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Original Article

Obesity, Leukocytes, and High-Sensitivity C-Reactive Protein Biomarkers Associated with Type 2 Diabetes Mellitus in South Korean Adults

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Abstract

Background: Type 2 diabetes (T2DM), a chronic disease, is associated with obesity and inflammation. This study investigated the effects of body mass index (BMI), leukocytes, and high-sensitivity C-reactive protein (hs-CRP) on type 2 diabetes mellitus in South Korean adults.

Methods: Secondary analysis of data from 5,420 adults' subject in the Korea National Health and Nutrition Examination Survey (KNHANES VII-3, 2018) was performed. The collected data were analyzed by n (%), mean ± SD, *t*-test, $\chi 2$ -test, and multiple logistic regression methods.

Results: BMI and leukocytes count were higher in the T2DM-diagnosed group. The probability of T2DM increased by 4.76 times for obesity compared to normal weight, but high obesity was not an influencing factor for T2DM. As the leukocytes increased, the probability of T2DM increased by 1.15 times. However, hs-CRP was not an influencing factor for T2DM. Age was higher in the T2DM-diagnosed group and appeared to be an influencing factor in T2DM.

Conclusion: Obesity and inflammation indicators, including WBC, appeared to be risk factors for T2DM. This study presented the basis of diet and exercise interventions for weight loss and white blood cell count in a T2DM prevention and management program.

Keywords: Body mass index; Leukocytes; C-reactive protein; Type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is related to Body Mass Index (BMI) and the prevalence of T2DM continues to increase (1) and by 2035, it is expected to affect 10% globally (2). The prevalence of adult T2DM in Korea is 10.4% (3). Obesity has continuously increased and has more than doubled the prevalence rate in adults over the past 20 years (4). Obesity causes insulin resistance, which is a predictor of T2DM and reduces the ability of insulin (5). In other words, adipose tissue increases insulin resistance and causes T2DM (6).

Obesity is an influencing factor for T2DM, and Body mass index (BMI) is generally used as a

standard for measuring obesity (7). BMI is positively correlated with fasting blood glucose and glycated hemoglobin, a T2DM diagnostic index because fat tissue increases the T2DM (6). WHO classified BMI≥30kg/m² is as obesity (7). Since this is a classification for Western population, it is not suitable for application to Asians (8). For Asians, BMI≥25kg/m² was suggested as obesity (9), and this study applied it as a criterion for obesity.

Obesity is related with inflammatory markers such as leukocytes (10), and C-reactive protein (CRP) (11). Obesity is a factor that affects leukocytosis (12, 13). The level of CRP, one of the earliest markers detected in inflammatory conditions, is also high in obesity (14), this is due to the increased secretion of CRP in the liver (11). Low-grade inflammation due to obesity can increase the prevalence of T2DM (15) and leukocytes causes complications such as impaired glucose tolerance (IGT) (16,17). In patients with T2DM, hs-CRP was found to be elevated because of CRP-induced insulin resistance (18). Therefore, the increase in WBC and CRP associated with obesity is clinically important because it affects chronic diseases such as T2DM.

Previous studies have reported associations between obesity and inflammation (10-14) and between obesity and diabetes (5, 6, 8). Inflammation indicators such as WBC (16,17) and CRP (18, 19) were associated with diabetes risk predictors. This was mostly a study of foreigners. However, T2DM is increasing in South Koreans, and there is an urgent need to prevent and manage diabetes by investigating the effects of inflammation and obesity on diabetes. Despite this importance, studies that confirm the effects of inflammatory indicators on T2DMs in Koreans are insufficient.

Therefore, this study verified the effect of BMI on diabetes. Particularly, given the increase of high obesity, it is classified as obesity (25–29.9kg/m²) and high obesity (BMI≥30kg/m²). Additionally, we verified the effects of WBC and hs-CRP, inflammation indicators that are positively correlated with obesity, on T2DM. Particularly, CRP is an indicator of inflammation in acute inflammation, whereas inflammation associated with obesity is a chronic inflammatory condition; therefore, hs-CRP, measured in a low range of 15mg/L or less, was used (19). The seventh Korea National Health and Nutrition Examination Survey is an appropriate sample because it is a large-scale data surveyed across the country.

