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Effects of Obstructive Sleep Apnea-Hypopnea Syndrome on Serum Carcinoembryonic Antigen Levels in Patients with Type 2 Diabetes Mellitus

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Background: Type 2 diabetes mellitus (T2DM) is related to the serum carcinoembryonic antigen (CEA) level, which is used as a marker of colorectal cancer. Obstructive sleep apnea-hypopnea syndrome (OSAS) has been recently reported to have cancer-promoting effects. The aim of our study was to observe the effect of OSAS on serum levels of CEA in patients with T2DM.

Material/Methods: We enrolled 401 T2DM patients in this study. There were 244 patients with OSAS and 157 patients without OSAS.

Results: The CEA level in T2DM patients with OSAS was higher than that in those without OSAS ($p<0.05$). The participants with AHI scores ≥30 had higher CEA levels than those with 5≤ AHI scores <30 ($p<0.05$). The AHI score and ODI score were independently associated with increased risk of high CEA level in T2DM patients (odds ratio [OR]=1.052, 95% confidence interval [CI]: 1.011~1.095) and (OR=1.214, 95% CI: 1.070~1.377). Moreover, among male T2DM patients, the AHI score and ODI score had a linear correlation with the CEA level; this association was also observed in T2DM patients who smoked, had an HbA1c level ≥7%, or had a BMI ≥28 kg/m^2 (all $p<0.05$).

Conclusions: The AHI score and ODI score were positively associated with the CEA level in T2DM patients. The relationship was stronger in male T2DM patients and in those who smoked, were obese, or had poor glycemic control. The mechanism may be related to metabolic disorders, and the potential increased risk of colorectal cancer should be investigated in a prospective study.

MeSH Keywords: Carcinoembryonic Antigen • Diabetes Mellitus • Sleep Apnea, Obstructive

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Background

Obstructive sleep apnea-hypopnea syndrome (OSAS) is a clinical syndrome that involves repeated episodes of obstruction of the upper airway, which are accompanied by apnea/hypopnea and sleep interruption. OSAS is a public health concern in modern society. The incidence of OSAS in males is higher than in females. The ratio of males to females with OSAS is reported to be between 3: 1 and 5: 1. However, other studies have reported a ratio as high as 10: 1 [1, 2].

Studies have shown that the incidence of OSAS in diabetic patients is up to 23% [3]. Eihorn et al. [4] found that approximately 48% of a diabetic population had apnea-hypopnea index >10/h. Recent evidence has suggested a link between type 2 diabetes mellitus (T2DM) and OSAS, due to factors including obesity, inflammation, and oxidative stress.

Carcinoembryonic antigen (CEA) is a highly glycosylated cell surface glycoprotein that is used as a tumor marker. The CEA level is abnormally elevated in patients with colorectal cancer. Recently, CEA was reported to be significantly elevated in patients with metabolic diseases such as T2DM [5]. Moreover, Nieto, whose study included 1522 investigators and was based on the community Wisconsin Sleep Cohort Study found there was a dose-response relationship between OSAS and cancer mortality, which was more significant in severely hypoxic patients [6]. The pro-oncogenic properties of the hypoxia caused by OSAS have been demonstrated by *in vitro* studies [7]. Chen Wen-Jone found increased levels of CEA in hypoxic-treated animal models [8]. Kokkonen et al. found that hypoxia-inducible factor 1α (HIF-1α), which was recognized as a hypoxia marker, can enhance CEA promoter activity and up-regulate CEA expression in an anoxic environment [9]. However, to the best of our knowledge, this is the first report on the association between OSAS and the CEA level in patients with T2DM. This study focused on the link between OSAS and serum CEA levels in T2DM patients.

Material and Methods

Subjects

Our study enrolled a total of 401 participants age 21–91 years diagnosed with T2DM, who were hospitalized at the Department of Endocrinology, Changzhou First People's Hospital from 2011 to 2016, including 244 patients with OSAS and 157 patients without OSAS. The exclusion criteria were [10]: diabetic ketoacidosis, diabetic nonketotic hyperosmolar coma, acute cardiovascular diseases, acute cerebrovascular diseases, acute infection, malignant disease, chronic liver disease, and subjects taking psychotropic drugs or who had surgery, trauma, or burns in the past 6 months. Approval from the local ethics committee of the Third Affiliated Hospital of Suzhou University was obtained.

