RESEARCH ARTICLE

Association of type 2 diabetes with anthropometrics, bone mineral density, and body composition in a large-scale screening study of Korean adults

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Abstract

Objectives

Type 2 diabetes mellitus (T2DM) is a common, chronic disease that is closely associated with anthropometric indices related to obesity. However, no study published to date has simultaneously examined the associations of T2DM with anthropometrics, bone mineral density (BMD), and body composition variables. The present study aimed to evaluate the associations of T2DM with anthropometrics, BMD and body composition variables and to identify the best indicator of T2DM in Korean adults.

Methods

The data used in this study were obtained from the Korea National Health and Nutrition Examination Survey conducted from 2008 to 2011. A total of 7,835 participants aged from 40 to 90 years were included in this study. A binary logistic regression analysis was performed to examine the significance of differences between the groups with and without T2DM, and the areas under the receiver operating characteristic (AUCs) curves were calculated to compare the predictive power of all variables.

Results

In men, waist-to-height ratio (WHtR) displayed the strongest association with T2DM (adjusted odds ratio (OR) = 1.838 [1.513-2.233], adjusted p<0.001), and waist circumference (WC) and WHtR were the best indicators (WC: AUC = 0.662 [0.639-0.685], WHtR: AUC = 0.680 [0.658-0.703]) of T2DM among all the variables. In women, left leg (LL) and right leg (RL) fat displayed strong negative associations with T2DM (LL fat: adjusted OR = 0.367 [0.321-0.419], adjusted p<0.001, RL fat: adjusted OR = 0.375 [0.329-0.428], adjusted p<0.001), and WC and WHtR were excellent indicators (WC: AUC = 0.730 [0.709-0.750], WHtR: AUC = 0.747 [0.728-0.766]) of T2DM among all the variables. In particular, the WHtR in men and LL and RL fat in women exhibited the strongest associations with



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Data Availability Statement: Data are available from the 2008-2011 Korea National Health and Nutrition Examination Survey (KNHANES IV-2, 3 and V-1, 2), conducted by the Korea Centers for Disease Control and Prevention (KCDCP), and are freely available from KCDCP (https://knhanes.cdc. go.kr). We confirm that we accessed the data used in our study in the same manner we expect future researchers to do so, and did not receive special privileges. **Funding:** This research was supported by the Bio and Medical Technology Development Program of the National Research Foundation of Korea (NRF) funded by the Korean government, MSIP (NRF-2015M3A9B6027139). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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T2DM, and the predictive power of the WC and WHtR was stronger than BMD, fat, and muscle mass variables in both men and women. Additionally, the predictive power of the WC and WHtR was stronger in women than in men.

Discussion

Of the anthropometric indices, BMD, and body fat and muscle variables, the best indicators of T2DM were WC and WHtR in both Korean men and women. The results of the present investigation will provide basic information for clinical studies of patients with T2DM and evidence for the prevention and management of T2DM.

Introduction

Diabetes is a common, chronic disease worldwide, and the number of patients continues to increase due to reduced physical activity and increased obesity [1]. The World Health Organization (WHO) has reported that the number of adults with diabetes in the world has increased from 108 million in 1980 to 422 million in 2014 [2]. The Korea Diabetes Association has reported that the prevalence of diabetes (fasting plasma glucose>126 mg/dL, HbAlC>6.5%) in Korean adults aged \geq 30 years increased from 12.4% in 2011 to 14.4% in 2016 and that the diabetic population is expected to reach approximately 6 million in 2050 [3]. In particular, the prevalence of diabetes mellitus is more than 10% in men aged \geq 40 years and women aged \geq 50 years. It is important to maintain proper blood glucose control in diabetes because it is likely to cause various complications such as chronic renal failure, vision loss, hypertension, dyslipidemia, heart failure, myocardial infarction, ischemic heart disease and stroke [3-6]. In this study, we focus on type 2 diabetes (T2DM) rather than type 1 diabetes mellitus (T1DM) or and gestational diabetes. T2DM is a disease that affects 90-95% of all adult diabetes patients and is caused by a lack of insulin secretion from the β -cells of the pancreas or by insulin resistance that arises from the inability of insulin to act normally in regulating nutrient metabolism in peripheral tissues [5]. Although the prevalence of diabetes continues to increase, there are still many patients who do not know they have the disease until complications arise. According to the International Diabetes Federation in 2017, an estimated 50% of all people aged 20-79 years with diabetes are unaware of their disease [7], and the Korea Diabetes Association has reported that 3 out of 10 diabetic patients are unaware of their disease [3]. Therefore, it is essential to develop indicators that can identify diabetes as early as possible based on various data from participants.

Many studies to date have assessed the association of T2DM with anthropometric indices, bone mineral density (BMD), and body composition variables. Among the anthropometric indices, many studies have reported the strongest association between the waist-to-height ratio (WHtR) and T2DM [8–15]. According to several studies, waist circumference (WC) [16–18] and body mass index (BMI) [9,17] are strongly associated with T2DM. In addition, some studies have reported that neck circumference (NC) in Brazilian women [19] and the Chinese visceral adiposity index (CVAI) in Chinese adults are strongly associated with T2DM [20]. Age has the greatest impact on diabetes in Ghana [21]. A study has shown that prediction of the fasting plasma glucose status using a combination of anthropometric measures was superior to individual measures alone [22]. Regarding body composition variables, some studies have reported that the association of T2DM with central fat or abdominal fat is stronger than the association with general fat [23–26]. Leg fat strongly correlates with T2DM [27]. With respect

to BMD parameters, several studies have reported that T2DM is associated with a higher BMD and, paradoxically, with increased fracture risk [28–36], while several studies have shown that diabetes affects bone loss [37,38]. In addition, some investigations have shown that patients with both T2DM and fractures have a low BMD [39,40], and several studies have reported that T2DM is not associated with a higher prevalence or incidence of vertebral fractures in older men [41,42]. Therefore, the association of T2DM with BMD remains inconsistent across studies. Additionally, although many studies have been conducted to find useful indicators of T2DM, the previous studies were based on only partial information, such as anthropometrics, BMD, and body fat mass. Comparisons of T2DM with various indicators are essential for finding the indicator with the greatest predictive power. Therefore, the aim of this study is to identify the associations and predictive power between T2DM and various indicators such as anthropometric indices, BMD, and body composition parameters. The results of the present investigation will provide basic information for clinical studies of patients with T2DM and evidence for the prevention and management of T2DM.