We investigated the effects of BMI, leukocytes, and hs-CRP on T2DM in Korean adults and provided fundamental data on Korean adults for T2DM prevention and management programs.

Methods

Study population

This study is a descriptive survey study and was conducted with adults over the age of 19 who participated in the KNHANES VII-3 2018 survey. The KNHANES VII-3 2018 survey consisted of a questionnaire survey and health examination, the survey method was well described in previous studies (20) . Of the 7992 participants, those who were below 19 yr (1503) or had missing data (1069) were excluded. Finally, 5,420 participants were included and divided into groups based on T2DM diagnosis: T2DM-diagnosed group (n=500, weighted 7.3%) and non-T2DM group (n=4920, weighted 92.7%) (Fig. 1).

Measuring Methods

The general characteristics included age, sex, and level of education. T2DM characteristics were investigated by age onset of T2DM, current T2DM status, ongoing treatment, and T2DM diagnosis. Whether the subject suffered from T2DM was investigated by the question, 'Have you ever been diagnosed with T2DM by a doctor in your lifetime?' About 7.3% of respondents answered 'yes' while 92.7% answered 'no.'

BMI measured the height and weight of participants in light clothing after fasting overnight for at least 8 hours. In this study, BMI was classified into underweight (less than 18.5 kg/m²), normal weight (18.5 ~ 24.9 kg/m²), obesity (25.0 ~ 29.9 kg/m²), and high obesity (more than 30 kg/m²) (9).

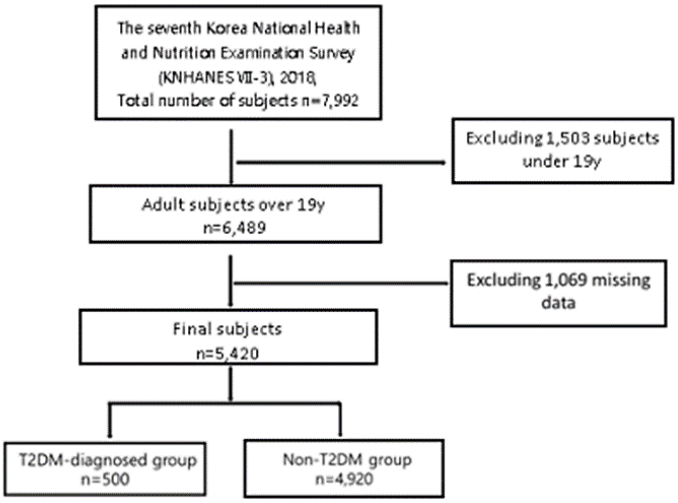

Fig. 1: A flow chart for study population

Blood samples were taken from the median cubital vein after fasting for at least 8 hours. Leukocytes were measured by laser flow cytometry and hs-CRP was measured by immune-turbidity (XN9000Sysmex, Japan).

Data analysis

The data in this study consisted of a complex sampling design. Group comparisons between the diagnosed with T2DM and non-T2DM groups were analyzed using *t*-test and $\chi 2$ tests for general characteristics, BMI, leukocytes and hs-CRP levels. Factors influencing T2DM were analyzed by multiple logistic regression. The adjusted odds ratio and 95% CI for each variable were calculated as dependent variables for T2DM diagnosis (SPSS win. 26.0 software, IBM Corp., Armonk, NY, USA).

Ethical approval

The KNHANES VII-3 survey data used in this study was approved by the Institutional Review Board (IRB; 2018-01-03-P-A), and personal information was coded with a serial number to ensure the anonymity of the subject.

Results

General characteristics of T2DM-diagnosed and non-T2DM groups

Participants age was 63.88 yr in the T2DM-diagnosed group and 46.35 yr in the non-T2DM group (t=21.059, *P*<.001). Regarding age, the most prevalent age group in the T2DM-diagnosed group was >65 yr (50.2%), while the most prevalent age group in the non-T2DM group was 35-50 yr (31.8%). The difference in T2DM prevalence according to age was significant (*P*<.001).

Regarding sex, males (55.4%) were more than females (44.6%) in the T2DM diagnosis group, while males (51.7%) were more than females (48.3%) in the non-T2DM group. The difference in T2DM prevalence according to sex was not significant (*P*=.221).

