARATIYOR MU?

ÖZ

Giriş: Son yıllarda yapılan çalışmalar vasküler risk faktörleri ve metabolik sendromun Alzheimer hastalığı sürecine katkıda bulunabileceğini göstermektedir. Bu çalışmanın amacı Alzheimer hastalığı etyopatogenezinde metabolik sendrom ve komponentlerini değerlendirmek ve patogenezde bu faktörlerin ve cinsiyetin olası etkisini değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 51 Alzheimer hastası dahil edildi. Bütün hastalara genel kötüleşme ölçeği ve standardize mini mental test (SMMT) uygulandı. Kognitif yakınması olmayan ve SMMT skorları normal olan 42 kişi kontrol grubunu oluşturdu. Metabolik sendrom tanı kriterleri olarak NCEP-ATP III kriterleri kullanıldı.

Bulgular: Elli bir hasta (18 erkek, 33 kadın) ve 42 kontrol (25 erkek, 17 kadın) arasında ortalama yaşlar arasında farklılık bulunmadı (sırasıyla 73.47±6.49 ve 73.04±4.61). Metabolik sendrom bulunma sıklığı (p=0.013) ve komponentleri [yüksek bel çevresi (p=0.001), hiperglisemi (p=0.05) ve hipertrigliseridemi (p=0.040)] kadın hastalarda erkek hastalara göre daha yüksek bulundu.

Sonuç: Bulgular kadınlarda metabolik sendrom ve komponentleri olan, yüksek bel çevresi, hiperglisemi, hipertrigliseridemi ile Alzheimer hastalığı arasındaki ilişkiyi desteklemektedir ve cinsiyete bağlı farklı fizyopatolojik mekanizmaların, bu nörodejeneratif süreçte etkili olabileceğini düşündürmektedir. Bunun da ötesinde kadınlardaki metabolik faktörler hastalık patogenezine daha belirgin olarak etki edebilir.

Anahtar Sözcükler: Metabolik Sendrom; Alzheimer Hastalığı; Demans; Risk Faktörleri.

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INTRODUCTION

Alzheimer's disease is the most frequent neurodegenerative disorder that causes dementia and it is one of the leading chronic diseases in developed countries (1). Recent studies have suggested that vascular risk factors and metabolic syndrome may contribute to the pathophysiology of Alzheimer's disease (2,3). According to the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III criteria, metabolic syndrome consists of the combinations of five cardiovascular risk factors: abdominal obesity, hypertriglyceridemia, low high density lipoprotein (HDL) cholesterol levels, hypertension, and hyperglycemia. The prevalence of metabolic syndrome increases with age, as with cognitive disorders, reaching 45% of the population over 60 years of age (4).

The aim of this study was to investigate the association of vascular risk factors and especially metabolic syndrome with the Alzheimer's type dementia, the relation of cognitive parameters with the metabolic syndrome components and possible gender influences.

MATERIALS AND METHOD

Patients who admitted to Ankara Numune Education and Research Hospital Neurology Outpatient Clinic and were diagnosed as Alzheimer type dementia were included in this hospital-based prospective study, unless they met the exclusion criteria. For the diagnosis of Alzheimer's disease, a detailed history of cognitive symptoms was recorded and physical and neurological examinations were performed in all patients. Brain imaging (computerized tomography (CT) or magnetic resonance imaging (MRI) and 12-hour fasting biochemical parameters (blood glucose, liver function tests, blood urea nitrogen, creatinine, electrolytes, albumin, globulin), lipid levels (low density lipoprotein (LDL) cholesterol, HDL cholesterol, very low density lipoprotein (VLDL) cholesterol, total cholesterol, and triglyceride), thyroid function tests, blood count, and sedimentation rate were obtained from all patients. Patients were excluded in accordance with the determined exclusion criteria as shown in Table 1.

Global deterioration scale (5) and the Turkish version of the Standardized Mini-Mental Test (SMMT) (6) or Standardized Mini-Mental State Examination for the illiterate population (SMME-E) (7) were performed in all individuals. National Institute of Neurological Communicative Disorders-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria were used to diagnose Alzheimer's type dementia, and according to the criteria (8), a total of 51 patients diagnosed as "Possible Alzheimer's disease" were included in the study.