Materials and methods

Study population and data source

The data used in this study were obtained from the 2008–2011 Korea National Health and Nutrition Examination Survey (KNHANES IV-2, 3 and V-1, 2), which is a prospective, crosssectional, nationally representative survey study conducted by the Korea Centers for Disease Control and Prevention [43,44]. The KNHANES datasets were approved by the Korea Ministry of Health and Welfare (2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, and 2011-02CON-06-C). The institutional review boards of the Korea Institute of Oriental Medicine and Konkuk University approved the access and analysis of open source data from the KNHANES in this study, with a waiver of documentation of informed consent (IRB No. I-1805/003-001 and 7001355-201802-E-063).

Health interviews and health examinations included in the KNHANES were performed at mobile examination centers (MECs). The health interviews, which requested information such as medical conditions, housing characteristics, socioeconomic status and alcohol use, were collected by a face-to-face interview and self-administered form. Health examinations requesting information such as height, weight, blood test and BMD were also measured at MECs [45].

The KNHANES I-VII were conducted from 1998 to 2016. BMD examinations were performed only from 2008 to 2011; therefore, we chose the KNHANES IV-2, 3 and V-1, 2 to find associations of T2DM with various bone and body composition variables. The KNHANES IV-2, 3 and V-1, 2 included 21,303 participants who completed blood tests, bone densitometry and body fat composition tests, along with a health examination. According to the Korean Diabetes Association [3], the prevalence of diabetes increases rapidly at age >40 years. T2DM is the most common type of diabetes, which affects 90–95% of all patients with diabetes [5,46]. Therefore, in the present study, we focused on participants aged 40 to 90 years with T2DM. The sample included 16,891 participants ranging in age from 40 to 90 years; 3,727 participants with impaired fasting glucose (IFG) levels, T1DM or missing values for T2DM were excluded. The KNHANES did not clearly distinguish T1DM from T2DM, and therefore, participants reporting a first diagnosis of diabetes at an age <30 years who started insulin therapy within 1 year of diagnosis were considered as having T1DM, in accordance with a previous study [47]. In total, 5,329 participants with missing values for BMD (1,940), blood tests (1,000), anthropometrics (1,157) and basic questionnaires (1,232) were excluded, and a sample of 7,835 participants was finally collected. The final sample consisted of 3,121 men (normal: 2,468 and



Fig 1. Sample selection procedure. T2DM, type 2 diabetes mellitus; IFG, impaired fasting glucose; BMD, bone mineral density.

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T2DM: 653) and 4,714 women (normal: 4,054 and T2DM: 660). Fig 1 shows a detailed schematic of the data preprocessing procedure.

Definition

Diabetes mellitus is defined as a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [5]. WHO and previous studies have reported that diabetes mellitus is defined as a fasting plasma glucose \geq 126 mg/dL, 2-hour plasma glucose \geq 200 mg/dL, or HbA1C \geq 6.5% [3,5]. In this study, the diagnosis of T2DM was based on a fasting plasma glucose level \geq 126 mg/dL, HbA1C level \geq 6.5%, the use of antidiabetic medications or glucose-lowering drugs, or physician-diagnosed diabetes.

Measurements

All anthropometric measurements, such as height, weight, WC, BMI, and WHtR, were recorded using standard methods. Height was measured to the nearest 0.1 cm using a Seca 225 portable stadiometer (Seca, Hamburg, Germany), and weight was measured with an accuracy of 0.1 kg using an electronic scale GL-6000-20 (Caskorea, Seoul, Korea). WC was measured at the midline between the lower rib margin and iliac chest to the nearest 0.1 cm. BMI was calculated as weight (kg)/square of height (m²). WHtR was calculated as WC divided by height. Blood samples were collected from the antecubital vein after an 8-hour fast. Fasting plasma glucose, total cholesterol, triglyceride (TG, \geq 12 hour fasting), and high-density lipoprotein-cholesterol (HDL) levels in all participants were measured enzymatically using a Hitachi

Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). The visceral adiposity index (VAI), a gender-specific index based on WC, BMI, TG and HDL, was calculated as follows [48]:

$$men: VAI = \left(\frac{WC}{39.38 + (1.88 + BMI)}\right) \times \left(\frac{TG}{1.03}\right) \times \left(\frac{1.31}{HDL}\right)$$
$$women: VAI = \left(\frac{WC}{36.58 + (1.89 + BMI)}\right) \times \left(\frac{TG}{0.81}\right) \times \left(\frac{1.52}{HDL}\right)$$

BMDs of the total femur, trochanter, intertrochanter, femoral neck, ward, lumbar spine, and whole body were measured using dual energy X-ray absorptiometry (DISCOVERY QDR-4500W fan-beam densitometer, Hologic, Inc., Bedford, MA, USA). Body fat composition was measured using the same equipment and methods as used for BMD. Body fat mass, lean body mass, weight (mass) and body fat percentage were measured in the trunk, left leg (LL), right leg (RL) and whole body. The lean body mass is the fat-free mass including the bone mineral content. Muscle mass (g) was calculated as the lean body mass minus the bone mineral content, assuming that all non-fat and non-bone tissue is muscle.

Statistical analysis

Statistical analyses were performed using SPSS 21 for Windows (SPSS, Inc., Chicago, IL, USA). In crude analyses and in the analyses adjusted for age and BMI, a binary logistic regression analysis was performed to identify associations between the group without T2DM and group with T2DM after applying standardized transformations to the datasets. Independent two-sample t-tests were performed to assess gender differences in statistical characteristics. Table 1 shows a detailed description of the demographic characteristics and values for all study variables in each group. The area under the receiver operating characteristic (AUC) curve is a major criterion for comparisons of the predictive ability of individual measures. Therefore, the present study used AUCs as indicators to evaluate whether a clinically meaningful improvement in the discrimination of T2DM was achieved by anthropometric, BMD, body fat and muscle variables.

Results

Women with T2DM were older than men with T2DM. Various indices, such as the BMI, VAI, WHtR and body fat mass, were significantly higher in women with T2DM than in men with T2DM. The WC was higher in men than in women, and the BMD was lower in women than in men.

Tables 2 and 3 list the associations of T2DM with anthropometric indices, BMD, body fat and muscle mass in Korean men and women. Among all the variables, the WHtR displayed the strongest association with T2DM in men in the crude analysis (OR = 1.951 [95% CI, 1.770–2.150], $p \le 0.001$), and the association remained highly significant after adjusting for age and BMI (adjusted OR = 1.838 [1.513–2.233], adjusted $p \le 0.001$). Of the BMD variables, the thoracic spine BMD displayed the strongest association with T2DM in both crude (OR = 1.347 [1.238–1.465], $p \le 0.001$) and adjusted analyses (adjusted OR = 1.222 [1.118–1.336], adjusted $p \le 0.001$). Among the body fat variables, trunk fat exhibited the strongest association with T2DM in the crude analysis (OR = 1.612 [1.477–1.760], $p \le 0.001$), and the association remained highly significant after adjusting for age and BMI (adjusted OR = 1.436 [1.237–1.667], adjusted $p \le 0.001$). Of the muscle mass variables, trunk muscle mass displayed the strongest association with T2DM in both the crude (OR = 1.346 [1.235–1.467], $p \le 0.001$) and adjusted analyses (adjusted OR = 1.375 [1.203–1.571], adjusted $p \le 0.001$).

