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The Association between Symptoms of Dry Eye Syndrome and Metabolic Outcome in a General Population in Korea

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Dry eye syndrome (DES) is recognized as a public health concern. One of the pathophysiologies in the development of DES is inflammation, and metabolic syndrome (MetS), which is highly prevalent in the general population, is a well-known chronic and systemic inflammatory condition. Despite the increasing interest regarding a relationship between DES and MetS, information is lacking on the association between DES and MetS and its individual components. We investigated the association between DES symptoms and MetS and its components among adults aged ≥ 19 years using population-based data from the Korea National Health and Nutrition Examination Survey V. A sample group of 15,294 adults (42.67% men and 57.33% women) completed household interviews in which they provided blood (for high-density lipoprotein cholesterol, triglyceride, and glucose) and anthropometric measurements (including waist circumference, weight, and height) to define MetS. We also collected information regarding sociodemographic and behavioral risk factors. The survey results showed that 11.50% of men and 22.35% of women experienced DES and 5.30% of patients had both DES and diagnosis of MetS, including 204 men and 606 women. Thus, no significant difference was observed between DES and the diagnosis of MetS according to sex ($P = 0.4008$ in men; $P = 0.0804$ in women); however, a significant association was observed between DES and hypertriglyceridemia in women (OR, 1.13; 95% CI, 1.01-1.29). Therefore, hypertriglyceridemia might be an important factor in the association between DES and MetS. Further longitudinal research is needed to evaluate this relationship.

Keywords: Adult; Dry Eye Syndrome; Korea; Metabolic Syndrome; National Health and Nutrition Examination Survey; Population

INTRODUCTION

Dry eye syndrome (DES) is increasingly recognized as a serious, worldwide public health concern (1). The Salisbury Eye Evaluation (SEE) study and the Beaver Dam Study reported the prevalence of DES based on symptoms to be 15.0% (2) and 14.4% (3), respectively. In Korea, the prevalence was reported to be 16.0% (4) with a diagnosis by doctor or with symptoms. In recent years, there has been an increasing interest in DES, as it is one of the main reasons that people visit the clinic. The United States announced the economic burden of DES that the average cost of 11,302 USD per patient and 55.4 billion USD overall (5). According to a previous study, a patient with Sjögren's syndrome paid an average monthly cost of about 30 USD for DES treatments. Several attempts have been made to understand the pathophysiology of DES, which is multifactorial disorder involving multiple interactions, have not fully understood. Several studies have documented the mechanisms of DES. DES may result from reduced aqueous tear flow or increased tear evaporation (6). The disrupted ocular surface could bring about abnormal tear film homeostasis, causing DES (7). Regardless of the initiating etiology, inflammation is usually a key factor in the development of DES (8). Furthermore, chronic inflammation may subsequently result in a vicious cycle of external structure of orbital instability (9).

The metabolic syndrome (MetS) is also a well-known chronic and systemic inflammatory condition, even in a low-grade state (10). Recently, investigators have examined the relationship between MetS and other inflammatory diseases (chronic obstructive pulmonary disease, obstructive sleep apnea, psoriasis, and polycystic ovary syndrome) (11). However, very few reports have studied the relationship between DES and MetS.

Therefore, we investigated the association between DES and MetS and its components among adults aged 20 years or older in a population-based study from the Korea National Health and Nutrition Examination Survey (KNHANES) V. We focused on chronic inflammation as a potential risk factor that might be linked to both DES and MetS. Additionally, we examined which components of MetS could affect DES.

