Serum CA19-9 as a predictor of incident metabolic syndrome in men over 50 years of age with obesity: a 9-year cohort study

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Abstract

Background

The tumor marker carbohydrate antigen (CA)19-9 is elevated in cancer and chronic diseases. However, the status of CA19-9 in metabolic syndrome (MetS), a common chronic disease in Asia, has not been thoroughly investigated.

Methods

From 2007 to 2015, 1750 participants were retrospectively reviewed, and their routine health checkup data were obtained. The participants were divided into three groups based on their CA19-9 level. Their body mass index (BMI), waist circumference, and blood pressure were determined. Blood samples were collected from individuals after fasting for 8 h to determine biochemical parameters and tumor markers. MetS was defined according to the revised National Cholesterol Education Program's Adult Treatment Panel III. Association between CA19-9 levels and incident MetS was evaluated using Cox regression models.

Results

The group with the highest CA19-9 level tended to exhibit incident MetS ($p = 0.002$, HR = 2.44, 95% CI 1.39–4.27), and type 2 diabetes mellitus ($p < 0.001$, HR = 4.27, 95% CI 2.07–8.12) after adjusting for covariates. The group with the highest CA19-9 level showed a significant correlation with the incidence of all MetS components: high systolic blood pressure (≥130 mm Hg; $p < 0.001$, HR = 2.45, 95% CI 1.50–4.00); high waist circumference (≥90 cm; $p < 0.001$, HR = 2.29, 95% CI 1.46–3.60); high fasting plasma glucose levels (≥100 mg/dL; $p = 0.001$, HR = 2.05, 95% CI 1.33–3.18); low high-density lipoprotein levels (≤50 mg/dL; $p = 0.001$, HR = 2.24, 95% CI 1.39–3.60); and high triglyceride levels (≥150 mg/dL; $p = 0.001$, HR = 2.20, 95% CI 1.40–3.48). Subgroup analyses of age, sex, and BMI-specific groups revealed that participants with obesity (BMI ≥ 24) in the highest CA19-9 tertile, male, and ≥ 50 years of age were significantly associated with incident MetS ($p = 0.002$, HR = 2.56, 95% CI 1.39–4.69; $p = 0.001$, HR = 1.88, 95% CI 1.28–2.76; and $p = 0.002$, HR = 2.75, 95% CI 1.44–5.25, respectively).

Conclusions

Our results revealed a positive correlation between CA19-9 levels and MetS in men over 50 years of age with obesity.

Background

Carbohydrate antigen 19-9 (CA19-9) was first described in 1979 [1] as a monoclonal antibody synthesized by the exocrine pancreas and biliary duct cells [2]. CA19-9 is also synthesized by other organs, such as the salivary glands, endometrium, and colon [2]. CA19-9 is a well-known and valuable tumor marker for pancreatic cancer, and has also been associated with malignancies of the upper

gastrointestinal tract, colorectal cancer, hepatocellular cancer, and ovarian cancer [3]. Moreover, CA19-9 is elevated in benign inflammatory conditions, including cholangitis [4], pancreatitis [5], and bronchiolitis [6].

Du et al. reported that a higher CA19-9 level was associated with a higher risk of incident diabetes mellitus (DM) and metabolic syndrome (MetS) in older Chinese individuals [7,8]. Furthermore, previous studies have shown that CA19-9 was positively correlated with glycemic control in DM [9–12] as well as microvascular complications [11,13]. CA19-9 has been demonstrated to be connected with insulin resistance in prediabetic individuals [14]. MetS is a complex disease characterized by hypertension, central obesity, glucose intolerance, dyslipidemia, and is associated with an increased risk of developing diabetes and cardiovascular diseases [15]. The glucose metabolism and lipid profiles of individuals with MetS are similar to those of patients with DM and both diseases often co-occur [16]. Here, we examined the association between CA19-9 and incident MetS in healthy individuals.

Methods

Ethics Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the tenets of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study design was approved by the Institutional Review Board of Tri-Service General Hospital, Taipei, Taiwan. All participants signed an informed consent form. The information obtained in this study was used for research purposes only. All participants' data were analyzed anonymously.