Table 1— Exclusion Criteria For The Patients and Controls

Exclusion Criteria
Systemic/metabolic disorders: Renal failure, hepatic failure, malignancy, hypothyroidism, collagen tissue diseases, vasculitis, AIDS
Alcohol and drug addiction
Central nervous system disorders: infectious diseases, mass occupying lesions, multiple sclerosis and other demyelinating diseases, vasculitis, development abnormalities, epilepsy, hereditary metabolical diseases
Vascular dementia
Other neurodegenerative causes of dementia: Lewy body dementia, fronto-temporal dementia, Parkinson's disease and associated degenerative disorders
Pre-morbid psychiatric and mental abnormalities

As the control group, 42 individuals admitted to our outpatient clinic, whose brain imaging and blood tests were performed for other reasons and revealed no cognitive symptoms and normal MMSE results, were selected. The same exclusion criteria as used in patients were applied to the control group.

Approval for the study was obtained from the Ankara Numune Education and Research Hospital local ethics committee and written and/or oral consent was taken from the patients or relatives and controls.

Height, weight and waist circumference measured from a median point of the 12th rib and iliac crest were obtained from both groups. Before the assessment of blood pressure, patients relaxed in a chair for five minutes and then the average of three values measured by manual manometer was recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. For diagnosing metabolic syndrome, NCEP-ATP III criteria were used. According to NCEP-ATP III, patients possessing three or more of the following components were diagnosed as metabolic syndrome:

1. Waist circumference>102cm in males, 88cm in females,
2. Blood triglyceride level >150mg/dl,
3. HDL cholesterol level <40mg/dl in males, 50 mg/dl in females,
4. Blood pressure level >130/85mmHg or patient is on anti-hypertensive therapy, and
5. Fasting blood glucose >110mg/dl or patient is on anti-diabetic therapy.

Metabolic syndrome and its five components (waist circumference, hypertriglyceridemia, hypo-HDL cholesterol, hypertension, hyperglycemia) were compared between the two groups. For statistical analysis, Student's t test, Pearson correlation test and chi-square non-parametric test were used. P<0.05 was determined as the significance limit. SPSS version 10.0 software was used for processing the data.

RESULTS

The study included 51 patients (18 males and 33 females) and 42 controls (25 males and 17 females. There was no statistically significant difference between the patient and control groups with respect to age (73.47±6.49 versus 73.04±4.61, respectively; p=0.724). Demographic features of the patients and controls are shown in Table 2. Level of education of the patients and controls are shown in Table 3.

When evaluating the frequency of metabolic syndrome and its components without regard to gender difference, we found no significant differences between the two groups with respect to the existence of high waist circumference (p=0.161), hyperglycemia (p=0.541), hypertriglyceridemia (p=0.519), hypo-HDL cholesterol, and metabolic syndrome (p=0.326); however, hypertension was found to be significantly more frequent in the patient group (p=0.023) (Table 4). We also evaluated the clustering of metabolic syndrome components (regardless of which component) in both groups. The combination of three components was prevalent in the patient group (n=18, 35.3%), followed by the combination of two components and four components (n=11, 21.6%; n=8, 15.7%, respectively). The combination of three components was also prevalent in the control group (n=17, 40.5%), followed by one component (n=10, 23.8%) and two components (n=8, 19%). Distributions of metabolic syndrome components in the patients and controls are shown in Figure 1.

Table 3— Educational Level of the Patients and Controls

Level of Education	Patients (n)	Controls (n)
Illiterate	21	11
Primary school	19	19
High School	9	4
University	2	8
Total	51	42

Table 2— Demographic Features of the Patients and Controls

		Patients		Controls	
Parameter		n= 51	%	n= 42	%
Gender	Female	18	35.3	17	40.5
	Male	33	64.7	25	59.5
Heart disease	Yes	11	21.6	6	14.3
	No	40	78.4	36	85.7
Diabetes Mellitus	Yes	9	17.6	10	23.8
	No	42	82.4	32	76.2
Hypertension	Yes	29	56.9	23	54.8
	No	22	43.1	19	45.2
Smoking	Yes	8	15.7	14	33.3
	No	43	84.3	28	66.7
Anti-hyper-tensive drug	Yes	25	49.0	19	45.2
	No	26	51.0	23	54.8
Anti-diabetic drug	Yes	7	13.7	9	21.4
	No	44	86.3	33	78.6
Anti-lipemic drug	Yes	4	7.8	3	7.1
	No	47	92.2	39	92.9
Obesity	Yes	16	31.4	9	21.4
	No	35	68.6	33	78.6
Family history for AD	Yes	4	7.8	2	4.8
	No	47	92.2	40	95.2