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MATERIALS AND METHODS

Subjects

The KNHANES V (2010-2012) study is a cross-sectional, population-based, and nationally representative survey of the health and nutritional status of the Korean population that is managed by the Korea Centers for Disease Control and Prevention (12). The participants were chosen using proportional systematic sampling with multistage stratification based on gender, geographical area, and age groups by household registries. Trained interviewers conducted surveys and administered questionnaires about demographic factors, socioeconomic status, dietary intakes, and medical history. Baseline examinations of KNHANES participants (n = 25,534) took place between 2010 and 2012. Information on DES was provided by 19,599 individuals aged 19 years and older who underwent comprehensive eye examination using slit-lamp differentiating other ocular surface disease. The discrepancy in number of participants exists due to the age restriction, no response, and missing data. A total of 15,294 patients were enrolled from 2010 to 2012, including 6,526 (42.67%) male patients and 8,768 (57.33%) female patients.

Dry eye syndrome

A panel of 17 dry-eye experts, who used the Delphi consensus method rather than relying primarily on current diagnostic tests, recommended basing diagnoses on patient signs and symptoms, including the presence or absence of lid margin disease and tear distribution anomalies, as well as on the severity of the disease as defined by multiple suggested criteria (13). However, no definite phased diagnostic tool has been established for DES and experts even say that there is no direct link between each diagnostic method. To investigate the prevalence of DES, participants were asked: "Until now, have you ever had dry eye symptoms before: for example, dryness of the eye or a sense of irritation?" with possible responses of "yes" or "no" (14,15).

Metabolic syndrome and its components

MetS was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III criteria (16) with Asia-Pacific abdominal obesity criterion (17). Metabolic syndrome was diagnosed by a co-occurrence of three or more of the following criteria: 1) waist circumference of $\geq$ 90 cm in males or $\geq$ 80 cm in females, 2) blood pressure $\geq$ 130/85 mmHg or antihypertensive drug treatment, 3) fasting glucose level of serum $\geq$ 100 mg/dL or use of medication for hyperglycemia, 4) blood triglyceride (TG) levels $\geq$ 150 mg/dL or specific treatment for elevated TG, and 5) high-density lipoprotein cholesterol (HDL) $<$ 40 mg/dL in males and $<$ 50 mg/dL in females or lipid-lowering medical treatment.

Other variants

Socioeconomic status was measured as a combination of education, household income, and residence. There were three levels of education categories, including below middle school, high school, or more than university graduation. The household income level was estimated using standardization methods according to classifications of sex and 5-year age groups compared to the standard Korean income level. Household income was divided into quartiles. The residence (urban-rural) was classified primarily by population size based on the Korean administrative units. The urban areas had a population $>$ 50,000 people.

A self-administered questionnaire was used to investigate health behavioral factors such as the history of smoking, alcohol consumption, and physical activity. Smoking history was categorized as never (fewer than 100 cigarettes in their lifetime), former (no longer smoke, but did in the past), or current smoker. For alcohol consumption, severe alcohol drinking consisted of consuming at least seven glasses of alcohol for men, or five glasses of alcohol for women, two or more times per week. The level of physical activity was characterized as no activity, light activity, or high activity. High level of physical activity entailed at least 20 minutes of breathless activity more than three times per week.

Statistical analysis

Data were analyzed using the SAS 9.3 (the SAS Institute Inc., Cary, NC, USA). First, the demographics of the study population and the prevalence of DES were calculated. Chi-square test and Student-t test were used to compare differences of baseline characteristics according to DES.

The odds ratio (OR) and 95% confidence intervals (95% CI) for the relationship between DES and MetS were estimated using a multivariate logistic regression model. In this study, two different logistic regression models to assess the relationship between DES and MetS were used: Model I adjusted for age and socioeconomic status (education, household income, and residence) and Model II adjusted for age, socioeconomic status, and health behavioral factors (alcohol drinking, smoking, and physical activity) after adjusting for the covariates from Model I.

Ethics statement

All participants provided written informed consent and all study protocols were carried out in accordance with the tenets of the Declaration of Helsinki. The study was approved by the institutional review board (IRB) of Korea Centers for Disease Control and Prevention (IRB: 2010-02CON-21-C, 2011-02CON-06-C, and 2012-01EXP-01-2C). The KNHANES data are open to the public (http://knhanes.cdc.go.kr).