Study Population

From 2007 to 2015, 44,563 participants who were determined to be healthy, as per a survey conducted by the Health Promotion Center of Tri-Service General Hospital, a medical center in Taipei, Taiwan, were included in our study. To reduce confounding effects, we excluded the following individuals: subjects with a history of dyslipidemia, coronary artery disease, hypertension, DM, hepatobiliary diseases, pancreatitis, and malignancy (including pancreatic cancer, ovarian cancer, and other malignancies), and those undergoing any drug-related medical treatments (N = 32 370). Additionally, subjects lacking data on MetS components, lipid profiles, blood biochemistry tests, tumor marker tests, medical history, and physical examinations were also excluded (N = 10 443).

This study involved 1 750 participants (Fig. 1). The participants were divided into three groups based on their CA19-9 level. The CA19-9 tertiles were as follows: T1 (≤ 6.58 U/mL), T2 (6.59–12.99 U/mL), and T3 (13–143 U/mL).

General Characteristics and Laboratory Measurements

Information regarding the participants' medical history was obtained using a questionnaire, and physical examinations were performed by experienced physicians. Body mass index (BMI) was estimated using

the following formula: . Waist circumference (WC) was measured using a constant tension tape at the level of the umbilicus to the nearest 1 cm while the participants were in the standing position. Blood pressure was measured using an automatic electronic sphygmomanometer while the participants were sitting after a 5 min rest.

Blood samples were collected from the participants after fasting for > 8 h via vacuum blood collection tubes containing EDTA. Serum biochemical parameters such as triglycerides (TGs), total cholesterol (TC), blood urine nitrogen (BUN), uric acid (UA), creatinine, C-reactive protein (CRP), high-density lipoprotein (HDL), low-density lipoprotein (LDL), albumin, and plasma glucose were measured using an automatic analyzer (Fuji Dri-Chem 3000 analyzer; Fuji Photo Film, Minato-Ku, Tokyo, Japan). The tumor markers CA19-9, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), and thyroid stimulating hormone (TSH) were measured using RIA (Architect i2000 analyzer; Abbott Diagnostics, Abbott Park, IL, USA).

Definition of MetS

According to the revised National Cholesterol Education Program's Adult Treatment Panel III [17], MetS was defined by the presence of at least three of the following parameters: WC cut-off ≥ 90 cm in men or ≥ 80 cm in women; serum TGs ≥ 150 mg/dL (1.7 mmol/L); HDL ≤ 40 mg/dL (1.03 mmol/L) in men or ≤ 50 mg/dL (1.29 mmol/L) in women; systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg; and fasting plasma glucose ≥ 100 mg/dL (5.6 mmol/L).

Data Analyses

Data analyses were performed using the SPSS Statistics software (released in 2009; PASW Statistics for Windows, Version 18.0; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± SD, whereas categorical variables were expressed as numbers and percentages. The association between CA19-9 and incident MetS was evaluated using Cox regression models. An extended model approach was used to adjust for covariates. Model 1 was not adjusted for any variables; model 2 was adjusted for sex, age, and BMI; and model 3 was adjusted for the variables in model 2 and TC, BUN, creatinine, UA, albumin, and CRP. Statistical significance was at p value < 0.05.

Results

Correlation of tumor markers with incident MetS

The correlation between incident MetS and tumor markers is shown in Table 1. CA19-9, CEA, and TSH were significantly associated with incident MetS. After adjusting for covariates, CA19-9 was significantly associated with incident MetS (hazard ratio [HR] = 1.03 [95% confidence interval (CI) 1.01–1.04]; p = 0.005).