Diagnostic criteria for T2DM and OSAS

All T2DM patients met the 1999 WHO diagnostic criteria for diabetes. The diagnostic criteria for OSAS were the guidelines for the diagnosis and treatment of OSAS developed by the Chinese Medical Association Respiratory Branch Sleep Disorders Group [11].

Clinical and laboratory evaluation

The body mass index (BMI) was calculated by the formula body weight (kg)/height $(m)^2$. Data on height, weight, blood pressure, cigarette-smoking habits, and alcohol consumption were collected for all patients.

We measured the serum levels of fasting blood glucose (FPG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), creatinine (Cr), C-reactive protein (CRP), glycosylated hemoglobin (HbA1c), fasting c-peptide (FCP), and carcinoembryonic antigen (CEA). The normal range of CEA was 0–5 ng/mL.

Overnight polysomnography (PSG) monitoring was performed using a Somnostar 4000 model (Sensor Medics, Inc., USA) and a Sandman polysomnography system. The apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) were recorded with the PSG monitoring indicator.

Statistical methods

SPSS version 22 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis. All measurement data were represented by the average ± standard deviation or the median (interquartile range). Normally distributed data were compared with *t* tests; otherwise, the data were analyzed by the Mann-Whitney U test. The proportions were expressed as% (n) and compared by chi-square tests. Correlations between different variables were analyzed by the Pearson or Spearman tests. Binary logistic regression and multiple linear regression analyses were performed to further determine the degree of correlation between OSAS and CEA level in T2DM patients. $P<0.05$ was considered statistically significant. The graphs were constructed using GraphPad Prism 6.0.

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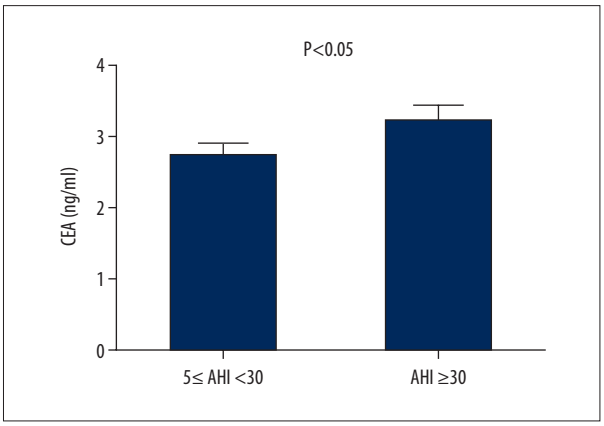
Table 1. Comparison of the clinical characteristics of the T2DM patients with and without OSAS.

Variables	T2DM with OSAS (n=244)		T2DM without OSAS (n=157)		*p* Value
Sex (Male/Female)	203/41		110/47		0.002
Age (years)	54.00	(46.00–63.00)	52.00	(42.50–61.50)	0.158
Duration of T2DM (months)	36.00	(2.00–108.00)	36.00	(6.00–84.00)	0.900
Current smoker (%)	93	(38.11)	46	(29.30)	0.070
Current alcohol consumption (%)	82	(33.61)	36	(22.93)	0.022
CEA (ng/mL)	2.54	(1.83–3.22)	2.24	(1.71–3.05)	0.035
SBP (mmHg)	138.00	(127.00–153.00)	134.50	(127.00–147.00)	0.110
DBP (mmHg)	85.00	(78.00–92.00)	82.00	(76.00–90.00)	0.015
BMI (kg/m2)	28.09	(25.87–30.08)	25.20	(23.24–26.97)	0.000
CRP (mg/L)	4.05	(3.50–5.50)	3.80	(3.50–4.20)	0.012
FBG (mmol/L)	8.69	(7.26–11.03)	8.70	(7.00–10.40)	0.429
FCP (ng/mL)	2.22	(1.73–3.04)	1.88	(1.49–2.63)	0.002
HbA1c (%)	8.70	(7.50–10.30)	9.10	(7.55–10.50)	0.379
TG (mmol/L)	3.07	(1.98–4.88)	3.04	(1.84–4.59)	0.575
TC (mmol/L)	4.56	(3.73–5.17)	4.60	(3.97–5.29)	0.242
LDL-C (mmol/L)	2.29±0.04		2.26±0.06		0.677
HDL-C (mmol/L)	0.90	(0.80–1.05)	0.97	(0.84–1.13)	0.002
Cr (μmol/L)	73.00	(63.00–86.90)	71.65	(62.18–84.85)	0.341
ALT (u/L)	27.00	(20.00–46.00)	25.00	(18.00–32.00)	0.019

Data were expressed as % (n), mean ± standard deviation and median (interquartile range). SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; FBG – fasting blood glucose; TC – total cholesterol; TG – triglyceride; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; ALT – alanine aminotransferase; Cr – creatinine; CRP – C-reactive protein; HbA1c – glycosylated hemoglobin; FCP – fasting c-peptide; CEA – carcinoembryonic antigen.