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RESULTS

Demographics and prevalence of symptoms of dry eye syndrome

Among subjects answering the questionnaire, 2,704 (17.68%) participants positively responded to the question of having DES and 4,447 (29.08%) had MetS. Of 15,294 subjects, 744 were male (11.50% of the total number of males) and 1,960 were female (22.35% of the total number of females), indicating that the prevalence of DES were twice as high in females as in males.

Table 1 shows sex stratification in baseline characteristics of study subjects with and without DES. Men and women respond differently to DES according to age; the prevalence of DES in males was higher as they got older, but in females reached its peak between 41 and 60 years old. The prevalence of DES in females was higher with lower educational level and lower household income, in males was higher with current or former smoker status.

Relationship between dry eye syndrome and metabolic syndrome

Table 2 shows the prevalence of DES according to MetS of study subjects. Among those who reported having DES, 810 subjects (5.30%) presented with MetS; of these, 204 were male (27.42% of males with DES) and 606 were female (30.92% of females with DES). The prevalence of MetS among those with DES or not was not significant in either males ($P = 0.401$) or females ($P = 0.080$); however, there was a tendency towards a higher frequency of MetS among female sufferers of DES (Table 2).

Next, we examined which component of MetS might be more

Table 1. Basic characteristics of study subjects by gender

Parameters	Men n = 6,526 (42.7%)			Women n = 8,768 (57.4%)		
	DES	non-DES	*P* value	DES	non-DES	*P* value
Total	744 (11.40)	5,782 (88.60)		1,960 (22.35)	6,808 (77.65)	
Age, yr			0.001			0.145
19-40	194 (26.08)	1,707 (29.52)		601 (30.66)	2,108 (30.96)	
41-60	256 (34.41)	2,197 (38.00)		715 (36.48)	2,613 (38.38)	
≥ 61	294 (39.52)	1,878 (32.48)		644 (32.86)	2,087 (30.66)	
Education			0.115			0.983
Middle school	201 (29.29)	1,694 (29.30)		811 (41.38)	2,806 (41.22)	
High school	258 (34.68)	2,094 (36.22)		623 (31.79)	2,179 (32.01)	
University	285 (38.31)	1,994 (34.49)		526 (26.84)	1,823 (26.78)	
House hold income			0.200			0.853
1st Q	139 (18.68)	968 (16.74)		385 (19.64)	1,363 (20.02)	
2nd Q	201 (27.02)	1,494 (25.84)		496 (25.31)	1,760 (25.85)	
3rd Q	189 (25.40)	1,669 (28.87)		529 (26.99)	1,839 (27.01)	
4th Q	215 (28.90)	1,651 (28.55)		550 (28.06)	1,846 (27.12)	
Residence			0.088			0.101
Urban	602 (80.91)	4,520 (78.17)		1,587 (80.97)	5,397 (79.27)	
Rural	142 (19.09)	1,262 (21.83)		373 (19.03)	1,411 (20.73)	
Smoking			0.012			0.216
Never	132 (17.74)	1,075 (18.59)		1,769 (90.26)	6,059 (89.00)	
Former	341 (45.83)	2,329 (40.28)		97 (4.95)	357 (5.24)	
Current	271 (36.42)	2,378 (41.13)		94 (4.80)	392 (5.76)	
Alcohol drinking			0.186			0.948
Never	127 (17.07)	909 (15.72)		722 (36.84)	2,509 (36.85)	
Moderate	489 (65.73)	3,723 (64.39)		1,160 (59.18)	4,039 (59.33)	
Severe	128 (17.20)	1,150 (19.89)		78 (3.98)	260 (3.82)	
Level of exercise			0.966			0.356
None	454 (61.02)	3,501 (60.55)		1,485 (75.77)	5,246 (77.06)	
Moderate	247 (33.20)	1,947 (33.67)		392 (20.00)	1,313 (19.29)	
High	43 (5.78)	334 (5.78)		83 (4.23)	249 (3.66)	
Anthropometrics (M ± SD)						
BMI, kg/m²	23.82 ± 2.95	24.05 ± 3.15	0.067	23.31 ± 3.53	23.47 ± 3.54	0.082
WC, cm	84.10 ± 8.54	84.66 ± 8.91	0.090	78.32 ± 9.84	78.78 ± 9.95	0.069
SBP, mmHg	121.7 ± 15.08	122.4 ± 15.97	0.231	117.7 ± 18.19	118.0 ± 18.03	0.540
DBP, mmHg	78.22 ± 10.07	79.05 ± 10.66	0.045	73.78 ± 9.55	74.31 ± 9.93	0.038
FPG, mg/dL	99.72 ± 21.28	100.4 ± 23.51	0.449	96.40 ± 20.07	95.82 ± 20.74	0.264
TG, mg/dL	149.30 ± 107.5	154.90 ± 127.20	0.252	116.5 ± 72.72	115.0 ± 82.33	0.453
HDL, mg/dL	49.12 ± 11.63	49.20 ± 11.98	0.850	55.01 ± 12.86	54.98 ± 12.80	0.930