Table 1. Correlation between tumor markers and incident MetS

Tumor marker	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
CA19-9	1.02 (1.01–1.04)	0.007	1.03 (1.01–1.04)	0.005
AFP	0.97 (0.91–1.03)	0.325	0.96 (0.90–1.03)	0.226
CEA	1.15 (1.01–1.30)	0.033	1.11 (0.96–1.29)	0.174
TSH	1.07 (1.02–1.12)	0.008	1.05 (0.99–1.10)	0.054

Data were adjusted for age, sex, family history, BMI, total cholesterol (TC), creatinine, and uric acid (UA). AFP, alpha-fetoprotein; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; MetS, metabolic syndrome; TSH, thyroid stimulating hormone.

Clinical characteristics of the participants in different CA19-9 tertiles

The clinical characteristics of participants are shown in Table 2. The mean age of participants was 46.6 years, and 86.7% were men. The individuals in the highest CA19-9 tertile tended to be women ($p < 0.001$), and they exhibited a lower BMI ($p = 0.004$) as well as a lower serum creatinine level ($p = 0.001$).

Table 2. General characteristics of the participants in different CA19-9 tertiles

Characteristic	CA19-9 tertile (U/mL)			Total	p for trend
	T1 (≤ 6.58)	T2 (6.59–12.99)	T3 (13–143)	(n = 1 750)	
	(n = 583)	(n = 582)	(n = 585)		
Males, n (%)	545 (93.5)	503 (86.4)	469 (80.2)	1 517 (86.7)	< 0.001
Age (years), mean (SD)	47.46 (12.464)	45.99 (12.984)	46.22 (13.224)	46.56 (12.904)	0.114
BMI (kg/m^2), mean (SD)	24.83 (3.204)	24.80 (3.436)	24.23 (3.468)	24.62 (3.381)	0.004
WC (cm), mean (SD)	85.25 (8.472)	84.37 (10.18)	83.56 (10.08)	84.35 (9.68)	0.116
SBP (mmHg), mean (SD)	123.18 (16.431)	123.26 (17.398)	124.34 (18.842)	123.60 (17.594)	0.471
DBP (mmHg), mean (SD)	79.61 (11.026)	79.52 (11.407)	79.78 (13.045)	79.64 (11.861)	0.933
TC (mg/dL), mean (SD)	189.49 (36.213)	191.27 (34.882)	194.36 (35.348)	191.75 (35.519)	0.121
TGs (mg/dL), mean (SD)	125.87 (70.462)	135.98 (148.83)	133.56 (121.89)	131.79 (118.007)	0.428
BUN (mg/dL), mean (SD)	13.71 (3.033)	13.59 (3.556)	13.80 (4.780)	13.70 (3.864)	0.671
UA (mg/dL), mean (SD)	6.24 (1.300)	6.19 (1.451)	6.09 (1.542)	6.17 (1.435)	0.176
Creatinine (mg/dL), mean (SD)	0.93 (0.152)	0.91 (0.186)	0.89 (0.202)	0.91 (0.182)	0.001
HDL cholesterol (mg/dL), mean (SD)	52.26 (13.566)	51.14 (12.910)	52.47 (15.063)	51.96 (13.885)	0.219
LDL cholesterol (mg/dL), mean (SD)	124.41 (31.771)	123.09 (32.154)	126.15 (34.383)	124.53 (32.815)	0.462
CRP (mg/dL),	0.248 (0.814)	0.219 (0.338)	0.261 (0.489)	0.243 (0.599)	0.806

mean (SD)					
Albumin (mg/dL), mean (SD)	4.69 (0.246)	4.69 (0.264)	4.68 (0.290)	4.69 (0.268)	0.628
MetS, n (%)	105 (18.0)	107 (18.4)	116 (19.8)	328 (18.7)	0.040
SBP (≥130 mmHg), n (%)	109 (18.7)	104 (17.9)	118 (20.2)	331 (18.9)	0.015
WC (≥90 cm), n (%)	84 (14.4)	81 (14.0)	79 (13.5)	244 (13.9)	0.069
Fasting plasma glucose (≥100 mg/dL), n (%)	82 (14.0)	81 (13.9)	84 (14.4)	247 (14.1)	0.041
HDL cholesterol (≤50 mg/dL), n (%)	92 (15.7)	88 (15.2)	93 (15.9)	273 (15.6)	0.319
Total TGs (≥150 mg/dL), n (%)	90 (15.4)	91 (15.6)	92 (15.7)	273 (15.6)	0.049

Data are expressed as mean (SD) or number (percentage). BMI, body mass index; BUN, blood urea nitrogen; CA19-9, carbohydrate antigen 19-9; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; n, number; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.