Table 4— Metabolic Syndrome Components and Laboratory Findings of the Patients and Controls

Parameter		Mean	sd	n	p
HDL	Patient	48.62	12.26	51	0.138
	Control	44.92	11.37	42	
Waist circumference	Patient	96.27	12.26	51	0.951
	Control	96.11	11.84	42	
SMMT	Patient	16.45	6.20	51	**<0.0001**
	Control	28.42	0.99	42	
Fasting blood glucose	Patient	109.52	46.87	51	0.797
	Control	106.88	52.06	42	
Urea	Patient	39.21	15.45	51	0.088
	Control	24.21	11.81	42	
Systolic BP	Patient	137.05	18.68	51	**0.011**
	Control	126.90	18.80	42	
Diastolic BP	Patient	81.56	10.27	51	**0.007**
	Control	75.23	11.73	42	
Total cholesterol	Patient	207.86	48.88	51	**0.038**
	Control	188.19	39.37	42	
Triglyceride	Patient	141.13	67.52	51	0.638
	Control	147.42	59.18	42	
LDL cholesterol	Patient	130.60	39.74	51	0.063
	Control	116.19	32.62	42	
Total protein	Patient	72.72	5.67	51	0.705
	Control	72.28	5.42	42	
Albumin	Patient	40.60	3.48	51	0.316
	Control	41.35	3.65	42	
Hemoglobin	Patient	13.08	1.10	51	**0.022**
	Control	13.69	1.42	42	
Hematocrit	Patient	38.67	3.86	51	0.128
	Control	40.08	4.98	42	
ESR	Patient	20.74	12.68	51	0.220
	Control	17.26	14.47	42	
Folic acid	Patient	6.09	2.72	51	**0.012**
	Control	6.83	3.35	42	
Vitamin B_{12}	Patient	198.66	107.82	51	**0.012**
	Control	281.66	199.33	42	

HDL: High density lipoprotein. SMMT: Standardized Mini-Mental Test. BP: Blood pressure. LDL: Low density lipoprotein. ESR: Erythrocyte sedimentation rate.

When we evaluated the male and female subgroups of the Alzheimer's disease patient group, metabolic syndrome was found to be significantly more frequent in females (p=0.013). High waist circumference (p=0.001), hyperglycemia (p=0.05) and hypertriglyceridemia (p=0.04) were also more frequent in the female patient subgroup as compared to males. There were no differences according to gender in hypertension (p=0.591) or low HDL (p=0.591) (Figure 2).

SMMT scores in the patient group revealed a negative correlation with age (r= -0.0334; p=0.017) and global deterioration scale values (r= -0.955; p <0.0001), but revealed a positive correlation with blood albumin levels (r=0.398; p=0.004). We also found that global deterioration scale values were positively correlated with age (r=0.72; p=0.054), but negatively correlated with body weight (r= -0.363; p=0.009) and blood albumin levels (r= -0.305; p=0.030). No significant correlation between SMMT scores and number of components was found.

The frequencies of metabolic syndrome (p=0.265), low HDL cholesterol (p=0.531), hyperglycemia (p=0.477),

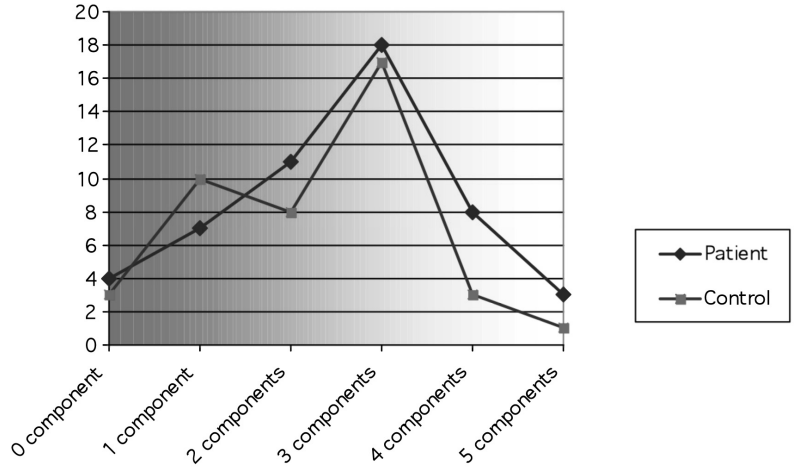

Figure 1— Distribution of metabolic syndrome components in the patients and controls.

hypertension (p=0.963), and hypertriglyceridemia (p=0.348) did not differ significantly between male and female subgroups of the control group. However, high waist circumference (p=0.002) and high LDL cholesterol (p=0.305) were more frequent in the female subgroup. Metabolic syndrome components in female and male patients are shown in Figure 2.