DES, dry eye syndrome; M, mean; SD, standard deviation; Q, quartile; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; HDL, high-density lipoprotein cholesterol.

Table 2. Gender-stratified prevalence of dry eye syndrome according to metabolic syndrome and its components

Metabolic syndrome related parameters	Men n = 6,526 (42.7%)			Women n = 8,768 (57.4%)		
	DES n = 744	non-DES n = 5,782	*P* value	DES n = 1,960	non-DES n = 6,808	*P* value
MetS	204 (27.42)	1,671 (28.90)	0.401	606 (30.92)	1,966 (28.88)	0.080
Central obesity	190 (25.54)	1,527 (26.41)	0.611	835 (42.60)	2,914 (42.80)	0.874
Hypertension	362 (48.66)	2,807 (48.55)	0.956	815 (36.48)	2,473 (36.32)	0.900
Hyperglycemia	277 (37.23)	2,037 (35.23)	0.283	509 (25.97)	1,628 (23.91)	0.062
Elevated TG	257 (34.54)	2,139 (36.99)	0.192	473 (24.13)	1,493 (21.93)	0.039
Decreased HDL	149 (20.03)	1,194 (20.65)	0.692	712 (36.33)	2,464 (36.19)	0.914

The numbers in parentheses refer to the percentage in each column.
DES, dry eye syndrome; Central obesity, waist circumference ≥ 90 in men or ≥ 80 cm in women; Hypertension, systolic- ≥ 130 or diastolic blood pressure ≥ 85 mmHg or taking medication for hypertension; Hyperglycemia, fasting plasma glucose ≥ 100 mg/dL or diagnosed diabetes history or taking medication for hyperglycemia; elevated TG, triglyceride ≥ 150 mg/dL or taking medication for hypertriglyceridemia; Decreased HDL, high-density lipoprotein cholesterol < 40 in men or < 50 mg/dL in women or taking medication for dyslipidemia.

Table 3. Odds ratio (OR) and 95% confidence intervals (95% CI) of dry eye syndrome using multiple logistic regression models by gender