Variables		Men		Women	Women	
		group without T2DM	group with T2DM	group without T2DM	group with T2DM	
Numbe	rs	2468	653	4054	660	
Age (mean, SD)		54.88 (11.65)	60.38 (10.22)	54.55 (11.29)	63.38 (10.32)	
Residen	tial areas (no. of participants, %)					
	City	1777 (72.00)	476.0 (72.90)	2968 (73.21)	469.0 (71.10)	
	Rural	691.0 (28.00)	177.0 (27.10)	1086 (26.79)	191.0 (28.90)	
Educati	on (no. of participants, %)					
	< = Elementary school	567.0 (22.97)	177.0 (27.10)	1531 (37.77)	454.0 (68.80)	
	Middle school	370.0 (14.99)	139.0 (21.30)	598.0 (14.75)	75.00 (11.40)	
	High school	799.0 (32.37)	213.0 (32.60)	1282 (31.62)	107.0 (16.20)	
	> = University	732.0 (29.66)	124.0 (19.00)	643.0 (15.86)	24.00 (3.600)	
Occupa	tion (no. of participants, %)					
	White-collar worker	362.0 (14.70)	62.00 (9.500)	281.0 (6.900)	7.000 (1.054)	
	Office worker	237.0 (9.600)	35.00 (5.344)	145.0 (3.600)	10.00 (1.506)	
	Service	304.0 (12.30)	62.00 (9.466)	615.0 (15.20)	60.00 (9.100)	
	Farmer and fisher	384.0 (15.60)	89.00 (13.59)	438.0 (10.80)	78.00 (11.75)	
	Blue-collar worker	508.0 (20.60)	107.0 (16.40)	135.0 (3.300)	9.000 (1.355)	
	Elementary occupations	209.0 (8.500)	64.00 (9.771)	478.0 (11.80)	67.00 (10.20)	
	Unemployed (housewife, etc.)	464.0 (18.80)	234.0 (35.73)	1962 (48.40)	429.0 (65.00)	
Househ	old incomes (no. of participants, %)					
	High class	728.0 (29.50)	138.0 (21.07)	1126 (27.78)	106.0 (16.10)	
	Middle class	1272 (51.54)	324.0 (49.60)	2035 (50.20)	290.0 (43.90)	
	Low class	468.0 (18.96)	191.0 (29.20)	893.0 (22.03)	264.0 (40.00)	
Alcohol	consumption (No. of participants, %)					
	Frequently drinks	979.0 (39.67)	251.0 (38.32)	313.0 (7.721)	32.00 (4.800)	
	Occasionally drinks	584.0 (23.66)	121.0 (18.47)	648.0 (15.98)	55.00 (8.300)	
	Rarely drinks	434.0 (17.59)	114.0 (17.41)	1452 (35.82)	192.0 (29.10)	
	Never drinks	295.0 (11.95)	115.0 (17.56)	639.0 (15.76)	130.0 (19.70)	
	Nonapplicable	176.0 (7.131)	52.00 (8.000)	1002 (24.72)	251.0 (38.10)	
Sleep duration (mean, SD)		6.926 (3.474)	6.860 (1.478)	6.744 (3.211)	6.930 (6.440)	
Vital sig	gns (mean, SD)					
	Pulse rate per 15 sec	17.31 (2.225)	18.07 (2.668)	17.41 (2.147)	18.36 (2.465)	
	Systolic BP (mmHg) [‡]	121.9 (15.99)	127.7 (16.20)	119.30 (17.72)	130.1 (18.14)	
	Diastolic BP (mmHg) [‡]	80.02 (10.62)	79.50 (10.55)	76.13 (10.26)	76.78 (9.783)	
Anthro	pometrics (mean, SD)					
	Body mass index (kg/m ²)	23.51 (2.935)	24.72 (2.974)	23.44 (3.041)	25.26 (3.411)	
	Visceral adiposity index	4.726 (5.734)	6.675 (8.348)	4.764 (3.951)	7.807 (6.049)	
	Height (cm) [‡]	168.3 (6.189)	167.2 (6.272)	155.5 (5.967)	153.6 (5.840)	
	Weight (kg) [‡]	66.76 (10.00)	69.28 (10.08)	56.72 (8.295)	59.68 (9.384)	
	Waist circumference (cm) [‡]	83.42 (8.393)	88.29 (8.810)	78.89 (8.803)	86.59 (9.395)	
	Waist-to-height ratio [‡]	0.496 (0.050)	0.528 (0.052)	0.508 (0.060)	0.564 (0.062)	
Blood p	arameters (mean, SD)					
	Total cholesterol (mg/dL) [‡]	188.7 (34.29)	182.6 (40.67)	193.6 (34.68)	196.2 (41.02)	
	HDL cholesterol (mg/dL) [‡]	45.85 (10.95)	42.48 (9.920)	50.05 (11.02)	45.22 (10.70)	
	Triglyceride (mg/dL) [‡]	150.5 (124.1)	194.8 (186.6)	116.3 (72.67)	165.1 (98.81)	
	Ferritin (ng/mL) [‡]	120.1 (124.7)	164.6 (294.5)	50.63 (43.56)	73.59 (65.27)	
	Aspartate aminotransferase (IU/L) [‡]	24.64 (14.19)	27.71 (18.80)	20.73 (6.986)	23.96 (11.80)	

(Continued)