Concerning the education level, the T2DM-diagnosed group had the highest number of elementary school graduates or less (36.6%), while the non-T2DM group had the highest number of college graduates or over (43.2%). The difference in T2DM prevalence according to level of education was significant (*P*<.001).

In the T2DM-diagnosed group, the age of onset was the highest at 50–59 yr (36.3%), the present T2DM status was 96.6%, and the current treatment was 93% (Table 1).

Table 1: General Characteristics of T2DM-diagnosed and non-T2DM groups (N=5,420)

Variables	*T2DM-diagnosed group N=500 7.3%(0.4%) unweighted(N) weighted% (SE%)*	*Non-T2DM group N=4920 92.7%(0.4%) unweighted(N) weighted% (SE%)*	*t/χ2 (P-value)*
Age(years, mean ± SD)	63.88±0.77	46.35±0.40	21.059 (<.001)
19~34	4	1030	3445.883
	1.8(1.0)	28.4(1.1)	(<.001)
35~50	43	1460	
	11.6(2.0)	31.8(1.1)	
51~64	160	1351	
	36.4(2.7)	25.6(0.9)	
Over 65	293	1079	
	50.2(2.9)	14.2(0..8)	
Sex			
Male	259	2211	2.008
	55.4(2.8)	51.7(0.7)	(.221)
Female	241	2709	
	44.6(2.8)	48.3(0.7)	
Education level			
Below elementary school	196	797	255.306
	36.6(3.0)	11.9(0.8)	(<.001)
Middle school graduate	87	439	
	16.0(1.9)	7.8(0.5)	
High school graduate	137	1630	
	32.3(2.6)	37.0(1.1)	
Over college graduate	63	1886	
	15.1(2.2)	43.2(1.4)	
Age of onset(year)			
*22-39	51		
	12.1(1.9)		
40-49	77		
	17.8(2.0)		
50-59	179		
	36.3(2.6)		
60-69	129		
	22.1(2.2)		
Over 70	64		
	11.7(11.7)		
N/A	4920		
	100(0.0)		
Present T2DM status			
No	13		
	3.4(1.2)		
Yes	487		
	96.6(1.2)		
N/A	4920		
	100(0.0)		
Present treatment			
No	31		
	7.0(1.5)		
Yes	469		
	93.0(1.5)		
N/A	4920		
	100(0.0)		

* The first age of T2DM diagnosis:22year, T2DM: Type 2 diabetes mellitus

BMI, leukocytes, and hs-CRP in the T2DM-diagnosed and non-T2DM Groups

The participants' BMI was higher in the T2DM-diagnosed group (25.12) than in the non-T2DM group (24.07; t=4.949, *P*=.026). Regarding the BMI classification, obesity was 39.7% and high obesity was 8.2% in the T2DM-diagnosed group. While in the non-T2DM group, obesity was 30.2% and high obesity was 5.9%. The difference in T2DM prevalence according to BMI was significant (*P*<.001).

The leukocytes were higher in the T2DM-diagnosed group (6.735) than in the non-T2DM group (6.234). The difference in T2DM prevalence according to WBC count was significant (*P*<.001).

The hs-CRP levels in the T2DM-diagnosed and non-T2DM groups were 1.23 mg/L and 1.12 mg/L, respectively. The difference in the prevalence of T2DM according to hs-CRP level was not significant (*P*=.081) (Table 2).

Table 2: BMI, WBC, and hs-CRP in the T2DM-Diagnosed and non-T2DM Groups (N=5420)

Variables	*T2DM-diagnosed group N=500 7.3%(0.4%) unweighted(N) weighted%(SE%)*	*Non-T2DM group N=4920 92.7%(0.4%) unweighted(N) weighted%(SE%)*	*t/χ2 (P-value)*
BMI(kg/m², mean ± SD)	25.12±0.17	24.07±0.06	4.949 (.026)
Low weight (<18.5)	2 0.2(0.2)	159 3.4(0.3)	30.065 (<.001)
Normal weight (18.5-24.9)	253 51.9(2.7)	3016 60.4(0.9)	
Obesity (25-29.9)	200 39.7(2.5)	1477 30.2(0.9)	
High obesity(≥30)	45 8.2(1.5)	268 5.9(0.5)	
WBC(Thous/uL, mean ± SD)	6.73±0.11	6.23±0.03	6.522 (<.001)
hs-CRP(mg/L, mean ± SD)	1.23±0.10	1.12±0.03	1.745 (.081)

