Association between metabolic syndrome and blepharoptosis in the Korean adults: the Korea National Health and Nutrition Examination Survey 2010–2012

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Background: Metabolic syndrome (MetS) is a complex disorder featuring chronic inflammation characterized by abdominal obesity, hyperglycemia, hypertension, and dyslipidemia. Recent studies have documented that MetS is associated with various diseases, including ocular disorders.

Objective: This cross-sectional study is based on data from the fifth Korea National Health and Nutrition Examination Surveys. We examined the association between MetS and its components with blepharoptosis in Korean adults aged 19 years or older.

Methods: MetS was defined using the criteria proposed by the American Heart Association and the National Heart, Lung, and Blood Institute together with the International Diabetes Federation in 2009. Blepharoptosis was defined as the marginal reflex distance 1 of <2 mm.

Results: The prevalence of blepharoptosis was 11.5%. As the number of MetS components increased, the prevalence of blepharoptosis also increased. After being controlled for various confounders, MetS was significantly associated with blepharoptosis (adjusted odds ratio [OR], 1.316; 95% confidence interval [CI], 1.133–1.529). In addition, blepharoptosis was associated with increased waist circumference, hypertension, and elevated triglyceride (adjusted OR, 95% CI: 1.281 [1.047–1.567], 1.165 [1.014–1.339], and 1.174 [1.013–1.36], respectively).

Conclusion: Consequently, MetS and its components were associated with blepharoptosis in Korean adults. Screening for blepharoptosis is warranted for patients with MetS.

Keywords: blepharoptosis; metabolic syndrome

Introduction

Blepharoptosis is defined as an abnormally low-lying upper eyelid margin in primary gaze [1]. Etiologically, blepharoptosis may be due to myogenic, neurogenic, aponeurotic, mechanical, or traumatic causes [1–3]. It is a frequent condition among oculoplastic patients, and its clinical picture varies from a mi-

nor cosmetic discomfort to severe visual dysfunction, depending on the pathogenesis and the degree of blepharoptosis [4]. Blepharoptosis is usually an isolated disease, which changes the patient's appearance, but may be associated with various conditions, such as immunological, degenerative, or congenital disorders, tumor, and vascular disease, and may be one of the early presenting symptoms of an underlying disease [1]. Blepharop-

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tosis may be caused by weakness of the levator palpebrae superioris or may damage nerves that control the muscle, resulting from diabetes. Diabetes and insulin-resistant state, such as impaired glucose tolerance, are also known to be associated with blepharoptosis [5,6]. The treatment of blepharoptosis depends on the underlying etiology. Successful treatment of underlying medical problems may sometimes correct blepharoptosis. Thus, early diagnosis and treatment are important prognostic factors in its management.

Metabolic syndrome (MetS) is a complex disorder featuring chronic inflammation characterized by abdominal obesity, hyperglycemia, hypertension, and dyslipidemia [7]. Its definition varies by the organization and expert group. MetS was defined based on the Joint Interim Statement proposed in 2009 from the International Diabetes Federation (IDF) and American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) [8]. A decade of small epidemiology studies provided evidence that early hyperglycemia or MetS is sufficient to damage the distal peripheral nerves [9-11]. Obesity was found to be one of the possible factors that cause blepharoptosis [12]. Furthermore, some conditions involve metabolic derangement, such as dyslipidemia, obesity, and diabetes, which have been shown to be possible risk factors for blepharoptosis [1,6,13,14].

To the best of our knowledge, no study has assessed the association between MetS and blepharoptosis in the population, which is representative of the entire population, including young and elderly people. Therefore, in this study, we investigated the relationship between MetS and blepharoptosis in the Korea National Health and Nutrition Examination Survey (KNHANES) conducted in 2010 and 2012.

Materials and methods

Study population

This study was based on data from the 2010 to 2012 KNHANES. The KNHANES, conducted by the Korea Centers for Disease Control and Prevention, is a nationwide representative, cross-sectional, population-based survey used to assess the health and nutritional status of Koreans. These surveys have been conducted periodically since 1998 by the Korean Ministry of Health and Welfare by using a rolling sampling design, involving a complex, stratified, multistage, probability cluster survey of a representative sample of the non-institutionalized civilian population to assess the health and nutritional status of the Korean population [15,16]. The survey consists of the health interview, health examination, and nutrition surveys. This

survey was reviewed and approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention, and all participants provided written informed consent.