Variables		Men		Women	Women	
		group without T2DM	group with T2DM	group without T2DM	group with T2DM	
	Alanine aminotransferase (IU/L) [‡]	24.06 (14.91)	30.21 (23.06)	17.55 (10.12)	23.92 (16.34)	
	Alkaline phosphatase (IU/L) [‡]	233.5 (64.69)	252.0 (92.06)	220.1 (71.56)	258.4 (86.62)	
	Hematocrit (%) [‡]	44.28 (3.208)	43.41 (3.781)	38.95 (2.966)	39.30 (3.135)	
	Vitamin D (ng/dL) [‡]	21.06 (7.233)	20.19 (7.250)	17.82 (6.700)	18.50 (7.471)	
	Blood urea nitrogen (mg/dL) [‡]	15.41 (4.507)	16.53 (4.920)	14.22 (3.978)	15.64 (5.020)	
	Creatinine (mg/dL) [‡]	0.946 (0.162)	0.990 (0.358)	0.708 (0.157)	0.750 (0.242)	
Bone r	nineral density (mean, SD)					
	Ward BMD (g/cm ²) [‡]	0.560 (0.134)	0.530 (0.128)	0.523 (0.156)	0.440 (0.145)	
	Lumbar spine BMD (g/cm ²) [‡]	0.944 (0.142)	0.980 (0.150)	0.881 (0.163)	0.840 (0.149)	
	Left rib BMD (g/cm ²) [‡]	0.686 (0.086)	0.710 (0.088)	0.619 (0.086)	0.600 (0.079)	
	Right rib BMD (g/cm ²) [‡]	0.688 (0.078)	0.700 (0.085)	0.623 (0.078)	0.600 (0.076)	
	Thoracic spine BMD (g/cm ²) [‡]	0.919 (0.139)	0.960 (0.148)	0.808 (0.149)	0.780 (0.133)	
	Pelvis BMD (g/cm ²) [‡]	1.098 (0.157)	1.120 (0.158)	1.029 (0.161)	0.990 (0.163)	
Fat ma	ss (mean, SD)					
	Trunk fat (g) [‡]	7982 (3149)	9511 (3011)	9699 (3222)	11870 (3482)	
	Left leg fat (g) [‡]	1976 (685.6)	1991 (654.7)	2998 (817.8)	2705 (829.5)	
	Right leg fat (g) [‡]	2016 (702.7)	2046 (671.6)	3069 (842.6)	2781 (853.4)	
	Body total fat (g) [‡]	13479 (4859)	15212 (4588)	18058 (5052)	19912 (5392)	
Muscle	e mass (mean, SD)					
	Trunk muscle (g) [‡]	24178 (3213)	25169 (3534)	18162 (2303)	19158 (2775)	
	Left leg muscle (g) [‡]	7877 (1231)	7823 (1265)	5435 (810)	5468 (880)	
	Right leg muscle (g) [‡]	8045 (1230)	7968 (1276)	5537 (819)	5563 (903)	
	Body total muscle (g) [‡]	45470 (6166)	46181 (6595)	32284 (4103)	33436 (4786)	

Table 1. (Continued)

The data are represented as numbers of participants and percentages, N (%), or as the mean and standard deviation (SD) for continuous and categorical variables, respectively. † p<0.05 and † p<0.001. These results indicate significant differences between men and women without stratification into groups, as determined using independent two-sample t-tests [means (standard deviations)]. HDL, high-density lipoprotein; BMD, bone mineral density. Frequently drinks: drinking more than twice a week. Occasionally drinks: drinking from twice to four times a month. Rarely drinks: drinking less than or equal to once a month. Sleep duration: the average daily amount of sleep.

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In women, the WHtR displayed the strongest association with T2DM in the crude analysis among all the variables (OR = 2.494 [2.276–2.733], p≤0.001), and the association remained highly significant after adjusting for age and BMI (adjusted OR = 2.390 [1.513–2.233], adjusted $p\leq0.001$). Of the BMD variables, ward BMD was negatively associated with T2DM in both the crude (OR = 0.545 [0.497–0.599], p \leq 0.001) and adjusted analyses (adjusted OR = 0.855 [0.748–0.970], adjusted p = 0.022). Among the fat mass variables, the trunk fat mass displayed the strongest association with T2DM in the crude analysis (OR = 1.856 [1.710–2.015], p \leq 0.001), and the association remained highly significant after adjusting for age and BMI (adjusted OR = 1.741 [1.480–2.047], adjusted p \leq 0.001). Of the muscle mass variables, trunk muscle mass displayed the strongest association with T2DM in both crude (OR = 1.483 [1.370–1.606], p \leq 0.001) and adjusted analyses (adjusted OR = 1.628 [1.447–1.831], adjusted p \leq 0.001).

In the comparison of the predictive power of all variables for identifying T2DM based on the AUC, the WHtR exhibited the highest AUC value in both men (AUC = 0.680 [0.658-0.703]) and women (AUC = 0.747 [0.728-0.766]).

Variables		Crude		Adjustment	:	AUCs
		Р	OR	Р	OR	
Age		< 0.001	1.607 (1.472-1.755)	-	-	0.644 (0.622-0.666)
Anthr	opometrics					
	Body mass index	< 0.001	1.502 (1.375-1.641)	-	-	0.616 (0.592-0.640)
	Visceral adiposity index	< 0.001	1.358 (1.226-1.503)	< 0.001	1.299 (1.172–1.439)	0.626 (0.602-0.650)
	Height	< 0.001	0.840 (0.771-0.916)	0.770	1.015 (0.920-1.119)	0.553 (0.528-0.578)
	Weight	< 0.001	1.282 (1.177-1.398)	0.771	1.029 (0.849-1.247)	0.575 (0.551-0.600)
	Waist circumference	< 0.001	1.804 (1.640-1.983)	< 0.001	1.769 (1.472–2.127)	0.662 (0.639-0.685)
	Waist-to-height ratio	< 0.001	1.951 (1.770-2.150)	< 0.001	1.838 (1.513-2.233)	0.680 (0.658-0.703)
Bone	mineral density					
	Ward BMD	< 0.001	0.807 (0.738-0.882)	0.315	0.945 (0.847-1.055)	0.563 (0.538-0.587)
	Lumbar spine BMD	< 0.001	1.251 (1.148-1.364)	< 0.001	1.188 (1.083-1.304)	0.560 (0.535-0.585)
	Left rib BMD	< 0.001	1.237 (1.135–1.349)	0.002	1.156 (1.054-1.269)	0.568 (0.543-0.593)
	Right rib BMD	< 0.001	1.215 (1.115–1.323)	0.007	1.140 (1.037-1.252)	0.554 (0.528-0.579)
	Thoracic spine BMD	< 0.001	1.347 (1.238–1.465)	< 0.001	1.222 (1.118–1.336)	0.589 (0.564-0.613)
	Pelvis BMD	0.001	1.156 (1.062-1.258)	0.012	1.137 (1.029–1.256)	0.549 (0.524–0.573)
Fat m	ass					
	Trunk fat	< 0.001	1.612 (1.477-1.760)	< 0.001	1.436 (1.237-1.667)	0.643 (0.620-0.665)
	Left leg fat	0.600	1.023 (0.939-1.115)	< 0.001	0.639 (0.563-0.724)	0.506 (0.482-0.531)
	Right leg fat	0.317	1.045 (0.959–1.138)	< 0.001	0.657 (0.579-0.745)	0.513 (0.489-0.538)
	Body total fat	< 0.001	1.421 (1.304–1.549)	0.520	1.049 (0.907-1.214)	0.608 (0.584-0.631)
Muscl	e mass					
	Trunk muscle	< 0.001	1.346 (1.235-1.467)	< 0.001	1.375 (1.203-1.571)	0.583 (0.558-0.608)
	Left leg muscle	0.325	0.957 (0.878-1.044)	< 0.001	0.796 (0.703-0.902)	0.511 (0.485-0.536)
	Right leg muscle	0.160	0.940 (0.862-1.025)	< 0.001	0.773 (0.682-0.876)	0.514 (0.488-0.539)
	Body total muscle	0.010	1.119 (1.027-1.220)	0.977	1.002 (0.876-1.146)	0.533 (0.508-0.559)

Table 2. Associations of diabetes with anthropometrics, BMD, body fat and muscle mass in Korean men.