T2DM: Type 2 diabetes mellitus, BMI: body mass index, WBC: white blood cell, hs-CRP: high sensitivity C-reactive protein

Predictive variables for T2DM

Factors influencing T2DM were BMI, leukocytes, age and education level (Table 3). In the BMI classification, the occurrence of T2DM increased in obese participants by 4.76-fold (95% CI 3.26 to 24.35; *P*<.001). In high-obese participants, T2DM increased 1.37-fold (95% CI 0.06 to 1.48; *P*=.329); however, this value was not significant. As the leukocytes increased, the occurrence of T2DM increased1.15-fold (95% CI 0.08 to 1.22; *P*<.001).

Regarding age, the occurrence of T2DM was 12.49-fold (95% CI 7.56 to 25.35; *P*<.001) in the 35–50 yr age group, 9.66-fold (95% CI 6.39 to 14.61; *P*<.001) in the 51–64 yr age group and 2.48-fold (95% CI 1.90 to 3.23; *P*<.001) in the 65 yr or older age group compared with the 19–34 yr age group.

Concerning the education level, the probability of T2DM occurrence was 0.11-fold lower (95% CI 0.07 to 0.16; *P*<.001) in the middle school graduate group, 0.16-fold lower (95% CI 0.11 to 0.25; *P*<.001) in the high school graduate group, and 0.39-fold lower (95% CI 0.27 to 0.56; *P*<.001) in the college graduate or above group compared with the below elementary school group.

Table 3: Predictive variables for T2DM (N=5420)

Variable	*Category*	*AOR† (95% CI)*	*P-value*
BMI (kg/m²)	Low weight (<18.5)	1.95(1.51-2.51)	<.001
	Normal weight(18.5~24.9)(reference)		
	Obesity (25~29.9)	4.76(3.26-24.35)	<.001
	High obesity(≥30)	1.13(0.06-1.48)	.329
	WBC (Thous/uL)	1.15(1.08-1.22)	<.001
	hs-CRP (mg/L)	1.03(0.98-1.08)	.230
Age (yr)	19~34 (reference)		
	35~50	12.49(7.56-25.35)	<.001
	51~64	9.66(6.39~14.61)	<.001
	Over 65	2.48(1.90~3.23)	<.001
Sex	Male (reference)		
	Female	0.86(0.67~1.09)	.222
Education level	Below elementary school(reference)		
	Middle school graduate	0.11(0.07~0.16)	<.001
	High school graduate	0.16(0.11~0.25)	<.001
	Over college graduate	0.39(0.27~0.56)	<.001

†AOR and p values were from a multiple logistic regression model adjusted for age, sex and education level.
AOR: adjusted odds ratio, CI: confidence intervals, BMI: body mass index, WBC: white blood cell, hs-CRP: high sensitivity C-reactive protein

Discussion

This study identified the effects of BMI, leukocytes, and hs-CRP on T2DM in South Korean adults. In this study, BMI was higher in the T2DM-diagnosed group and appeared to be an influencing factor in T2DM; the probability of T2DM increased 4.76 times among obese participants. However, high obesity (≥30 kg/m²) was not a predictor of T2DM. The BMI increase has a high prevalence of T2DM (8). In the case of obesity, a large amount of insulin is produced, which reduces the function of β cells that produce insulin. It further leads to insulin resistance, which causes T2DM (5). Moreover, obesity increases inflammation, and inflammation increases insulin resistance (4, 6). Adipocytokines released from adipose tissue affect the WBC count and interferes with their functioning (16).

Inflammation is considerably elevated in high-obese people (BMI >30kg/m²) (10). It causes insulin resistance, especially in cells with insulin-dependent glucose transport and the consequent development of diabetes (16,17). High obesity is not an influencing factor for T2DM, which is different from our study results (10, 16, 17).

