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REGULAR ARTICLE

Serum triglyceride levels in relation to high-density lipoprotein cholesterol (TG-HDL) ratios as an efficient tool to estimate the risk of sleep apnea syndrome in non-overweight Japanese men

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Abstract
Objectives Several studies have reported the association between sleep apnea syndrome and insulin resistance. Being overweight is known risk factor both for sleep apnea syndrome and insulin resistance. However, no studies have reported on the association between serum triglyceride levels in relation to high-density lipoprotein cholesterol (TG-HDL) ratios (a marker of insulin resistance) and sleep apnea syndrome accounting for body mass index (BMI) status.
Methods Subjects for the present cross-sectional study consisted of 1,528 men aged 30–69 years undergoing pulse oximetry at a sleep disorders clinic for sleep apnea syndrome. Sleep apnea syndrome was diagnosed as a 3 % oxygen desaturation index (ODI) of ≥15 events/h.
Results Among study participants, 241 men were diagnosed with sleep apnea syndrome. Independent of classical cardiovascular risk factors, TG-HDL was significantly positively associated with sleep apnea syndrome in participants with a BMI <25 kg/m^2, but not in participants with a BMI ≥25 kg/m^2. The multivariable adjusted odds ratio (OR) and 95 % confidence interval (95 % CI) of sleep apnea syndrome per Log TG-HDL was 2.03 (95 % CI: 1.36–3.03) for a BMI <25 kg/m^2 and 1.23 (95 % CI: 0.89–1.70) for a BMI ≥25 kg/m^2.
Conclusions An independent positive association between TG-HDL levels and risk of sleep apnea syndrome was observed in participants with a BMI of <25 kg/m^2, but not in participants with a BMI ≥25 kg/m^2. TG-HDL levels could be an efficient tool to estimate the risk of sleep apnea syndrome in non-overweight Japanese men.

Keywords Triglycerides · HDL-cholesterol · Sleep apnea syndrome · Non-overweight

Introduction

Recently, numerous studies have reported an independent association between insulin resistance and sleep apnea syndrome [1–5].

On the other hand, a high TG-HDL cholesterol ratio (TG-HDL) has been found to indicate insulin resistance in the general population [6].

However, no studies have reported on the association between TG-HDL and sleep apnea syndrome.

Furthermore, a previous Japanese study on sleep apnea syndrome reported a significant correlation between apnea index (AI) and body mass index (BMI), with the former being higher in participants with a BMI ≥25 kg/m^2 than in participants with a BMI <25 kg/m^2 [7]. Another study reported a strong association between BMI and insulin resistance [8]. Therefore, the association between TG-HDL and sleep apnea syndrome should account for BMI status.

To investigate these associations, we conducted a cross-sectional study of Japanese men undergoing screening for sleep apnea syndrome.

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Materials and methods

Study populations

The survey population comprised 1,558 men aged 30–69 referred for pulse oximetry at a sleep disorders clinic (Inoue Hospital, Nagasaki, Japan) from June 2012 to May 2013. Those from whom data (30) were not available were excluded, leaving 1,528 subjects participating in this study.

Data collection and laboratory measurements

Trained interviewers obtained information on medical history. Fasting blood samples were also obtained. Serum triglyceride (TG), serum HDL-cholesterol, serum aspartate aminotransferase (AST), serum alanine transaminase (ALT), serum γ-glutamyltranspeptidase (γ-GTP), serum creatinine, and fasting blood sugar were measured using standard laboratory procedures. Glomerular filtration rate (GFR) was estimated using an established method proposed by a working group of the Japanese Chronic Kidney Disease Initiative [9]. A pulse oximeter (PULSOX-Me300, KONICA MINOLTA, INC, Osaka, Japan) was used to measure 3 % oxygen desaturation index (ODI), and sleep apnea syndrome was diagnosed as a 3 % ODI of ≥15 events/h, as described in a previous study [10], since a 3 % ODI ≥15 events/h was considered equivalent to an apnea-hypopnea index (AHI) ≥20 events/h as determined by PSG, with a recommendation for treatment with CPAP for subjects showing AHI ≥20 events/h [11–13].

Statistical analyses

Differences in age-adjusted mean values or prevalence of potential confounding factors by TG-HDL quartile were calculated using covariance or generalized linear models, and logistic regression models were used for calculating odds ratios (OR) and 95 % confidence intervals (CI) to determine the association between sleep apnea syndrome and TG-HDL. In addition, subjects were stratified by BMI status. Because TG-HDL had a skewed distribution, logarithmic transformation was performed for calculating OR and 95 % CI to determine the association between sleep apnea syndrome and TG-HDL.