Correlation of the CA19-9 tertiles with incident MetS and its components

Cox proportional-hazards models, after adjusting for covariates, were used to further assess the relationship between CA19-9 levels and incident MetS as well as type 2 DM. After adjusting for covariates, individuals in the highest CA19-9 tertile were more likely to exhibit MetS (HR = 2.44 [95% CI 1.39–4.27]; p = 0.002) and type 2 DM (HR = 4.27 [95% CI 2.07–8.12]; p < 0.001) compared with those in the lowest tertile (Table 3).

Table 3. Cox proportional-hazards ratios of incident MetS and type 2 DM according to CA19-9 tertiles

MetS			
Model	**CA19-9 tertile**	**HR (95% CI)**	P
Model 1	T2 vs. T1	1.72 (0.96–3.09)	0.067
	T3 vs. T1	1.98 (1.16–3.38)	0.013
Model 2	T2 vs. T1	1.98 (1.09–3.61)	0.026
	T3 vs. T1	2.46 (1.42–4.26)	0.001
Model 3	T2 vs. T1	2.02 (1.10–3.70)	0.023
	T3 vs. T1	2.44 (1.39–4.27)	0.002
Type 2 DM			
Model	**CA19-9 tertile**	**HR (95% CI)**	**P**
Model 1	T2 vs. T1	0.61 (0.17–2.17)	0.443
	T3 vs. T1	3.81 (1.86–7.79)	< 0.001
Model 2	T2 vs. T1	0.62 (0.17–2.24)	0.469
	T3 vs. T1	4.06 (1.98–8.32)	< 0.001
Model 3	T2 vs. T1	0.69 (0.19–2.49)	0.567
	T3 vs. T1	4.27 (2.07–8.12)	< 0.001

Adjusted covariates: Model 1 = unadjusted. Model 2 = adjusted for sex, age, and body mass index. Model 3 = model 2 + adjusted for total cholesterol, blood urea nitrogen, creatinine, uric acid, albumin, and C-reactive protein. CA19-9, carbohydrate antigen 19-9; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; MetS, metabolic syndrome.

To further investigate the relationship between CA19-9 and MetS components, we used Cox regression models with adjusted covariates for each MetS component as follows: high SBP (≥ 130 mmHg), high WC (≥ 90 cm), high fasting plasma glucose levels (≥ 100 mg/dL), low HDL levels (≤ 50 mg/dL), and high TG levels (≥ 150 mg/dL). As shown in Table 4, after adjusting for covariates, individuals in the highest CA19-9 tertile were significantly associated with high SBP (HR = 2.45 [95% CI 1.50–4.00]; p < 0.001), high WC (HR = 2.29 [95% CI 1.46–3.60]; p < 0.001), high fasting plasma glucose levels (HR = 2.05 [95% CI 1.33–3.18]; p = 0.001), low HDL levels (HR = 2.24 [95% CI 1.39–3.60]; p = 0.001), and high TG levels (HR = 2.20 [95% CI 1.40–3.48]; p = 0.001).

Table 4. Cox proportional-hazards ratios of incident MetS components according to CA19-9 tertiles