In the present analysis, we limited the study population to adults aged 19 years or older who participated in all three parts of the survey in addition to ophthalmologic interviews and examinations. Our final study population for the analysis included 16,595 participants.

Assessment of blepharoptosis

Blepharoptosis was defined when the marginal reflex distance 1 (MRD1) was <2 mm [13,14,17]. MRD1 was measured as follows: After positioning at the eye level of the physician, each participant was instructed to look straight ahead and relax while focusing on a distant target. Using a penlight directed into the eye, the distance from the corneal light reflex to the upper eyelid margin was measured in millimeters [13]. The five stages of upper eyelid level (blepharoptosis severity) were defined as follows: stage 1=MRD1 ≥ 4 mm; stage 2=MRD1 3–3.9 mm; stage 3=MRD1 2–2.9 mm; stage 4=MRD1 1–1.9 mm; and stage 5=MRD1 <1 mm [12]. Subjects of stages 4 and 5 were considered to have blepharoptosis. All MRD1s were measured by specially trained ophthalmic resident physicians with >3 years of experience.

Definition of MetS

MetS was defined based on the Joint Interim Statement proposed in 2009 from the IDF and AHA/NHLBI [8]. Subjects were classified as having MetS if any three of the following five characteristics were present: (1) abdominal obesity (waist circumference [WC] ≥ 90 cm in men or ≥ 80 cm in women, based on the IDF criteria), (2) fasting triglyceride (TG) level ≥ 150 mg/dl or cholesterol-lowering medication use, (3) HDL cholesterol level <40 mg/dl in men or <50 mg/dl in women or cholesterol-lowering medication use, (4) systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or current use of medication for hypertension, and (5) fasting glucose ≥ 100 mg/dl or use of oral medication or insulin.

Measurement

The health interview survey was performed by trained interviewers. The demographic and socioeconomic characteristics, including education, income, smoking, drinking, and exercise, were obtained from the participants.

Anthropometric measurements of the participants were performed by specially trained examiners. WC was measured to

the nearest 0.1 cm in a horizontal plane at the level of the mid-point between the iliac crest and the costal margin at the end of a normal expiration. The body mass index (BMI) was calculated as the individual's weight in kilograms divided by the square of the individual's height in meters. Blood pressure was measured three times on the right arm while the individual was in a seated position after at least 5 minutes of rest by using a mercury sphygmomanometer (Baumanometer; Baum, Copiague, NY, USA). The final blood pressure value was obtained by averaging the values of the second and third blood pressure measurements.

Blood samples were obtained after a minimum fasting time of 8 hours. Serum glucose, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and TG levels were measured using the Hitachi automatic analyzer 7600 (Hitachi, Tokyo, Japan).

Statistical analysis

All data are presented as the mean±standard error (SE) for continuous variables or as proportions (with SEs) for categorical variables. Statistical analyses were conducted using the SAS (version 9.2; SAS Institute, Cary, NC, USA) survey procedure; this considered the complex sampling design (with sampling weights) of KNHANES and yielded nationally representative estimates of prevalence. We used two independent t-tests to compare continuous variables and the Rao-Scott chi-squared test to compare categorical variables. Multiple logistic regression analyses were performed to estimate the magnitude of the association between blepharoptosis and Mets. We used two statistical models, depending on the characteristics of the variables evaluated. The ORs and 95% CIs were estimated after adjustment for potential confounders. Model 1 was adjusted for age, sex, and BMI. Model 2 was further adjusted for smoking, drinking, exercise, income, and education. $p < 0.05$ was consid-