The results were obtained from the crude analysis and analyses adjusted for age and BMI using binary logistic regression analyses. AUC values were calculated by creating ROC curves using SPSS software. OR, odds ratio; AUC, area under the receiver operating characteristic curve.

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Discussion

T2DM is a representative metabolic disease associated with various diseases, such as hypertension [49,50], heart disease, stroke [51–53], kidney disease [54] and fracture [55–57]. In the present study, we identified the associations and the best indicator of T2DM among anthropometrics, BMD and body composition variables in Korean adults.

Our findings indicate that WC and WHtR are the best indicators of T2DM in Korean adults and showed that the power of general anthropometric indices for the identification of T2DM was better than those of BMD and body composition variable. The WC and WHtR are known as obesity indicators. Numerous studies have investigated the association of obesity indicators with T2DM and attempted to identify the best indicators of T2DM. As shown in the study by Tulloch-Reid and colleagues [9], BMI and WHtR are excellent predictors of T2DM risk in Pima Indians. Cabrera and colleagues [10] and Xu and colleagues [11] reported that WHtR was the main predictor of diabetes in approximately 5521 adults in the Canary Islands and was the best predictor for T2DM in approximately 7,567 Chinese adults aged 20–79 years. In recent studies by Zhang and colleagues and Mirzaei and colleagues [12,13], WHtR was also the best indicator of diabetes in approximately 1,185 adults aged 40–89 years in Southwest China and

Variables		Crude		Adjustment		AUCs
		Р	OR	Р	OR	
Age		< 0.001	2.134 (1.958-2.327)	-	-	0.720 (0.701-0.740)
Anthro	pometrics					
	Body mass index	< 0.001	1.715 (1.583–1.858)	-	-	0.661 (0.638-0.683)
	Visceral adiposity index	< 0.001	1.686 (1.567-1.814)	< 0.001	1.415 (1.313–1.524)	0.708 (0.687-0.728)
	Height	< 0.001	0.728 (0.670-0.790)	0.070	1.095 (0.993-1.207)	0.591 (0.568-0.613)
	Weight	< 0.001	1.389 (1.284-1.503)	0.068	1.182 (0.987-1.414)	0.596 (0.572-0.620)
	Waist circumference	< 0.001	2.305 (2.109-2.519)	< 0.001	2.465 (2.074-2.930)	0.730 (0.709-0.750)
	Waist-to-height ratio	< 0.001	2.494 (2.276-2.733)	< 0.001	2.390 (1.990-2.870)	0.747 (0.728-0.766)
Bone n	nineral density					
	Ward BMD	< 0.001	0.545 (0.497-0.599)	0.022	0.855 (0.748-0.970)	0.663 (0.640-0.685)
	Lumbar spine BMD	< 0.001	0.767 (0.706-0.835)	0.009	1.164 (1.038–1.304)	0.581 (0.559-0.604)
	Left rib BMD	< 0.001	0.794 (0.724-0.871)	0.744	1.019 (0.911-1.139)	0.567 (0.543-0.591)
	Right rib BMD	< 0.001	0.777 (0.713-0.847)	0.612	1.029 (0.922-1.148)	0.579 (0.555-0.602)
	Thoracic spine BMD	< 0.001	0.806 (0.738-0.881)	0.148	1.073 (0.975-1.180)	0.560 (0.537-0.583)
	Pelvis BMD	< 0.001	0.751 (0.688-0.820)	0.497	1.037 (0.933-1.154)	0.586 (0.563-0.610)
Fat ma	SS					
	Trunk fat	< 0.001	1.856 (1.710-2.015)	< 0.001	1.741 (1.480-2.047)	0.682 (0.660-0.703)
	Left leg fat	< 0.001	0.675 (0.616-0.740)	< 0.001	0.367 (0.321-0.419)	0.606 (0.582-0.630)
	Right leg fat	< 0.001	0.689 (0.629-0.754)	< 0.001	0.375 (0.329-0.428)	0.601 (0.576-0.625)
	Body total fat	< 0.001	1.407 (1.300-1.523)	0.005	0.793 (0.674–0.934)	0.603 (0.579–0.626)
Muscle	mass					
	Trunk muscle	< 0.001	1.483 (1.370-1.606)	< 0.001	1.628 (1.447-1.831)	0.605 (0.581-0.630)
	Left leg muscle	0.331	1.041 (0.960-1.130)	0.471	1.041 (0.933-1.161)	0.513 (0.489-0.537)
	Right leg muscle	0.394	1.036 (0.955-1.125)	0.713	1.021 (0.914-1.140)	0.509 (0.485-0.534)
	Body total muscle	< 0.001	1.300 (1.200-1.408)	< 0.001	1.345 (1.199–1.510)	0.573 (0.548-0.598)

Table 3. Associations of diabetes with anthropometrics, BMD, body fat and muscle mass in Korean women.

The results were obtained from the crude analysis and analyses adjusted for age and BMI using binary logistic regression analyses. AUC values were calculated by creating ROC curves using SPSS software. OR, odds ratio; AUC, area under the receiver operating characteristic curve.

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approximately 9,293 adults of Yazd City in Iran. According to Kodama and colleagues [8], Browning and colleagues [14], and Rådholm and colleagues [15] from the ADVANCE-ON study, WHtR might be an effective screening tool for diabetes. As another indicator of diabetes, WC was significantly associated with T2DM in the Henan Rural Cohort Study [16], in a cross-sectional study [17], and in 11,937 Korean adults [18]. The CVAI was strongly associated with T2DM in approximately 2,383 Chinese adults in a study by Wu and colleagues [20], and age had the greatest impact on diabetes in approximately 5,573 participants in Ghana, according to the study by Nawfal and colleagues [21]. Because body fat distribution is associated with T2DM [25,26], Vasan and colleagues showed that leg fat is strongly associated with T2DM [27]. Our finding was consistent with the results of previous studies [8–15], indicating that WC and WHtR had the strongest predictive power for T2DM.