Results

Clinical characteristics of the T2DM subjects with and without OSAS

The baseline characteristics of the study population are shown in Table 1. There were 244 T2DM patients with OSAS and 157 T2DM patients without OSAS. Compared with those without OSAS, there were more male patients with OSAS. Furthermore,

Figure 1. Comparison of CEA levels between groups with various AHI scores. CEA – carcinoembryonic antigen; BMI – body mass index; HbA1c – glycosylated hemoglobin; LDL-C – low-density lipoprotein cholesterol.

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Table 2. Correlation analysis between serum CEA levels and other selected variables.

Variables	Pearson's coefficient	*p* Value	Variables	Pearson's coefficient	*p* Value
Duration of T2DM	–0.034	0.548	FBG	0.133	0.015
Age	0.047	0.383	HbA1c	0.138	0.011
Sex	0.200	0.000	FCP	0.050	0.402
Current smoking	0.156	0.004	ALT	0.005	0.928
Current alcohol consumption	0.032	0.564	Cr	0.054	0.385
AHI	0.242	0.000	CRP	–0.052	0.447
ODI	0.155	0.013	TG	0.073	0.183
BMI	0.065	0.230	TC	–0.041	0.458
SBP	0.018	0.736	HDL-C	–0.079	0.155
DBP	0.048	0.377	LDL-C	0.000	0.996

SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; FBG – fasting blood glucose; TC – total cholesterol; TG – triglyceride; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; ALT – alanine aminotransferase; AHI – apnea-hypopnea index; ODI – oxygen desaturation index; Cr – creatinine; CRP – C-reactive protein; HbA1c – glycosylated hemoglobin; FCP – fasting c-peptide; CEA – carcinoembryonic antigen.

Table 3. Logistic regression analysis of the median CEA in T2DM patients.

		OR	(95% CI)	*P* value
Model 1	AHI	1.021	(1.008–1.034)	0.002
	ODI	1.017	(1.004–1.030)	0.012
Model 2	AHI	1.02	(1.005–1.035)	0.008
	ODI	1.017	(1.002–1.034)	0.031
Model 3	AHI	1.052	(1.011–1.095)	0.013
	ODI	1.214	(1.070–1.377)	0.003

Model 1 was not adjusted. Model 2 was adjusted for age, sex, T2DM duration, current smoking, and current alcohol consumption. Model 3 was adjusted for age, sex, T2DM duration, current smoking, current alcohol consumption, systolic blood pressure, diastolic blood pressure, body mass index, and the levels of C-reactive protein, hemoglobin A1c, total cholesterol, triacylglycerol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, fasting c-peptide, alanine aminotransferase, and creatinine. OR – odds ratio; CI – confidence interval; AHI – apnea-hypopnea index; ODI – oxygen desaturation index; CEA – carcinoembryonic antigen.

compared with those without OSAS, the patients with OSAS had higher levels of alcohol consumption, CEA, DBP, BMI, ALT, CRP, and FCP and lower levels of HDL-C ($p<0.05$). We further divided the patients into 2 groups according to AHI score, as follows: mild-to-moderate OSAS (5≤ AHI <30) and severe OSAS (AHI ≥30). As shown in Figure 1, the serum CEA level in the severe OSAS group was significantly higher than that in the mild-to-moderate OSAS group ($p<0.05$).

Relationship between OSAS and the CEA level

We analyzed the correlations between the CEA level and other variables (Table 2). The results indicated that the level of serum CEA was related to male sex and smoking. Simultaneously, the level of CEA was positively correlated with AHI, ODI, FBG, and HbA1c ($p<0.05$).