Table 1. Characteristics of participants with or without blepharoptosis

Characteristic	Blepharoptosis		p-value
	No (n=14,684)	Yes (n=1,911)	
Age (yr)	43.7±0.2	59.2±0.7	<0.0001
BMI (kg/m ²)	23.6±0	24.4±0.1	<0.0001
WC (cm)	80.7±0.1	84.6±0.3	<0.0001
SBP (mmHg)	117.3±0.2	125.6±0.6	<0.0001
DBP (mmHg)	76.4±0.1	77.1±0.3	0.0808
Fasting glucose (mg/dl)	95.8±0.2	104.3±0.7	<0.0001
HDL-C (mg/dl)	52.9±0.2	49.4±0.4	<0.0001
LDL-C (mg/dl)	109.9±0.4	112.1±1.0	0.038
TG (mg/dl) ^{a)}	106.7 (105.3–108.1)	128.5 (124.1–133.2)	<0.0001
TC (mg/dl)	187.9±0.4	190.9±1.0	0.0088

Values are presented as mean±standard error for continuous variables.

Two independent t tests for quantitative data was performed.

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol.

^{a)}Geometric mean (95% Confidence interval).

Table 2. Prevalence of metabolic syndrome (Mets) components according to upper eyelid level stage

MetS component	Upper eyelid level stage ^{a)}					p-value
	≥4 mm	3–3.9 mm	2–2.9 mm	1–1.9 mm	<1 mm	
WC (≥90 or ≥80 cm)	26.5 (0.8)	32.3 (1.0)	38.5 (1.4)	46.5 (1.8)	53.5 (3.3)	<0.0001
Hypertension	26.8 (0.8)	37.6 (1.0)	46.5 (1.5)	57.0 (1.9)	67.0 (3.0)	<0.0001
Hyperglycemia	19.0 (0.7)	26.4 (0.9)	31.8 (1.2)	41.6 (1.9)	43.9 (3.0)	<0.0001
Hypertriglyceridemia	26.3 (0.8)	32.0 (0.8)	36.0 (1.1)	44.1 (2.0)	45.7 (3.1)	<0.0001
Low HDL-C	25.2 (0.7)	30.1 (0.8)	34.1 (1.0)	40.4 (1.8)	45.0 (2.7)	<0.0001
MetS	18.1 (0.6)	26.5 (0.8)	33.4 (1.2)	45.6 (1.7)	54.0 (3.1)	<0.0001

Values are presented as weighted % (standard error).

Rao-Scott chi-square test was performed.

MetS, metabolic syndrome; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol.

^{a)}By marginal reflex distance 1.

ered statistically significant.

The study was approved by the Institutional Review Board at The Catholic University of Korea and adhered to the tenets of the Declaration of Helsinki.

Results

Table 1 shows the characteristics of the participants, including MetS components by blepharoptosis status. Compared with subjects without blepharoptosis, those with blepharoptosis had higher mean age, BMI, WC, systolic blood pressure, fasting glucose, total cholesterol (TC), LDL cholesterol, and TG; meanwhile, they had lower HDL cholesterol.

Table 2 shows the prevalence of MetS components in accordance with upper eyelid level stage. As the upper eyelid level stage increased, the prevalence of MetS and its components increased.

Fig. 1 shows the prevalence of blepharoptosis based on the number of MetS components. As the number of MetS components increased, the prevalence of blepharoptosis also in-

Fig. 1. Prevalence of blepharoptosis based on the number of metabolic syndrome components ($p < 0.0001$ by chi-square test).

creased.

The adjusted ORs (aOR) and their 95% CIs of MetS components for blepharoptosis are shown in Table 3. We used three models with progressive degrees of adjustment. Model 1 was not adjusted. Model 2 was adjusted for age, sex, and BMI. Model 3 was further adjusted for smoking, drinking, exercise, income, and education. After being controlled for confounders, MetS was significantly associated with blepharoptosis (aOR, 1.316; 95% CI, 1.133–1.529). Increased WC, hypertension, and elevated TGs were also significantly associated with blepharoptosis (aOR, 95% CI; 1.281 (1.047–1.567), 1.165 (1.014–1.339), and 1.174 (1.013–1.36), respectively).

Discussion

This study investigated whether MetS and its components are associated with blepharoptosis in Korean adults. We found that MetS and its components showed a strong association with blepharoptosis in the Korean population. The positive association of MetS with blepharoptosis remained significant even after adjusting for confounding factors (Table 3). Interestingly, as the number of MetS components increased, the prevalence of blepharoptosis also increased (Fig. 1; $p < 0.0001$). As the upper eyelid level stage increased, the prevalence of MetS and its components increased (Table 2).