Several studies (6, 21) do not distinguish between obesity and high obesity, thereby limiting comparisons with the present study results. Additionally, the number of participants with high obesity (5.7%) was relatively small compared to the number of participants with obesity (30.9%). Therefore, there are limits to generalizing the results of this study.

Lnfluencing factor in T2DM; the probability of T2DM increased by 1.15 times. Leukocytes were higher in T2DM, and significant correlations between BMI and CRP concentrations were observed (22). When the leukocytes increased by 1,000 cells/mm^3, the risk of T2DM increased by 7.6%. Additionally, obese participants with relatively low leukocytes had a significantly lower risk

for T2DM than those with high levels of leukocytes (23); after adjusting for age and sex, leukocytes were independently related to BMI (22). Since chronic inflammation in obese subjects is the cause of insulin resistance (5), it is necessary to incorporate novel inflammatory markers into the diabetes risk-prediction model (8). Indeed, a meta-analysis found a positive association with increased leukocytes, CRP and T2DM occurrence (14).

There was no difference in hs-CRP levels between the T2DM diagnostic group and the non-T2DM group. Therefore, hs-CRP was not an influencing factor for T2DM. In another study of the T2DM diagnostic and non-diagnostic groups, CRP was not related to T2DM incidence, and CRP was not a factor influencing T2DM even after adjustment for confounding factors (24). The same results were found in this study. However, obesity interacted between CRP and T2DM, resulting in an increase in CRP in T2DM patients (21). Because elevated CRP induces insulin resistance (25).

The inflammation score based on CRP, leukocytes, and interleukin-6 (IL-6) predicted diabetes in Whites but not in African Americans (26). In China (27) and Korea (21), the CRP level of T2DM patients was high, and CRP was reported as an independent predictor of T2DM. The CRP levels and incidence of T2DM related to each race were different. After adjusting for age, sex, race, and parental diabetes and hypertension history, CRP and IL-6 levels had a positive relationship with T2DM. However, after additional adjustments for obesity indexes, glucose, and insulin, only IL-6 level was associated significantly with incident diabetes (26).

The inflammation index CRP and incidence of DM differed according to race and adjustment variables. Accordingly, a study is needed to identify differences according to race by applying the same adjustment variables.

In this study, age was higher in the T2DM-diagnosed group and appeared to be an influencing factor in T2DM. The probability of T2DM increased with age, but sex was not an influencing factor for T2DM. In Korea, CRP and T2DM risks were found to be significantly associated only in the elderly group (over 50 yr) but not in young men and women (21). In women aged 55-74 yr, CRP levels were high and the prevalence of T2DM was increased (28).

After adjusting age, socioeconomic and educational status, and lifestyle and metabolic parameters, increased CRP were related with increased T2DM. Although higher CRP levels were found in men, the relationship between CRP and T2DM was more pronounced in women (21). Another study, high CRP in both men and women was associated with T2DM (29). In another study, women with high CRP levels are CRP levels T2DM has increased compared to lower women (30). This is because the women's sex hormones and high body fat rate (29). CRP levels vary depending on age, socioeconomic status, education, smoking, alcohol consumption, etc. Additionally, depending on the adjusted variable, the effect of sex on the increased risk of T2DM may be different (21).

This study described the effects of BMI and inflammatory factors, including leukocytes, on T2DM in South Korean adults. This study provides the basis for an intervention program for the prevention of T2DM.

Conclusion

BMI and leukocytes were higher in the T2DM-diagnosed group. Unlike high obesity, obesity appeared to be an influencing factor in T2DM. Leukocytes appeared to be an influencing factor in T2DM, but hs-CRP was not an influencing factor for T2DM. Obesity and leukocytes have been shown to affect the probability of T2DM. BMI should be considered when diagnosing T2DM. It is also necessary to include interventions for diet and exercise for weight loss and leukocytes in T2DM prevention and management programs.

Obesity and leukocytes in South Korean adults are factors affecting T2DM. The inflammation index CRP and incidence of T2DM were different according to race, genetic factors, and ad-

justment variables. Accordingly, it is necessary to identify differences according to race and genetic factors by applying the same adjustment variables and classifying BMI to include obesity and high-obesity to identify differences according to obesity level.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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