The results of the logistic regression analysis in T2DM patients are listed in Table 3. When confounding factors were not

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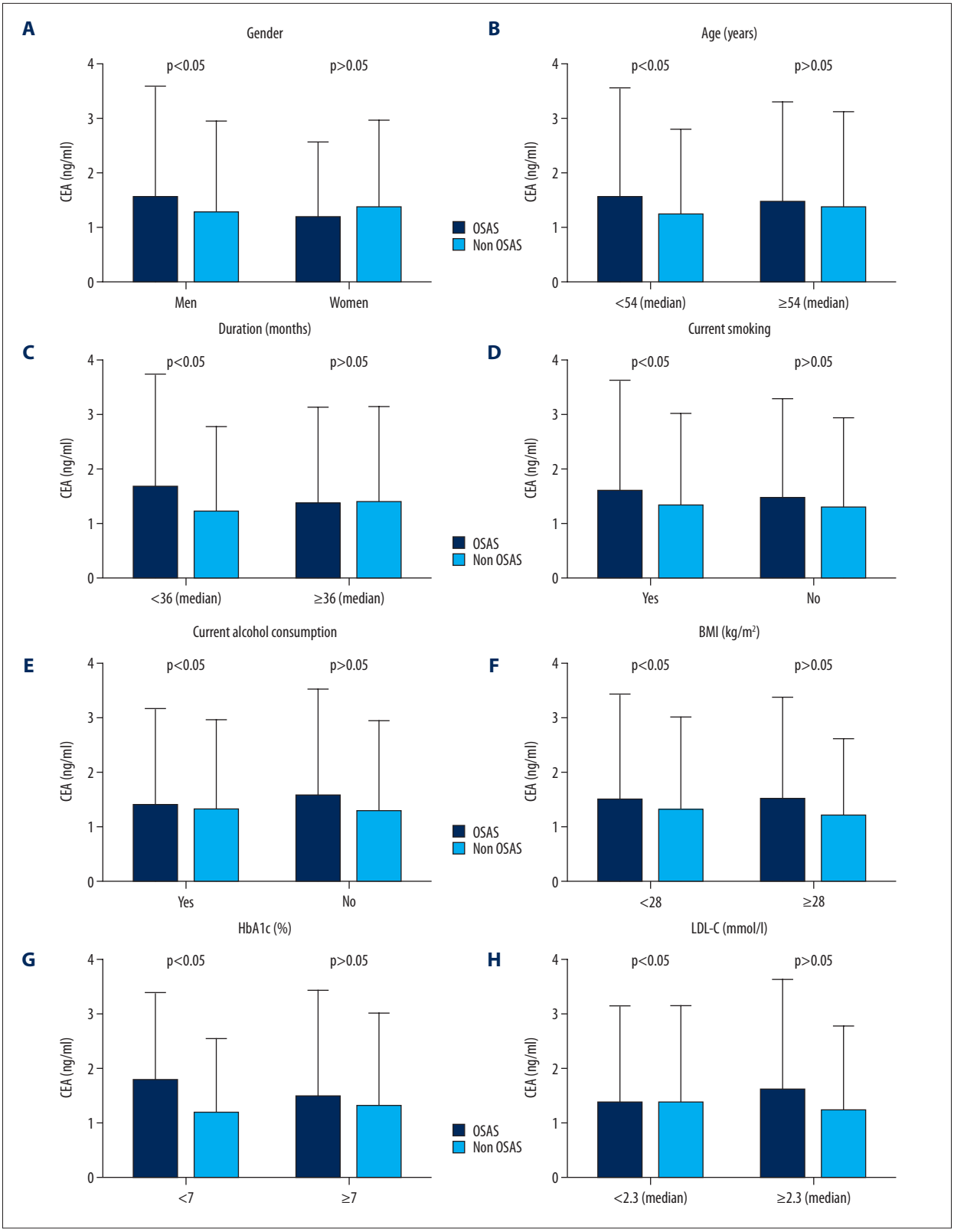

Figure 2. (**A–H**) Comparison of serum CEA levels between T2DM patients with and without OSAS in different subgroups. CEA – carcinoembryonic antigen; AHI – apnea-hypopnea index; ODI – oxygen desaturation index; BMI – body mass index; HbA1c – glycosylated hemoglobin.