Clinical manifestations	Model I	Model II
	OR (95% CI)	OR (95% CI)
Men		
MetS	0.88 (0.74-1.05)	0.89 (0.75-1.06)
Central obesity	0.93 (0.78-1.11)	0.94 (0.79-1.12)
Hypertension	0.92 (0.79-1.09)	0.93 (0.79-1.09)
Hyperglycemia	1.03 (0.88-1.22)	1.04 (0.88-1.23)
Elevated TG	0.90 (0.76-1.05)	0.91 (0.77-1.07)
Decreased HDL	0.93 (0.77-1.13)	0.93 (0.76-1.12)
Women		
MetS	1.10 (0.98-1.25)	1.11 (0.98-1.25)
Central obesity	0.98 (0.88-1.09)	0.98 (0.87-1.09)
Hypertension	0.97 (0.85-1.10)	0.97 (0.85-1.10)
Hyperglycemia	1.11 (0.98-1.25)	1.11 (0.98-1.25)
Elevated TG	**1.13 (1.00-1.28)**	**1.13 (1.01-1.29)**
Decreased HDL	1.00 (0.90-1.11)	1.01 (0.90-1.12)

Model I adjusted for age and sociodemographic risk factors (house hold income, education, and residence); Model II model I + adjusted for health behavioral risk factors (smoking, alcohol drinking, and level of exercise); Bolds are statistical significance.
DES, dry eye syndrome; Central obesity, waist circumference ≥ 90 in men or ≥ 80 cm in women; Hypertension, systolic- ≥ 130 or diastolic blood pressure ≥ 85 mmHg or taking medication for hypertension; Hyperglycemia, fasting plasma glucose ≥ 100 mg/dL or diagnosed diabetes history or taking medication for hyperglycemia; elevated TG, triglyceride ≥ 150 mg/dL or taking medication for hypertriglyceridemia; Decreased HDL, high-density lipoprotein cholesterol < 40 in men or < 50 mg/dL in women or taking medication for dyslipidemia.

likehood of DES symptoms (Table 3). In the final multivariate models, the adjusted OR (95% CI) of MetS related to the presence or absence of DES was 1.11 in females (95% CI 0.98-1.25). Using model II, which adjusted for age, socio-demographic factors, and health behavior factors (smoking, alcohol drinking, and level of exercise), we found that in females, the OR for serum TG ≥ 150 mg/dL or specific treatment for elevated TG was 1.13 (95% CI 1.01-1.29) and the OR for fasting serum glucose level ≥ 100 mg/dL or use of medication for hyperglycemia was 1.11 (95% CI 0.98-1.25). With respect to the diverse components of MetS, a significant association was only observed between the DES and hypertriglyceridemia in females in the final multivariate models (interaction $P < 0.05$). The proportion of subjects with elevated fasting serum glucose levels tended to be higher in those with DES in the multivariate models (interaction $P = 0.10$).

DISCUSSION

To the best of our knowledge, this is the first study to research the association between DES and metabolic outcomes in Asia. The prevalence of DES was higher for women (22.35% vs. 11.5% for men) and those of older age. Similarly, the Koumi study in Japan reported DES prevalences of 12.5% in men and 21.6% in women (18). Changes in sex hormones in women might alter meibomian gland secretion (19), particularly for women in their 40s and 50s who experience postmenopausal changes or are undergoing hormone replacement therapy (HRT) (15). Furthermore, tear evaporation might increase, and tear volume might decrease with age in both sexes (3).

In this study, female participants with elevated TG were more likely to have DES. This association was not attenuated even after adjustment for age, household income, education, residence, smoking, alcohol drinking, and level of exercise. The observed association between DES and MetS in this study was not significant. However, in females, we found that DES was closely linked to MetS (OR, 1.11; 95% CI, 0.98-1.25) and hyperglycemia (OR, 1.11; 95% CI, 0.98-1.25) in the full adjusted logistic regression model.

There is a possible explanation for the significant association between elevated TG and DES. People with DES have aqueous-deficient or evaporative tear deficient status in the ocular surface. Insufficient tear was related to excess of meibum lipid profiles including TG, and aggravated symptoms of DES. A previous study indicated that reducing TG might play a key role of managing symptoms of DES (20). In the present study, DES was related with elevated TG. Therefore, elevated TG might also be an important factor in the association between DES and MetS. For women specifically, TG levels can increase with HRT, meno-

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pause, and polycystic ovary syndrome (21-23).