In addition, diabetes affects bone metabolism [30–32]. We analyzed the association of T2DM with BMD, and our findings showed that T2DM was associated with the thoracic spine BMD in men, and ward BMD in women. Many studies have also shown that T2DM is associated with higher BMD and, paradoxically, with increased fracture risk [28–31]. According to Strotmeyer and colleagues [32], in 2,979 white and black men and women aged 70–79 years, T2DM was associated with higher hip BMD, and lower spine bone volume. Dennison and

colleagues [33] reported that the total femur and femoral neck BMD had a positive correlation with IR, with stronger results observed in women. As shown in the study by Vestergaard P [34], the BMD Z-score is increased in the spine and hip in patients with T2DM and the increase in fracture risk is higher and BMD is lower in participants with complications from diabetes. According to an analysis based on 15 observational studies of approximately 3,437 participants with diabetes and 19,139 control subjects by Ma and colleagues [36], significantly higher BMD of the femoral neck, hip and spine is observed in patients with T2DM. The BMD in the left femur and total hip was significantly greater in insulin-resistant women in a study by Arikan and colleagues [37]. In contrast, several studies have shown that diabetes affects bone loss [33,38]. According to an analysis of a 4-year change in BMD data from a cohort of white and black well-functioning men and women 70-79 years of age in a study by Dennison [33], white women with diabetes had more rapid bone loss at the femoral neck than women with a normal glucose metabolism. As shown by changes in the BMD data of 4,960 Canada women aged >40 years over a period of approximately 4.3 years in the study of Leslie and colleagues [38], diabetes was associated with a slightly greater BMD loss at the femoral neck but not at other measurement sites. In addition, participants with both T2DM and fracture have a low BMD [39,40]. In 150 older women with T2DM observed by Yamamoto and colleagues in Japan [39], prevalent vertebral fractures were associated with a lower, but not significantly different, lumbar spine BMD Z-score. In a study of 150 older women with T2DM in England by Patel and colleagues [40], participants with a previous fracture had lower lumbar-spine and total-hip BMD Z scores, but the differences were not statistically significant. As shown in a report analyzing data from the MrOS study [41], which enrolled 5,994 men aged \geq 65 years from March 2000 through April 2002 [42], T2DM is not associated with a higher prevalence or incidence of vertebral fractures in older men, and a higher spine BMD is associated with a lower prevalence and incidence of vertebral fractures in patients with T2DM. In men, our finding was consistent with the results of previous studies [34-37], indicating that the BMD was increased in various sites such as the hip, lumbar spine, and thoracic spine. However, in women, our finding contrasted with that of Arikan and colleagues [37], indicating that the BMD in the left femur and total hip was significantly greater in insulin-resistant women. Through the previous studies, we know that T2DM influences bone metabolism and fracture, but the correlation of T2DM with BMD remains inconsistent across studies.

Some studies have investigated gender differences in correlations between T2DM and obesity measures [8], such as BMI, WC, waist-to-hip ratio (WHR) and WHtR, as well as BMD. Our findings showed that various indices such as age, BMI, VAI, WHtR and body fat mass in patients with T2DM were significantly higher in women than in men, and the increase in WC was also higher in women than in men; however, the BMD was lower in women than in men, probably because of the older age of the women. According to the Henan Rural Cohort study of 38,466 participants aged 18–79 years conducted by Tian and colleagues [16], there are gender-specific differences between obesity measures and T2DM. In women, WC is independently associated with an increased risk of T2DM, regardless of BMI status, whereas both BMI and WC positively correlate with the risk of T2DM in men. Sallam and colleagues investigated the gender differences among participants with T2DM (64 men and 50 women) with and without cardiovascular disease (CVD) [17]. Age, body weight, BMI, and systolic blood pressure (SBP) were significantly higher in women with CVD than in participants without CVD. Rianon and colleagues reported that BMD was not altered for women with T2DM but was significantly higher in men with T2DM compared with men without diabetes, in approximately 149 Mexican American older men and women [41]. Our results support the findings from recent studies identifying gender differences in correlations of T2DM with WC, BMI, and BMD [16,17,41].

The present study had several limitations. First, cause-effect associations were difficult to determine because of the cross-sectional design. Second, our results were limited to Korean adults because we used data from the KNHANES in this study. Third, since KNHANES does not contain detailed information on medication use, a more precise analysis was not possible. Fourth, a large number of values were missing in the original data samples, resulting in the exclusion of a number of the samples during the sample selection process, and only 36.78% of samples were selected. Therefore, we were unable to conclude that the results of this paper represent the frequency of T2DM in Koreans. Fifth, the datasets from KNHANES may be affected by response bias because self-reported data from participants such as "the current use of antidiabetic medications or glucose-lowering drugs, or physician-diagnosed diabetes" are also used in the diagnosis of T2DM.

Conclusions

In the present study, we evaluated the associations of T2DM with anthropometrics, BMD, body fat mass and muscle mass in Korean adults. The WHtR in men and LL and RL fat in women displayed the strongest associations with T2DM, and the WC and WHtR in both men and women exhibited the highest predictive power for T2DM. Moreover, age, VAI, WC and WHtR exhibited greater predictive power in women than in men. Our findings provide clinical information that may identify patients with T2DM during initial screening steps. Further studies are needed to build a model for accurate identification based on a combination of BMD, anthropometric, and fat mass data.

Author Contributions

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Methodology: Bum Ju Lee.

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References

- Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011; 94(3):311–321. https://doi.org/10.1016/j. diabres.2011.10.029 PMID: 22079683
- Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes care. 2004; 27(5):1047–1053. https://doi.org/10.2337/diacare.27.5. 1047 PMID: 15111519
- Korean Diabetes Association. Diabetes Fact Sheet in Korea 2018. Korean Diabetes Association, Seoul, Korea; 2018.