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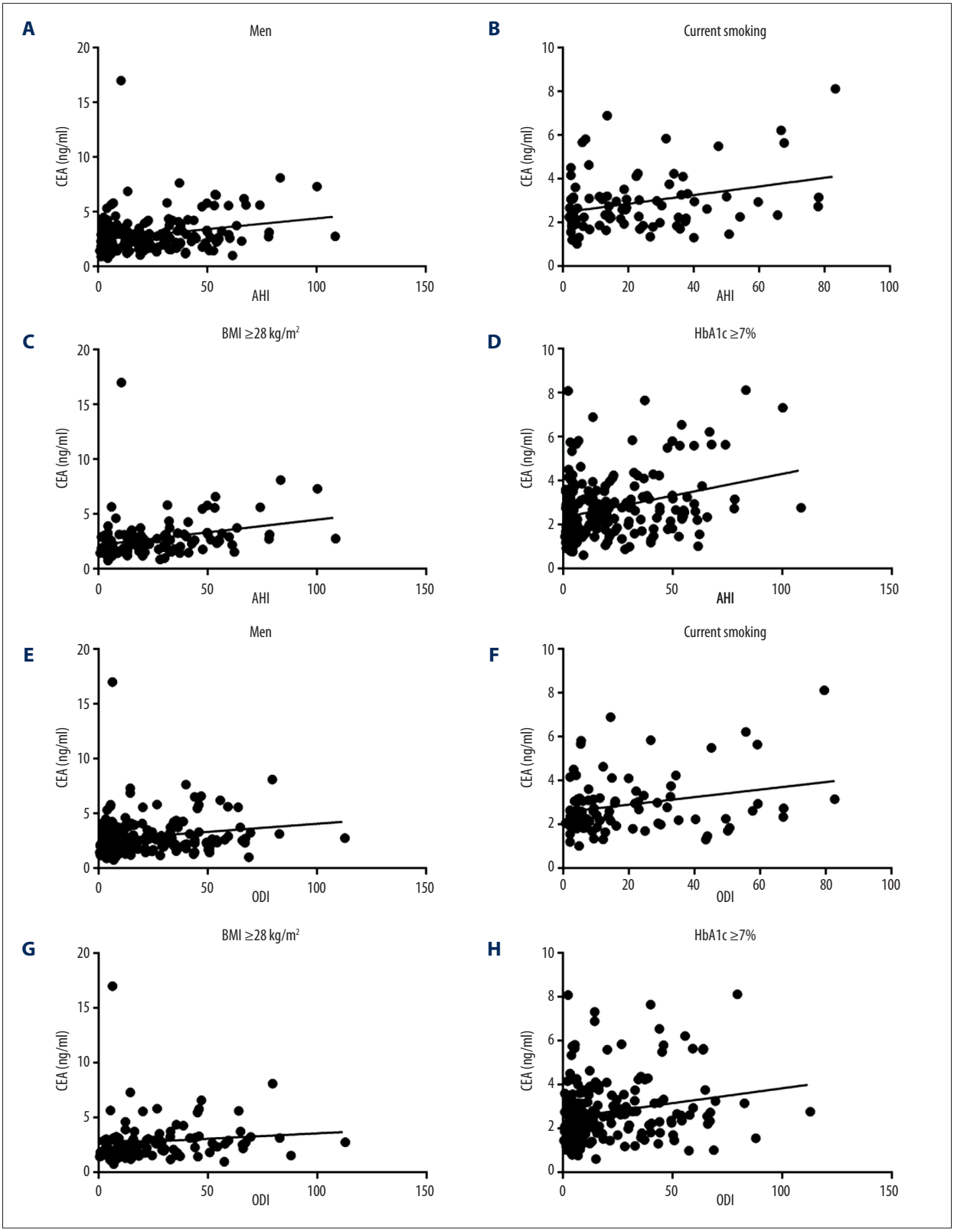

Figure 3. (**A–H**) Multiple linear regression analysis of serum CEA levels in different subgroups.

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adjusted in the model, the AHI score was an independent risk factor for increased CEA levels (OR=1.021, 95% CI: 1.008–1.034, p=0.002). After adjusting for age, gender, duration of T2DM, current smoking, current alcohol consumption, SBP, DBP, BMI, CRP, HbA1c, TC, TG, LDL-C, HDL-C, FBG, FCP, ALT, and Cr, the AHI score remained associated with the CEA level (OR=1.052, 95% CI: 1.011~1.095, p=0.013). Similar results were also observed in the relationship between ODI and CEA after adjusting for other variables (OR=1.214, 95% CI: 1.070~1.377, p=0.003).

Levels of CEA in different subgroups

We further divided the participants into different subgroups according to the clinical characteristics that were investigated, as shown in Figure 2. The results indicated that in men, patients age <54 years, patients with T2DM duration <36 months, current smokers, patients who do not consume alcohol, patients with BMIs ≥28 kg/m^2, patients with HbA1c levels ≥7%, and patients with LDL-C levels ≥2.3 mmol/l, those with OSAS had higher levels of CEA than those without OSAS (p<0.05).