Three different approaches were used to make adjustments for confounding factors. First, data were adjusted only for age (Model 1). Next, further adjustment was made BMI (Model 2). Finally, other potential confounding factors were included, such as smoking status (never-smoker, former smoker, current smoker), alcohol consumption [non-drinker, current light drinker (<23 g/week), current moderate drinker (23–68 g/week), current heavy drinker (≥69 g/week)], systolic blood pressure, antihypertensive medication use, antidiabetic medication use, antihyperlipidemic medication use, serum aspartate aminotransferase (AST), serum γ-glutamyltranspeptidase (γ-GTP), fasting blood sugar, and glomerular filtration rate (GFR) (Model 3). Although diastolic blood pressure and ALT are known cardiovascular risk factors, they were not analyzed as confounding factors, since interaction between systolic blood pressure and diastolic blood pressure was $r = 0.87$, ($p < 0.001$), and interaction between AST and ALT was $r = 0.80$ ($p < 0.001$).

All statistical analyses were performed with the SAS system for Windows (version 9.3; SAS Inc., Cary, NC). p values < 0.05 were regarded as being statistically significant.

Ethical considerations

This study was approved by the Ethics Committee for Human Use of Nagasaki University (project registration number 15033077). Written consent forms were available in Japanese to ensure comprehensive understanding of the study objectives, and informed consent was provided by the participants.

Results

Characteristics of the study populations

Among the survey population comprised of 1,528 men, 971 had a BMI <25 k/m^2 and 557 had a BMI ≥25 kg/m^2.

Table 1 shows the age-adjusted characteristics of the study populations for total subjects stratified by BMI status.

We also found that participants with a BMI ≥25 kg/m^2 had significantly higher values for fasting blood sugar and TG-HDL than participants with a BMI <25 kg/m^2. Age-adjusted values for fasting blood sugar were 100 and 107 in patients with a BMI <25 kg/m^2 and a BMI ≥25 kg/m^2, respectively ($p < 0.001$); and for TG-HDL were 2.06 and 3.26 in patients with a BMI <25 kg/m^2 and a BMI ≥25 kg/m^2, respectively ($p < 0.001$).

Associations between TG-HDL and sleep apnea syndrome

Table 2 shows the associations between TG-HDL and sleep apnea syndrome in total subjects stratified by BMI status. For total subjects, with the lowest quartile of TG-HDL as reference group, the age-adjusted OR of sleep apnea syndrome for the highest quartile of TG-HDL was 5.63 (95 % CI: 3.48–9.10). After further adjustment for BMI, this association slightly weakened but remained

Table 1 Age-adjsuted mean values of patient characteristics according TG-HDL levelquar tiles

Parameters	Total subjects					BMI <25kg/m^2					BMI <25kg/m^2				*p*
	TG-HDL ratios				*p*	TG-HDL ratios				*p*	TG-HDL ratios				
	Q1 (low)	Q2	Q3	Q4 (high)		Q1 (low)	Q2	Q3	Q4 (high)		Q1 (low)	Q2	Q3	Q4 (high)	
No. at risk	382	382	382	382		331	261	218	161		51	121	164	221	
Age, years	48.9 ± 9.8	49.4 ± 8.9	48.5 ± 9.3	48.1 ± 8.4		48.7 ± 9.9	49.2 ± 9.1	48.8 ± 9.5	49.6 ± 8.4		50.6 ± 8.8	49.9 ± 8.4	48.0 ± 9.0	47.1 ± 8.3	
3 % ODI	6.68	8.77	9.41	12.19	<0.001	5.92	6.59	7.43	8.50	<0.001	11.89	13.52	12.02	14.83	0.084
Body mass index (BMI), kg/m^2	22.3	24.1	24.8	25.9	<0.001	21.7	22.4	22.8	23.1	<0.001	26.7	27.7	27.5	27.9	0.008
Systolic blood pressure, mmHg	126	129	129	130	<0.001	125	126	125	127	0.389	132	134	133	132	0.749
Diastolic blood pressure, mmHg	79	81	82	83	<0.001	78	79	79	80	0.108	84	85	86	85	0.840
Current drinker, %	78.2	78.3	75.5	70.6	0.043	78.6	79.6	78.0	72.6	0.360	75.3	75.3	72.1	69.4	0.644
Current smoker, %	22.6	27.6	34.4	42.1	<0.001	22.9	28.8	35.3	40.5	<0.001	22.2	25.6	33.3	42.6	0.002
Antihypertensive medication use, %	13.1	16.6	16.0	19.0	0.151	11.5	12.1	15.3	13.1	0.572	24.0	26.0	16.8	23.4	0.216
Antidiabetic medication use, %	2.3	3.5	5.0	3.8	0.260	2.5	3.4	3.7	3.0	0.856	1.5	3.8	6.8	4.3	0.391
Antihyperlipidemic medication use, %	2.5	8.8	5.6	10.5	<0.001	2.6	7.6	5.6	10.3	0.003	2.5	11.5	5.6	10.7	0.074
Serum aspartate aminotransferase (AST), IU/L	22	23	24	26	<0.001	22	21	22	23	0.186	24	28	27	28	0.326
Serum alanine transaminase (ALT), IU/L	22	27	31	38	<0.001	20	22	26	29	<0.001	33	39	39	44	0.049
Serum y-glut amy kransferase (y-GTP), IU/L	38	49	53	67	<0.001	36	44	48	69	<0.001	50	59	59	66	0.207
Serum triglycerides, mg/dL	61	93	127	232	<0.001	61	93	127	231	<0.001	63	93	127	232	<0.001
Serum HDL-cholesterol, mg/dL	73	61	54	46	<0.001	74	62	54	48	<0.001	67	60	53	45	<0.001
Fasting blood sugar, mg/dL	98	102	103	108	<0.001	98	100	101	106	<0.001	101	106	106	109	0.312
Glomerular filtration rate (GFR), mL/min/1.73m^2	75.0	74.6	74.8	74.4	0.902	75.0	75.3	75.8	75.4	0.905	74.4	73	73.5	73.7	0.921