SBP (≥ 130 mmHg)				WC (≥ 90 cm)			
Model	**CA19-9 tertile**	**HR (95% CI)**	**P**	**Model**	**CA19-9 tertile**	HR (95% CI)	P
Model 1	T2 vs. T1	1.98 (1.20–3.29)	0.008	Model 1	T2 vs. T1	2.13 (1.38–3.29)	0.001
	T3 vs. T1	2.39 (1.50–3.81)	< 0.001		T3 vs. T1	2.06 (1.35–3.14)	0.001
Model 2	T2 vs. T1	2.15 (1.29–3.56)	0.003	Model 2	T2 vs. T1	2.60 (1.65–4.08)	< 0.001
	T3 vs. T1	2.62 (1.63–4.21)	< 0.001		T3 vs. T1	2.55 (1.64–3.95)	< 0.001
Model 3	T2 vs. T1	2.21 (1.31–3.72)	0.003	Model 3	T2 vs. T1	2.57 (1.63–4.05)	< 0.001
	T3 vs. T1	2.45 (1.50–4.00)	< 0.001		T3 vs. T1	2.29 (1.46–3.60)	< 0.001
Fasting plasma glucose (≥ 100 mg/dL)				**HDL cholesterol (≤ 50 mg/dL)**			
Model 1	T2 vs. T1	1.57 (0.98–2.51)	0.061	Model 1	T2 vs. T1	2.13 (1.32–3.42)	0.002
	T3 vs. T1	1.84 (1.20–2.84)	0.005		T3 vs. T1	2.19 (1.39–3.45)	0.001
Model 2	T2 vs. T1	1.66 (1.03–2.66)	0.036	Model 2	T2 vs. T1	1.99 (1.23–3.23)	0.005
	T3 vs. T1	1.93 (1.25–2.96)	0.003		T3 vs. T1	2.72 (1.44–3.59)	< 0.001
Model 3	T2 vs. T1	1.78 (1.10–2.87)	0.020	Model 3	T2 vs. T1	2.14 (1.31–3.49)	0.002
	T3 vs. T1	2.05 (1.33–3.18)	0.001		T3 vs. T1	2.24 (1.39–3.60)	0.001
Total TGs (≥ 150 mg/dL)							
Model 1	T2 vs. T1	1.40 (0.83–2.34)	0.206				
	T3 vs. T1	2.10 (1.35–3.26)	0.001				
Model 2	T2 vs. T1	1.34 (0.80–2.24)	0.271				
	T3 vs. T1	2.28 (1.47–3.56)	< 0.001				
Model 3	T2 vs. T1	1.38 (0.82–2.32)	0.230				

	T3 vs. T1	2.20 (1.40–3.48)	0.001

Adjusted covariates: Model 1 = unadjusted. Model 2 = adjusted for sex, age, and body mass index. Model 3 = model 2 + adjusted for total cholesterol, blood urea nitrogen, creatinine, uric acid, albumin, and C-reactive protein. CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference.

Subgroup analysis of the correlation between CA19-9 levels and incident MetS

We further conducted subgroup analyses of the correlation between CA19-9 levels and incident MetS using age-, sex-, and BMI-specific groups. Male participants in the highest CA19-9 tertile (HR = 2.56 [95% CI 1.39–4.69]; p = 0.002), aged ≥ 50 years (HR = 1.88 [95% CI 1.28–2.76]; p = 0.001), and with obesity (BMI ≥ 24 kg/m^2; HR = 2.75 [95% CI 1.44–5.25]; P = 0.002) were significantly associated with incident MetS (Table 5).

Table 5. Cox proportional-hazards ratios of incident MetS according to CA19-9 tertiles: subgroup analyses