Discussion

In this case-control study, there was no significant difference in metabolic syndrome frequency between Alzheimer's disease patients and controls. However, metabolic syndrome was more frequent in women with Alzheimer's disease when compared with the male patients. This gender-related frequ-

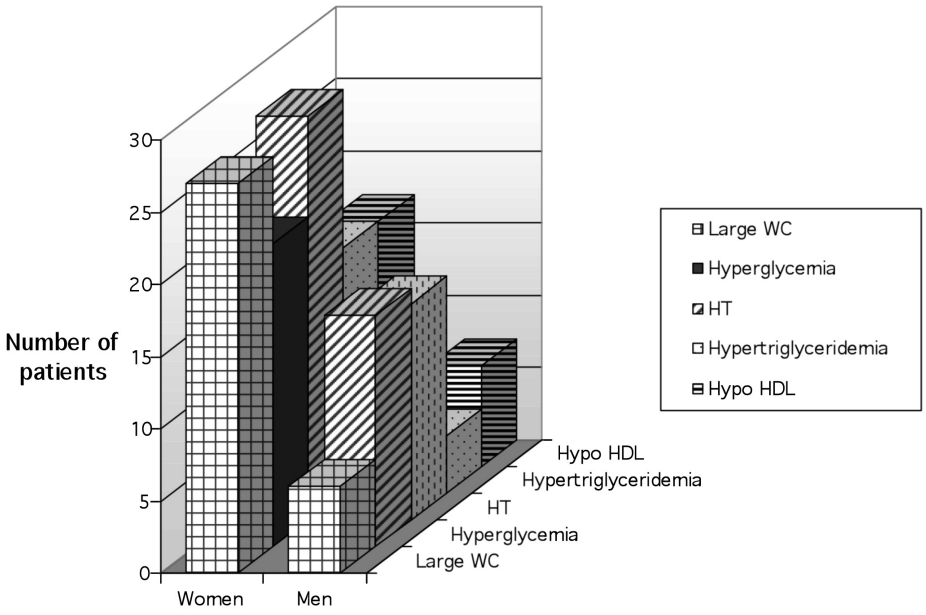

Figure 2— Metabolic syndrome components in female and male patients.

ency difference in the patient group was not observed in the control group. This result can not be explained only by the fact that metabolic syndrome is more frequent in women in the general population. Other possible explanations may be the early mortality of men with metabolic syndrome or the different effects of metabolic syndrome on cognition according to gender (9).

Some studies have previously investigated the effect of metabolic syndrome on cognition with regard to gender differences. Vanhanen et al. followed 959 individuals aged 69-78 in their study and suggested that metabolic syndrome may be an independent risk factor of Alzheimer's disease in women but not in men. Nevertheless, as researchers have remarked, the low number of men with Alzheimer's disease in their study or the early mortality in men with metabolic syndrome may have had an effect on the results in the studies (9).

We investigated metabolic syndrome components separately in our study and thus found that hypertension was associated with Alzheimer's disease independent of gender. Few studies investigating the role of hypertension in Alzheimer's disease have been published. Large studies have indicated that hypertension in mid-ages may be associated with Alzheimer's disease in old ages (1,10,11). Our study supports the opinion that hypertension may be a risk factor for Alzheimer's disease since hypertension was seen more frequently in patients than controls.

Diabetes mellitus (DM), which is another component of metabolic syndrome, is the most frequently studied possible risk factor. Results of many studies have suggested the association of DM with Alzheimer's disease. Cukierman et al. reviewed the prospective studies that investigated the association of DM with Alzheimer's disease and concluded that the cognitive decline demonstrated by MMSE is faster in diabetic patients than nondiabetics (12). In the Framingham study, however, DM was not found to be an independent risk factor, but it increased the Alzheimer's disease risk in a few subgroups (male gender, systolic blood pressure >180 mmHg, ApoE ε4 +) (13).