Ages are given as mean ± standard deviation. Median values of the TG-HDL ratio (traditional units): 0.88, 1.50, 2.33, and 4.10

ODI oxygen desatuation index

Table 2 Odds ratios (OR) and 95 % confidence intervals (CI) for sleep apnea syndrome

	TG-HDL ratios quartiles				*p* for trend	Log TG-HDL ratio
	Q1 (Low)	Q2	Q3	Q4 (High)		
Total subjects						
No. at risk	382	382	382	382		
No. of cases (%)	23 (6.0)	51 (13.4)	67 (17.5)	100 (26.2)		
Model 1	1.00	2.40 (1.43–4.01)	3.35 (2.04–5.51)	5.63 (3.48–9.10)	<0.001	2.24 (1.83–2.75)
Model 2	1.00	1.39 (0.81–2.39)	1.70 (1.00–2.88)	2.19 (1.30–3.69)	0.001	1.46 (1.15–1.85)
Model 3	1.00	1.38 (0.80–2.39)	1.73 (1.01–2.96)	2.24 (1.31–3.88)	0.001	1.49 (1.17–1.92)
Subjects with a BMI <25kg/m^2						
No. at risk	331	261	218	161		
No. of cases (percentage)	11 (3.3)	17 (6.5)	22 (10.1)	23 (14.3)		
Model 1	1.00	2.02 (0.92–4.38)	3.28 (1.55–6.93)	4.82 (2.28–10.18)	<0.001	2.11 (1.49–2.99)
Model 2	1.00	1.65 (0.75–3.64)	2.51 (1.17–5.38)	3.41 (1.57–7.39)	<0.001	1.79 (1.24–2.59)
Model 3	1.00	1.77 (0.79–3.94)	2.65 (1.22–5.77)	4.20 (1.85–9.50)	<0.001	2.03 (1.36–3.03)
Subjects with a BMI ≥25kg/m^2						
No. at risk	51	121	164	221		
No. of cases (%)	12 (23.5)	34 (28.1)	45 (27.4)	77 (34.8)		
Model 1	1.00	1.28 (0.60–2.74)	1.26 (0.60–2.63)	1.80 (0.89–3.65)	0.054	1.41 (1.05–1.88)
Model 2	1.00	0.97 (0.44–2.13)	1.01 (0.47–2.16)	1.30 (0.62–2.71)	0.250	1.25 (0.92–1.69)
Model 3	1.00	0.95 (0.42–2.12)	1.04 (0.48–2.27)	1.25 (0.58–2.68)	0.313	1.23 (0.89–1.70)

Model 1 adjusted for age only, *Model 2* adjusted further for body mass index (BMI), *Model 3* adjusted further for systolic blood pressure, alcohol intake, smoking, antihypertensive medication use, antidiabetic medication use, antihyperlipidemic medication use, serum aspartate aminotransferase (AST), serum γ-glutamyltranspeptidase (γ-GTP), fasting blood sugar, and glomerular filtration rate (GFR). Median values of the TG-HDL ratio (traditional units) were 0.88, 1.50, 2.33, and 4.10

significant; the adjusted-OR for the corresponding value was 2.19 (95 % CI: 1.30–3.69). However, after further adjustment for other classical cardiovascular risk factors, the magnitude remained the same at 2.24 (95 % CI: 1.31–3.88). We also found that these significant associations were limited to participants with a lower BMI (<25 kg/m^2). Further analysis showed a risk of sleep apnea syndrome in participants with a higher BMI status. Compared to participants with a BMI <25 kg/m^2, the age-adjusted OR of sleep apnea syndrome in participants with a BMI ≥25 kg/m^2 was 5.41(95 % CI: 4.01–7.31; $p < 0.001$).