Furthermore, we analyzed the interactions between the confounders such as age, sex, lifestyle factors, T2DM duration, obesity, the status of glucose control, and other metabolism-related factors and levels of AHI to the risk of increased CEA, the negative results were found(p>0.05). The results of the multiple linear regression analysis are shown in the scatter plots in Figure 3. The results revealed the AHI was positively linearly correlated with the level of CEA in men, smokers, patients with BMIs ≥28 kg/m^2 and patients with HbA1c levels ≥7%, with coefficients of 0.027, 0.049, 0.025 and 0.022, respectively (p<0.05). Similar results were also observed in the relationship between ODI and CEA, with coefficients of 0.022, 0.043, 0.024, and 0.022, respectively (p<0.05)

Discussion

The CEA level is commonly used as an early tumor screening index. Recent studies have found that the level of CEA is elevated in other diseases, such as liver disease, kidney dysfunction, hypothyroidism, and acute/chronic infectious diseases. Kyu-Nam Kim [12] reported that increased CEA levels are found in metabolic diseases such as diabetes. Simultaneously, a relationship between OSAS and cancer has been reported in recent years [10,13]. However, there have been few studies about CEA levels in patients with diabetes with OSAS.

The results of this study demonstrate that patients with T2DM and OSAS had significantly higher CEA levels than T2DM patients without OSAS, and those higher levels were associated with sex, obesity, smoking, and poor glycemic control.

Therefore, we believed that there was a relationship between OSAS and the serum CEA levels in T2DM patients, and hypoxemia might be the possible mechanism. Kent reported [14] that hypoxemia caused by OSAS can promote insulin resistance and obesity in T2DM patients by aggravating the inflammatory response, activating oxidative stress, and aggravating glucose metabolism disorders, and all of these may play an important role in the link between OSAS and serum CEA levels in T2DM patients. Insulin produces mitogenic effects that affect the growth of epithelial cells via insulin-like growth factor-1 (IGF-1) [15]. Zhang et al. [16] reported that blocking the corresponding IGF sequence with the antisense IGF-I gene can reduce serum CEA levels. Therefore, insulin resistance may be associated with an increase in CEA levels.

Most OSAS patients are obese. Clinical studies have shown that tumors are associated with diet and weight gain [17]. Obesity promotes the secretion of insulin and IGF-1 to promote the survival and production of tumor cells [18]. Through weight loss and gastric volume reduction surgery, the incidence of cancer can be reduced and the quality of life can be improved [19]. The study by Almendros et al. on tumors in OSAS patients in 2012 showed that obesity can increase tumor growth independent of hypoxemia [20]. Second, visceral fat accumulation is associated with insulin resistance and obesity in T2DM patients. Visceral fat releases a greater number of adipokines that are associated with cancer [21]. Lee et al. found that CEA is associated with visceral fat area and is considered as a mediator that links metabolic disorders and tumorigenesis in patients with visceral obesity [22].

Inflammation is a characteristic response of tumors. Inflammatory cells, inflammatory chemokines, and cytokines regulate the growth, metastasis, and differentiation of tumors [23]. The mechanisms include the production of auxin, the promotion of angiogenesis, inducing DNA damage, altering extracellular matrix components, and escaping host immune defenses by coating tumor cells [24]. Kim et al. reported the components of metabolic syndrome are positively correlated with the CEA level and considered CEA as a tumor marker that was simultaneously associated with chronic inflammation [12].

Oxidative stress that plays an important role in OSAS [25], and diabetes [26] is one of the main drivers of cancer development [27]. The onset of cancer is regulated by high levels of reactive oxygen species, triggering DNA mutations that affect the transmission of oncogene signaling and leading to the development of aggressive cancer [27]. Hasan et al. reported that in diabetes patients, CEA is positively correlated with malondialdehyde (MDA), which is a known oxidative stress marker [28].

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Conclusions

In summary, this study suggests that T2DM patients who have OSAS are prone to abnormal increases in serum CEA levels. We should consider the effects of metabolic disorders on CEA levels. As CEA is an indicator that is sensitive to tumor prediction, we think the risk of tumor development in T2DM patients with OSAS will increase significantly in the future. Further research is needed to confirm our findings.

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