- Pilon R, Bailey PH, Montgomery P, Bakker D. The future is the present: diabetes complication stories. J Nurs Healthc Chronic Illn. 2011; 3(3):234–244.
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care. 2014; 37(Supplement 1):S81–S90.
- 6. Korean Diabetes Association. Diabetes Fact Sheet in Korea 2013. Korean Diabetes Association, Seoul, Korea, 2013.
- 7. International Diabetes Federation (IDF), IDF Diabetes atlas 8th edition. 2017; International Diabetes Federation.
- Kodama S, Horikawa C, Fujihara K, Heianza Y, Hirasawa R, Yachi Y, et al. Comparisons of the strength of associations with future type 2 diabetes risk among anthropometric obesity indicators, including waist-to-height ratio: a meta-analysis. Am J Epidemiol. 2012; 176(11):959–969. https://doi.org/10.1093/ aje/kws172 PMID: 23144362
- Tulloch-Reid MK, Williams DE, Looker HC, Hanson RL, Knowler WC. Do measures of body fat distribution provide information on the risk of type 2 diabetes in addition to measures of general obesity?: comparison of anthropometric predictors of Type 2 diabetes in Pima Indians. Diabetes care. 2003; 26 (9):2556–2561. https://doi.org/10.2337/diacare.26.9.2556 PMID: 12941718
- de León AC, Coello SD, González DA, Díaz BB, Rodríguez JC, Hernández AG, et al. Impaired fasting glucose, ancestry and waist-to-height ratio: main predictors of incident diagnosed diabetes in the Canary Islands. Diabet Med. 2012; 29(3):399–403. <u>https://doi.org/10.1111/j.1464-5491.2011.03420.x</u> PMID: 21883429
- Xu Z, Qi X, Dahl AK, Xu W. Waist-to-height ratio is the best indicator for undiagnosed Type 2 diabetes. Diabet Med. 2013; 30(6):e201–e207. https://doi.org/10.1111/dme.12168 PMID: 23444984
- 12. Zhang F, Wan Q, Cao H, Tang L, Li D, Lü Q, et al. Identical anthropometric characteristics of impaired fasting glucose combined with impaired glucose tolerance and newly diagnosed type 2 diabetes: anthropometric indicators to predict hyperglycaemia in a community-based prospective cohort study in southwest China. BMJ Open. 2018; 8(5):e019735. https://doi.org/10.1136/bmjopen-2017-019735 PMID: 29743321
- Mirzaei M, Khajeh M. Comparison of anthropometric indices (body mass index, waist circumference, waist to hip ratio and waist to height ratio) in predicting risk of type II diabetes in the population of Yazd, Iran. Diabetes Metab Syndr. 2018; 12(5):677–682. <u>https://doi.org/10.1016/j.dsx.2018.04.026</u> PMID: 29680518
- Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0. 5 could be a suitable global boundary value. Nutr Res Rev. 2010; 23(2):247–269. https://doi.org/10.1017/S0954422410000144 PMID: 20819243
- Rådholm K, Chalmers J, Ohkuma T, Peters S, Poulter N, Hamet P, et al. Use of the waist-to-height ratio to predict cardiovascular risk in patients with diabetes: Results from the ADVANCE-ON study. Diabetes Obes Metab. 2018; 20(8):1903–1910. https://doi.org/10.1111/dom.13311 PMID: 29603537
- Tian Z, Li Y, Li L, Liu X, Zhang H, Zhang X, et al. Gender-specific associations of body mass index and waist circumference with type 2 diabetes mellitus in Chinese rural adults: The Henan Rural Cohort Study. J Diabetes Complications. 2018; 32(9):824–829. https://doi.org/10.1016/j.jdiacomp.2018.06.012 PMID: 30017434
- Sallam RM, Alayoubi SMZ, Al-Daghri NM, Alhammad AA, Alfadda AA. Gender-Specific profiles of cardiovascular disease in type 2 diabetes mellitus: A cross-sectional study. J Nat Sci Med. 2018; 1(2):74– 81.
- Lee BJ, Ku B, Nam J, Pham DD, Kim JY. Prediction of Fasting Plasma Glucose Status using Anthropometric Measures for Diagnosing Type 2 Diabetes. IEEE J Biomed Health Inform. 2014; 18(2):555–561 https://doi.org/10.1109/JBHI.2013.2264509 PMID: 24608055
- Stabe C, Vasques ACJ, Lima MMO, Tambascia MA, Pareja JC, Yamanaka A, et al. Neck circumference as a simple tool for identifying the metabolic syndrome and insulin resistance: results from the Brazilian Metabolic Syndrome Study. Clin Endocrinol (Oxf). 2013; 78(6):874–881.
- Wu J, Gong L, Li Q, Hu J, Zhang S, Wang Y, et al. A Novel Visceral Adiposity Index for Prediction of Type 2 Diabetes and Pre-diabetes in Chinese adults: A 5-year prospective study. Sci Rep. 2017; 7 (1):13784. https://doi.org/10.1038/s41598-017-14251-w PMID: 29062099
- Nawfal ES, Unson C, Okeke C, Abada E. Predictive Factors Associated With Hypertension Alone, Diabetes Alone And The Coexistence Of Both Among Adults In Ghana. International journal of scientific and technology research. 2017; 6(11):99–112.
- Lee BJ, Kim JY. Identification of Type 2 Diabetes Risk Factor using Phenotypes consisting of Anthropometry and Triglycerides based on Machine Learning. IEEE J Biomed Health Inform. 2016; 20(1):39– 46. https://doi.org/10.1109/JBHI.2015.2396520 PMID: 25675467