We found no difference between the patient and control groups concerning DM frequency. However, the influence of DM on cognition also depends on time and serial examinations, which we did not perform, and these could have revealed more reliable results. However, DM was more frequent in the female patient subgroup in our study, when compared to the male patient subgroup; a similar association was not seen in the control group. Yaffe et al., in a study investigating the relation of cognitive performance with DM in 7027 women, indicated that diabetics, prediabetics and individuals with impaired fasting glucose have a higher risk of developing impaired cognitive function. In their study, diabetic women showed worse cognitive performance at the basal examination and after four years of follow up, when compared to controls (14). However, the above-mentioned studies did not investigate the same relation in the male subgroup, so they were limited by the absence of interpretation about the influence of diabetes according to gender. On the contrary, in the Framingham trial, diabetes was found to be related with Alzheimer's disease in the male population (13).

HDL cholesterol and triglyceride levels in Alzheimer's disease have also been investigated widely. Sabbagh et al. examined the relation of lipid profiles with cognition and determined that the blood level of triglyceride is below 200 mg/dl in patients with Alzheimer's disease. However, in their study, they did not use the standard values of metabolic syndrome, nor did they examined the lipid levels in a control group (15). The SALSA trial, in which standard metabolic syndrome criteria were used, demonstrated that hypertriglyceridemia is not associated with MMSE and DelRec scores (16).

However, in the study of Vanhanen et al., both hypo-HDL and hypertriglyceridemia were observed more frequently in the Alzheimer's disease group than in the control group; thus, the researchers claimed that atherogenic dyslipidemia may contribute to the disease physiopathology (9). Razay et al. also found triglyceride levels significantly higher in Alzheimer patients as compared with controls, and they ascertained that vascular atherogenic changes in Alzheimer brains could be explained by this result (17). By using the standard metabolic syndrome criteria, our findings support that hypertriglyceridemia, but not hypo-HDL cholesterol, may enhance Alzheimer's disease risk in women.

The data in the literature about the role of obesity in Alzheimer's disease are inconsistent. Middle age obesity has been seen to increase the risk, but body weight loss after the onset of the disease makes it difficult to determine the obesity as a consequent risk factor. Kivipelto et al. indicated that middle age obesity raises the risk of Alzheimer's disease in older ages (18). Whitmer et al. claimed that obesity in the ages of 40-45 significantly increases the risk of Alzheimer's disease for the subsequent 36 years. In their study, obese individuals have a three times higher risk of Alzheimer's disease than individuals with normal BMI (19). Trials with broad patient series and long follow-up periods have also revealed the increased risk of Alzheimer's disease in obese individuals (20-22). However, in a Honolulu-Asia trial male cohort, high BMI was shown to have no relation with Alzheimer's disease (23).

Studies that investigated obesity as a risk factor in old ages indicated that old age obesity is associated with Alzheimer's disease in women but not in men. These results were related to a real metabolic phenomenon or a different fat distribution specific to the female gender (24). The relation of Alzheimer's disease and body weight is entirely controversial from another point of view. Some researchers believe that the onset of Alzheimer's disease and ongoing disease-related factors are also responsible for the weight loss. For instance, atrophies in the medial temporal lobe and hippocampus, which are known to start before the clinical onset of dementia, are also associated with the impairment of weight control; likewise, hypometabolism of the cingulate gyrus or hypothalamus may disrupt weight control and may contribute to body mass loss before the evident cognitive decline (24). The other possible reasons for weight loss are self neglect, apraxia, agnosia, memory deficits, changes in the senses of taste and smell, augmented energy loss, impairments with respect to shopping and cooking, impaired communication and motor skills, depression, and refusal to eat (25).

Based on these results, one could assert that the influence of obesity on cognition appears in time and that this influence is more prominent with middle age obesity, but in view of the initiation of weight loss several years before the onset of clinical dementia, the determination of obesity as a risk factor becomes complicated.

Our results support a relation between metabolic syndrome and its components (high waist circumference, hyperglycemia and hypertriglyceridemia) with Alzheimer's disease in women, and also the hypothesis that the metabolic syndrome has more influence than the sum of its components in this subgroup. These findings support the association of Alzheimer's disease with metabolic syndrome and vascular risk factors, as well as suggest that different physiopathological mechanisms according to gender may be effective in this neurodegenerative process. Furthermore, metabolic factors in elderly women may contribute significantly more to the disease pathogenesis. Our study has limitations and that further longitudinal studies have to be done to examine this phenomenon in depth.

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