Elevated TG, which is one of the components of MetS, might play an important role clinically. Elevated TG increases the risk for cardiovascular events, even in the absence of hypercholesterolemia (24). Elevated TG is a notable contributor to systemic inflammation and vice versa (25). Elevated TG caused the pro-inflammatory cytokine interleukin-6 (IL-6), which decreases lipoprotein lipase activity and increases macrophage uptake of lipids, leading to systemic inflammation and adverse metabolic outcomes (26). A study on the pathophysiology of DES reported that DES is caused by the inflammation of the ocular surface, which disrupts normal homeostasis at the ocular surface (7). Aqueous tear deficiency is directly linked to chronic inflammation (8) and cell hyperosmolarity, resulting in further tear film instability (9). On the other hand, tear evaporation is in correlation with atrophy of meibomian glands through eyelid inflammation triggered a pathogenic lipid profile and lipidic changes (27). Our statistically significant finding of an association between DES and elevated TG could be linked to the early phase of inflammation as mentioned above.

We focused on the association between DES and MetS because they are both consequences of chronic inflammatory conditions; however, we were unable to confirm a statistically significant association. One reason might be that the inflammation caused by IL-6 is a trigger for the earlier stages of metabolic outcome or low-grade inflammatory status, so there might be a time lag in the progression of the diseases. In addition, chronic inflammatory conditions worsen through multiple and complex cascades in the face of different spatio-temporal distribution. Another reason for this unanticipated finding is that both DES and MetS are considered syndromes and not diseases; a syndrome can refer to a medical condition with a greater likelihood of developing the disease. Also, certain risk factors for DES, such as dry air or wind and blinking less while reading or working at a computer that increase tear evaporation, are not necessarily associated with MetS. Although genetic factors are a potential confounder of MetS, we were unable to adjust for genetic factors in the analysis model; therefore, genetic factors might have affected MetS.

Our study has several significant advantages. To our knowledge, this is the first study to investigate associations between the DES and individual components of MetS. So far, previous research on the association between dyslipidemia and DES focused on hypercholesterolemia; the importance of the relationship between DES and elevated TG has been overlooked. Our study employed a large sample size that included nationwide sampling of the study participants, meaning that our results are representative of the general population.

One of the limitations of our study is the cross-sectional study design, which cannot illuminate the causal relationship between DES and MetS, including its individual components. We were able to describe the association between each component of MetS and DES. Well-designed longitudinal studies are required to define the relationship between DES and MetS and its components. Another limitation was that DES diagnosis was restricted to symptoms determined through administered questionnaires; however, asking about the symptoms associated with DES is one of the most reliable ways to diagnose or approach DES in the clinic. However, the diagnosis of DES remains challenging because there is no definite universal consensus in the guidelines for the most conventional tests such as Schirmer's test and break-up time, and the pathophysiology is not fully understood (28,29). In addition, potential and important confounders such as hyperthyroidism, changes in sex hormones with menopause, and lagophthalmos were not available in the dataset. Furthermore, it is difficult to determine the influence of medical co-morbidities such as autoimmune diseases (e.g., Sjögren's syndrome), which are rare, on DES. However, we adjusted for well-known confounders in the present study, including age, socioeconomic status (household income, education, and residence), and health behavior factors (alcohol drinking, smoking, and physical activity), and the reported association between DES and metabolic outcomes is important for future studies.

In conclusion, our results suggest that elevated TG levels, as a MetS component, might be linked with DES in female patients. The magnitude of this association persisted even after controlling for age, socioeconomic status, and health behavior. Further research in this area could investigate the longitudinal relationship and explore pathways between DES and MetS and its components.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Study concept and design of article: Park HW, Park JW. Data collection and analysis: Park HW. Writing draft: Park HW. Revision: Park HW, Park JW. Approval of final manuscript and agreement of submission: all authors.

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