BMI (< 24 kg/m^2)				BMI (≥ 24 kg/m^2)			
Model	**CA19-9 tertile**	**HR (95% CI)**	**P**	**Model**	**CA19-9 tertile**	**HR (95% CI)**	**P**
Model 1	T2 vs. T1	0.51 (0.06–4.47)	0.541	Model 1	T2 vs. T1	2.13 (1.13–4.00)	0.019
	T3 vs. T1	1.16 (0.28–4.93)	0.836		T3 vs. T1	2.37 (1.31–4.31)	0.005
Model 2	T2 vs. T1	0.47 (0.05–4.32)	0.500	Model 2	T2 vs. T1	2.19 (1.16–4.13)	0.016
	T3 vs. T1	1.30 (0.30–5.74)	0.726		T3 vs. T1	2.48 (1.36–4.54)	0.003
Model 3	T2 vs. T1	0.41 (0.04–3.85)	0.438	Model 3	T2 vs. T1	2.09 (1.09–4.00)	0.026
	T3 vs. T1	1.20 (0.25–5.74)	0.819		T3 vs. T1	2.56 (1.39–4.69)	0.002
Males				**Females**			
Model	**CA19-9 tertile**	**HR (95% CI)**	**P**	**Model**	**CA19-9 tertile**	**HR (95% CI)**	**P**
Model 1	T2 vs. T1	1.58 (1.08–2.32)	0.020	Model 1	T2 vs. T1	0.18 (0.04–0.82)	0.027
	T3 vs. T1	1.79 (1.23–2.60)	0.002		T3 vs. T1	0.40 (0.12–1.39)	0.151
Model 2	T2 vs. T1	1.67 (1.13–2.46)	0.010	Model 2	T2 vs. T1	0.32 (0.06–1.84)	0.208
	T3 vs. T1	1.93 (1.32–2.82)	0.001		T3 vs. T1	0.65 (0.16–2.66)	0.553
Model 3	T2 vs. T1	1.65 (1.11–2.43)	0.012	Model 3	T2 vs. T1	0.33 (0.05–2.00)	0.226
	T3 vs. T1	1.88 (1.28–2.76)	0.001		T3 vs. T1	0.50 (0.11–2.24)	0.362
Age (< 50 years)				**Age (≥ 50 years)**			
Model	**CA19-9 tertile**	**HR (95% CI)**	**P**	**Model**	**CA19-9 tertile**	**HR (95% CI)**	**P**
Model 1	T2 vs. T1	1.05 (0.36–3.05)	0.925	Model 1	T2 vs. T1	1.93 (0.96–3.85)	0.064
	T3 vs. T1	1.05 (0.34–3.24)	0.929		T3 vs. T1	2.31 (1.25–4.26)	0.007
Model	T2 vs. T1	1.14 (0.39–	0.808	Model	T2 vs. T1	2.57 (1.25–	0.010

2	T3 vs. T1	3.33) 1.24 (0.40–3.86)	0.708	2	T3 vs. T1	5.29) 2.85 (1.50–5.40)	0.001
Model 3	T2 vs. T1 T3 vs. T1	1.13 (0.38–3.42) 0.84 (0.25–2.90)	0.825 0.786	Model 3	T2 vs. T1 T3 vs. T1	2.73 (1.31–5.72) 2.75 (1.44–5.25)	0.008 0.002

Adjusted covariates: Model 1 = unadjusted. Model 2 = adjusted for sex, age, and BMI. Model 3 = model 2 + adjusted for total cholesterol, blood urea nitrogen, creatinine, uric acid, albumin, and C-reactive protein. BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio.

Discussion

This study demonstrated that a high CA19-9 level may be associated with incident MetS and its components, after adjusting for covariates. Furthermore, subgroup analysis showed that a high serum CA19-9 level may represent a predictor of incident MetS in healthy men aged 50 and over. Our results warrant a close follow-up of metabolic conditions in high-risk individuals with a high CA19-9 level.

In Taiwan, during adult health checkups, tumor markers such as CA19-9, CEA, AFP, and TSH, are usually measured; however, a small number of participants had elevated tumor markers and no tumor was found through a series of examinations. We investigated the potential reasons for the elevated tumor markers using the database of the Health Promotion Center. CA19-9 is secreted by duct cells of the exocrine pancreas and is elevated in conditions involving pancreatic tissue damage and specific malignancies [3]. Besides its role as a tumor marker, CA19-9 has been confirmed to be associated with hemoglobin A1c, and fasting plasma glucose levels, early-phase insulin secretion, and insulin resistance in individuals with prediabetes [14]. Patients with DM and a high CA19-9 level were associated with poor disease control and β-cell functionality [13,18,19]. Moreover, a high CA19-9 level has been shown to predict the risk of DM in older Chinese individuals [7]. Taken together, CA19-9 not only plays a major role in monitoring DM but also acts as a predictor of incident DM.