Both MetS and blepharoptosis are important health issues. Diabetes and insulin-resistant state, such as impaired glucose tolerance, are also known to be associated with blepharoptosis [5]. A recent study showed that diabetes is an independent risk factor for blepharoptosis in the general Korean population [6]. However, to the best of our knowledge, no study has assessed the association of MetS with blepharoptosis in the population, which is representative of the entire population, including young and elderly people. Interestingly, increased WC, hypertension, and elevated TG, as well as MetS, also increased the

Table 3. Odds ratios (95% confidence intervals) for blepharoptosis according to components of MetS

MetS components	Model 1 ^{a)}	Model 2 ^{b)}	Model 3 ^{c)}
WC (≥ 90 or ≥ 80 cm)	2.01 (1.779, 2.271)	1.299 (1.07, 1.578)	1.281 (1.047, 1.567)
Hypertension	2.81 (2.46, 3.21)	1.146 (1, 1.313)	1.165 (1.014, 1.339)
Hyperglycemia	2.278 (2.005, 2.59)	1.14 (0.992, 1.309)	1.144 (0.992, 1.319)
Hypertriglyceridemia	1.838 (1.597, 2.116)	1.198 (1.034, 1.389)	1.174 (1.013, 1.36)
Low HDL-C	1.708 (1.498, 1.947)	1.117 (0.958, 1.303)	1.078 (0.927, 1.253)
MetS	2.783 (2.476, 3.128)	1.343 (1.164, 1.55)	1.316 (1.133, 1.529)

Multiple logistic regression analysis was performed.

MetS, metabolic syndrome; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol.

^{a)}Unadjusted, ^{b)}adjusted for age, sex, and body mass index (BMI), ^{c)}adjusted for age, sex, BMI, smoking, drinking, exercise, income, and education.

prevalence of blepharoptosis.

Blepharoptosis is defined as abnormally low-lying upper eyelid margin in primary gaze, resulting in narrowing of the palpebral opening and fissure and covering part of the eye. The normal adult upper lid margin is 0.5–2 mm below the superior corneal limbus and is highest just nasal to the pupil (upper lid height) [18,19]. The deficient function may be due to weakness of the muscle responsible for lid retraction (either the levator palpebrae superioris muscle and its aponeurosis or Muller's muscle), or damage to the nerves that control these muscles [1]. The prevalence of blepharoptosis in Korean adults older than 19 years was 11.5%, which was similar to the result of the previous study at $11.0 \pm 0.8\%$ [13].

The prevalence of the MetS, a cluster of cardiovascular risk factors associated with obesity and insulin resistance, is dramatically increasing in Western and developing countries. This disorder consists of metabolic conditions, such as hypertriglyceridemia, hyper-LDL cholesterol, hypo-HDL cholesterol, insulin resistance, abnormal glucose tolerance, and hypertension, that in combination with genetic susceptibility and abdominal obesity are risk factors for type 2 diabetes, vascular inflammation, atherosclerosis, and renal, liver and heart diseases [20]. One of the defects in MetS and its associated diseases is excess of reactive oxygen species. Reactive oxygen species generated by the mitochondria, or from other sites within or outside the cell, cause damage to mitochondrial components and initiate degradative processes. Such toxic reactions contribute significantly to the aging process [21]. In this study, the patients with MetS were more likely to be older compared with the participants who lacked MetS (Table 1, $p < 0.0001$).

We have established some hypotheses regarding the association of MetS and its components with blepharoptosis. First, increased reactive oxygen species resulting from MetS may cause damage to the nerve that control the levator palpebrae superioris muscle. Second, it is highly possible that blepharoptosis patients who have MetS are obese and have diffuse fatty infiltration in the levator palpebrae superioris muscle and its aponeurosis.

In conclusion, in this nationally representative population-based cross-sectional study, we found that MetS was positively associated with blepharoptosis in Korean adults. Especially, the more patients had the number of MetS components, the more severe blepharoptosis digress was. Therefore, screening for blepharoptosis is warranted for patients with MetS.

Conflicts of interest

The authors have nothing to disclose.

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