- Williams SR, Jones E, Bell W, Davies B, Bourne MW. Body habitus and coronary heart disease in men. A review with reference to methods of body habitus assessment. Eur Heart J. 1997; 18(3):376–393. https://doi.org/10.1093/oxfordjournals.eurheartj.a015258 PMID: 9076375
- Gastaldelli A. Abdominal fat: does it predict the development of type 2 diabetes? Am J Clin Nutr. 2008; 87(5):1118–1119. https://doi.org/10.1093/ajcn/87.5.1118 PMID: 18469227
- Ohlson LO, Larsson B, Svärdsudd K, Welin L, Eriksson H, Wilhelmsen L, et al. The influence of body fat distribution on the incidence of diabetes mellitus: 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes. 1985; 34(10):1055–1058. https://doi.org/10.2337/diab.34.10.1055 PMID: 4043554
- Carey VJ, Walters EE, Colditz GA, Solomon CG, Willet WC, Rosner BA, et al. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women: the Nurses' Health Study. Am J Epidemiol. 1997; 145(7):614–619. https://doi.org/10.1093/oxfordjournals.aje.a009158 PMID: 9098178
- Vasan SK, Osmond C, Canoy D, Christodoulides C, Neville MJ, Di Gravio C, et al. Comparison of regional fat measurements by dual-energy X-ray absorptiometry and conventional anthropometry and their association with markers of diabetes and cardiovascular disease risk. Int J Obes (Lond). 2018; 42 (4):850–857.
- Schwartz AV, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Study of Osteoporotic Fractures Research Group. Older women with diabetes have an increased risk of fracture: a prospective study. J Clin Endocrinol Metab. 2001; 86(1):32–38. https://doi.org/10.1210/jcem.86.1.7139 PMID: 11231974
- Strotmeyer ES, Cauley JA, Schwartz AV, Newman AB. Nontraumatic fracture risk with diabetes mellitus and impaired fasting glucose in older white and black adults: the health, aging, and body composition study. Arch Intern Med. 2005; 165(14):1612–1617 https://doi.org/10.1001/archinte.165.14.1612 PMID: 16043679
- McNair P, Madsbad S, Christensen MS, Christiansen C, Faber OK, Binder C, et al. Bone mineral loss in insulin-treated diabetes mellitus: studies on pathogenesis. Acta endocrinological. 1979; 90(3):463–472.
- McNair P, Christiansen C, Christensen MS, Madsbad S, Faber OK, Binder C, et al. Development of bone mineral loss in insulin-treated diabetes: a 1 1/2 years follow-up study in sixty patients. Eur J Clin Invest. 1981; 11(1):55–59. PMID: 6783430
- 32. Strotmeyer ES, Cauley JA, Schwartz AV, Nevitt MC, Resnick HE, Zmuda JM, et al. Diabetes is associated independently of body composition with BMD and bone volume in older white and black men and women: The Health, Aging, and Body Composition Study. J Bone Miner Res. 2004; 19(7):1084–1091. https://doi.org/10.1359/JBMR.040311 PMID: 15176990
- 33. Dennison EM, Syddall HE, Sayer AA, Craighead S, Phillips DIW, Cooper C. Type 2 diabetes mellitus is associated with increased axial bone density in men and women from the Hertfordshire Cohort Study: evidence for an indirect effect of insulin resistance? Diabetologia. 2004; 47(11):1963–1968. https://doi. org/10.1007/s00125-004-1560-y PMID: 15565368
- 34. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. Osteoporos Int. 2007; 18(4):427–444. <u>https://doi.org/10.1007/s00198-006-0253-4 PMID: 17068657</u>
- Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. JAMA. 2011; 305(21):2184– 2192. https://doi.org/10.1001/jama.2011.715 PMID: 21632482
- Ma L, Oei L, Jiang L, Estrada K, Chen H, Wang Z, et al. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. Eur J Epidemiol. 2012; 27(5):319– 332. https://doi.org/10.1007/s10654-012-9674-x PMID: 22451239
- Arikan S, Tuzcu A, Bahceci M, Ozmen S, Gokalp D. Insulin resistance in type 2 diabetes mellitus may be related to bone mineral density. J Clin Densitom. 2012; 15(2):186–190. https://doi.org/10.1016/j. jocd.2011.11.005 PMID: 22321655
- Leslie WD, Morin SN, Majumdar SR, Lix LM. Effects of obesity and diabetes on rate of bone density loss. Osteoporos Int. 2018; 29(1):61–67. https://doi.org/10.1007/s00198-017-4223-9 PMID: 28917003
- Yamamoto M, Yamaguchi T, Yamauchi M, Kaji H, Sugimoto T. Bone mineral density is not sensitive enough to assess the risk of vertebral fractures in type 2 diabetic women. Calcif Tissue Int. 2007; 80 (6):353–358. https://doi.org/10.1007/s00223-007-9003-7 PMID: 17549536
- Patel S, Hyer S, Tweed K, Kerry S, Allan K, Rodin A, et al. Risk factors for fractures and falls in older women with type 2 diabetes mellitus. Calcif Tissue Int. 2008; 82(2):87–91. https://doi.org/10.1007/ s00223-007-9082-5 PMID: 18175036
- 41. Rianon N, Ambrose CG, Buni M, Watt G, Reyes-Ortiz C, Lee M, et al. Trabecular Bone Score Is a Valuable Addition to Bone Mineral Density for Bone Quality Assessment in Older Mexican American

Women With Type 2 Diabetes. J Clin Densitom. 2018; 21(3):355–359. https://doi.org/10.1016/j.jocd. 2018.02.004 PMID: 29685494

- Napoli N, Schwartz AV, Schafer AL, Vittinghoff E, Cawthon PM, Parimi N, et al. Vertebral fracture risk in diabetic elderly men: the MrOS study. J Bone Miner Res. 2018; 33(1):63–69. <u>https://doi.org/10.1002/jbmr.3287 PMID: 28861910</u>
- **43.** Ministry of Health and Welfare of Korea, Korea Centers for Disease Control and Prevention. The Fourth Korea National Health and Nutrition Examination Survey Data User Guide (KNHANES IV), 2007–2009. Korea Centers for Disease Control and Prevention. Korea, 2009.
- 44. Ministry of Health and Welfare of Korea, Korea Centers for Disease Control and Prevention. The Fifth Korea National Health and Nutrition Examination Survey Data User Guide (KNHANES V), 2010–2012. Korea Centers for Disease Control and Prevention. Korea, 2012.
- 45. Kweon S, Kim Y, Jang MJ, Kim Y, Kim K, Choi S, et al. Data resource profile: the Korea National Health and Nutrition Examination Survey (KNHANES). Int J Epidemiol. 2014; 43:69–77. <u>https://doi.org/10.1093/ije/dyt228 PMID: 24585853</u>
- Centers for Disease Control and Prevention. National Diabetes Statistics Report. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services. US, 2017.
- Fan T, Fedder DO, Koro CE, Bowlin SJ, Ethnic disparities and trends in glycemic control among adults with type 2 diabetes in the U.S from 1988 to 2002. Diabetes Care. 2006; 29(8):1924–1925 <u>https://doi.org/10.2337/dc05-2238 PMID: 16873805</u>
- Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral adiposity index (VAI): a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes care. 2010; 33(4):920–922. https://doi.org/10.2337/dc09-1825 PMID: 20067971
- 49. Daly B, Toulis KA, Thomas N, Gokhale K, Martin J, Webber J, et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: A population-based cohort study. PLoS Med. 2018; 15(1):e1002488. https://doi.org/10.1371/journal.pmed.1002488 PMID: 29337985
- He Q, Dong M, Pan Q, Wang X, Guo L. Correlation between changes in inflammatory cytokines and the combination with hypertension in patients with type 2 diabetes mellitus. Minerva Endocrinol. 2018. https://doi.org/10.23736/S0391-1977.18.02822–5
- Ryde L, Berne C, Cosentino F, Danchin N, Escaned J, Hammes HP, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2013; 34(39):3035–3087. https://doi.org/10.1093/eurhearti/eht108 PMID: 23996285
- Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol. 2015; 3(2):105–113. https://doi.org/10.1016/S2213-8587(14)70219-0 PMID: 25466521
- Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ. 2006; 332(7533):73–78. <u>https://</u> doi.org/10.1136/bmj.38678.389583.7C PMID: 16371403
- 54. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: US department of health and human services, centers for disease control and prevention. 2011; 201(1).
- Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol. 2007; 166:495–505. <u>https://doi.org/10.1093/aje/kwm106</u> PMID: 17575306
- 56. Janghorbani M, Feskanich D, Willett WC, Hu F. Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. Diabetes Care. 2006; 29:1573–1578. https://doi.org/10.2337/dc06-0440 PMID: 16801581
- Leslie WD, Lix LM, Prior HJ, Derksen S, Metge C, O'Neil J. Biphasic fracture risk in diabetes: a population-based study. Bone. 2007; 40(6):1595–1601. https://doi.org/10.1016/j.bone.2007.02.021 PMID: 17392047