MetS is a well-established risk factor for DM as well as cardiovascular diseases [20] and it increases the risk of all-cause and cardiovascular mortality in older populations [21]. MetS components, such as hypertension, central obesity, insulin resistance, and dyslipidemia, are risk factors for type 2 DM and cardiovascular diseases [22]. The prevalence of MetS is high and increasing worldwide [23], probably due to the rising percentages of obesity and the popularity of western diets [24,25]. Decreased physical activity and diets high in fat and carbohydrates play a major role in central obesity and insulin resistance, which are the major pathophysiological characteristics of MetS [26]. Insulin resistance and diminished β-cell function occur before the occurrence of MetS [27]. Furthermore, β-cell function has been shown to be negatively correlated with the severity of MetS [28]. Additionally, it has been shown that altered β-cell function may affect the exocrine activity of the pancreas, leading to an increased serum CA19-9 level [29].

It has also been proposed that CA19-9 biosynthesis is affected by insulin via the regulation of intestinal galactosyltransferase activity [14,30].

MetS components differ between women and men owing to the differences in hormones, lean body mass, and body fat; men have a higher lean body mass, less body fat, and lower insulin sensitivity than women [31]. Insulin resistance is more prominent in men than in women [32,33]. In summary, our study revealed that a high serum CA19-9 level is a significant predictor of incident MetS risk in men. This may be attributed to the correlation of CA19-9 levels and MetS with β-cell function and the effects of sex on MetS components.

Given the adverse outcomes of MetS and the large population at risk, researchers need to focus on disease prevention and underlying risk factor management. Obesity, physical inactivity, smoking, and an atherogenic diet constitute acquired risk factors for MetS. Clinical management should focus on reducing these underlying risk factors according to an individual's risk status [15]. Our findings suggest that monitoring of random serum CA19-9 levels may predict the risk of incident MetS, which may be useful for disease prevention. Moreover, our findings are in agreement with those of Du et al. [9], who described a positive association between CA19-9 levels and incident DM. In brief, the serum CA19-9 level may provide physicians with an indication of the presence of a specific metabolic condition and influence further approaches toward disease prevention. Therefore, the CA19-9 level should be determined during routine health check-ups. A high CA19-9 level not only indicates the possibility of cancer but also warrants a close follow-up of metabolic conditions.

Our study has several limitations. First, although adjustments for major potential confounders were made, we could not exclude the possibility of unmeasured confounders. Nevertheless, as the participants in our study were relatively healthy, the influence of unknown confounders should be minimal. Second, this was a retrospective observational study, wherein the serum CA19-9 level was analyzed only once during the health check-up program. The participants were not subjected to surveillance and long-term follow-up. Thus, prospective cohort studies are warranted to validate the present results. Third, individuals with a high CA19-9 level are more likely to visit a physician for further follow-up, and exhibit a higher possibility of MetS diagnosis than individuals with a low CA19-9 level. However, the large number of participants in our study may have reduced this bias. Finally, a few participants were excluded due to inadequate information or no follow-up; therefore, a selection bias may have occurred.

Conclusions

A high CA19-9 level was associated with incident MetS in men over 50 years of age with obesity. Additionally, a high CA19-9 level correlated with MetS components. CA19-9 may be a useful marker for predicting MetS and can be routinely monitored during health check-ups. Further prospective studies with a larger sample are warranted to confirm our findings.

Abbreviations

AFP: Alpha-fetoprotein; BMI: Body mass index; BUN: Blood urine nitrogen; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; CI: Confidence interval; CRP: C-reactive protein; DBP: Diastolic blood pressure; DM: Diabetes mellitus; HDL: High-density lipoprotein; HR: Hazard ratio; LDL: Low-density lipoprotein; MetS: Metabolic syndrome; SBP: Systolic blood pressure; TC: Total cholesterol; TGs: Triglycerides; TSH: Thyroid stimulating hormone; UA: Uric acid; WC: Waist circumference.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Tri-Service General Hospital, Taipei, Taiwan.

The data of all participants were analyzed anonymously. All participants signed an informed consent form.

Consent for publication

Not applicable.

Availability of data and materials

All datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

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Figures

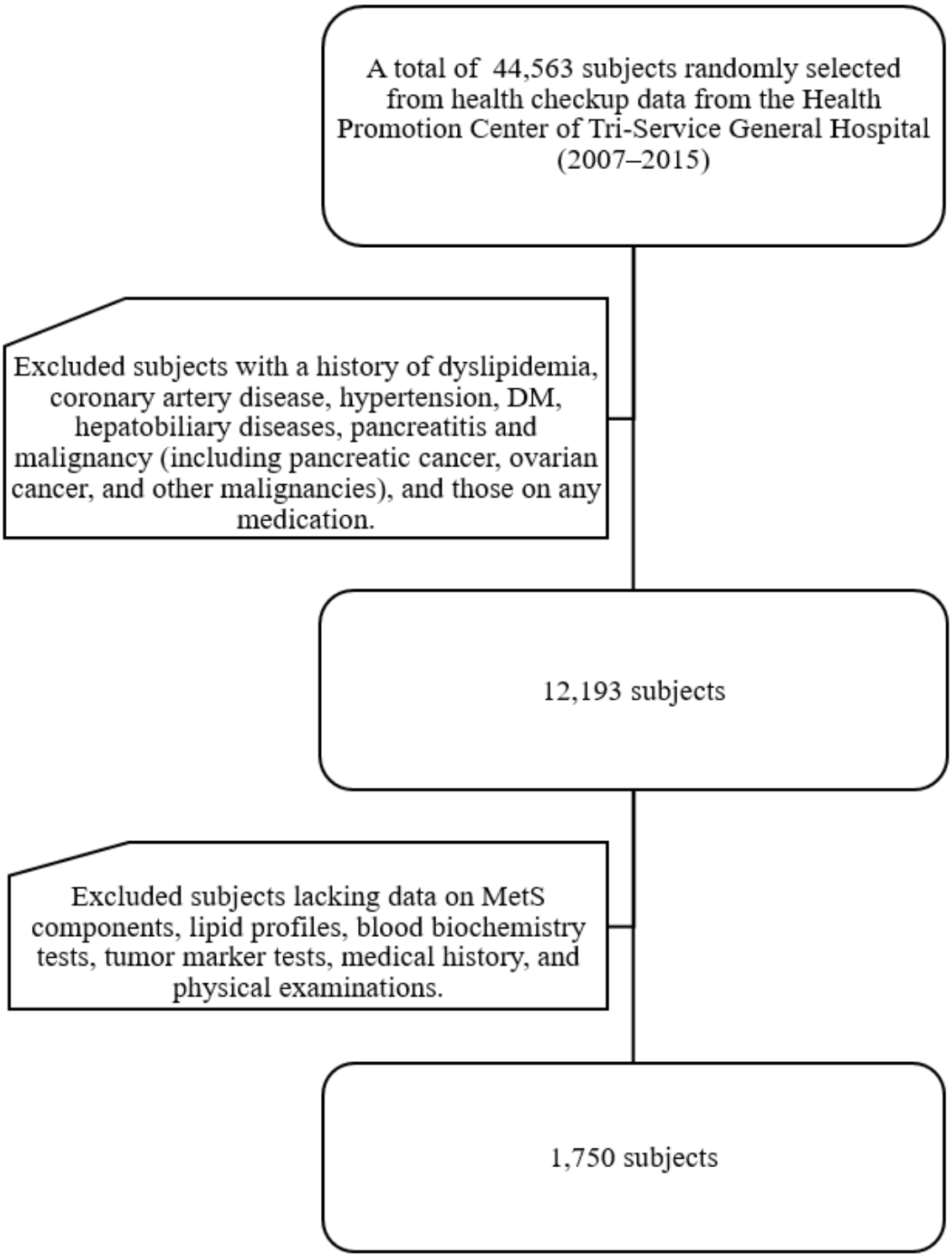

Figure 1

Study flowchart.