Interaction between TG-HDL level and two BMI categories on sleep apnea syndrome

Since our study population was compromised of non-overweight ($n = 971$) and overweight ($n = 557$) subjects, to avoid the influence of sample size bias on the correlation between TG-HDL and sleep apnea syndrome, we evaluated the interaction between TG-HDL levels and two BMI categories on sleep apnea syndrome. An investigation of the effects of interaction between TG-HDL level and two BMI categories (BMI ≥25 kg/m^2 and BMI <25 kg/m^2) on sleep apnea syndrome revealed significant interaction between TG-HDL level and BMI category, with an age-adjusted p value for the effect of this interaction on sleep apnea syndrome of $p = 0.040$.

Correlation between fasting blood sugar and 3 % ODI by BMI status

We also evaluated the correlation between blood sugar and 3 % ODI by BMI status, and found that the fasting blood sugar correlated with 3 % ODI in participants with a BMI <25 kg/m^2, but not a BMI ≥25 kg/m^2 with a simple correlation coefficient (Pearson) and p value of $r = 0.15$ ($p < 0.001$) in participants with a BMI <25 kg/m^2, and $r = 0.03$ ($p = 0.533$) in participants with a BMI ≥25 kg/m^2 (Table 3).

Discussion

A major finding of the present study was a positive association between TG-HDL level and sleep apnea syndrome in Japanese men with a lower BMI (<25 kg/m^2) but not with a higher BMI (≥25 kg/m^2).

Table 3 Correlation between fasting blood sugar and 3 % ODI

Simple correlation coefficient
Subjects with a BMI <25kg/m^2
$r = 0.15$ ($p < 0.001$)
Subjects with a BMI ≥25kg/m^2
$r = 0.03$ ($p = 0.533$)

A previous case–control cross-sectional study with non-obese subjects reported that obstructive sleep apnea syndrome is independently associated with dyslipidemia [14]. Additionally, another study reported that respiratory disturbance index is positively correlated with triglycerides and inversely correlated with HDL-cholesterol among participants aged <65 years, but not participants aged ≥65 years [15]. These studies are compatible with our present study showing that TG-HDL is significantly positively associated with sleep apnea syndrome. Further, we found additional evidence that this positive association was limited to non-obese subjects.

Since our present study investigated the association between TG-HDL and sleep apnea syndrome, the impact of triglycerides, HDL-cholesterol, and TG-HDL on sleep apnea syndrome is important. Conduction of additional analyses after dividing the values for triglycerides, HDL-cholesterol, and TG-HDL into quartiles separately showed that sleep apnea syndrome had no linear association with triglycerides and HDL, while a linear association was observed for TG-HDL. Among participants with BMI <25 kg/m^2, in the reference group of the lowest quartile (Q1) of triglycerides, the multivariable ORs of sleep apnea syndrome were 1.29 (0.58–2.86) for Q2, 2.84 (1.37–5.90) for Q3, and 2.59 (1.16–5.77) for Q4. Additionally, in the reference group of the lowest quartile (Q1) of HDL-cholesterol, the multivariable ORs of sleep apnea syndrome were 0.63 (0.32–1.26) for Q2, 0.71 (0.35–1.44) for Q3, and 0.41 (0.19–0.89) for Q4, while in the reference group of the lowest quartile (Q1) of TG-HDL, the multivariable ORs of sleep apnea syndrome were 1.77 (0.79–3.94) for Q2, 2.65 (1.22–5.77) for Q3, and 4.20 (1.85–9.50) for Q4. Accordingly, instead of triglycerides and HDL, the ratio of TG-HDL should be used to evaluate the risk of sleep apnea syndrome.

TG-HDL has been found to be correlated with insulin resistance [16–18], as has sleep apnea syndrome [1–5]. Furthermore, the Sleep Heart Health Study of community dwelling subjects reported that those with sleep-disordered breathing (respiratory disturbance index (RDI) of ≥15 events/h) have higher values for the homeostasis model assessment (HOMA) index than participants with an RDI <5.0 and an RDI 5.0–14.9 [5]. This study is compatible with our results showing a significant positive association between TG-HDL and sleep apnea syndrome. Although insulin resistance may play an important role in the correlation between TG-HDL and sleep apnea syndrome, the underlying mechanism of this correlation is not yet clarified. Sleep apnea syndrome leads to several physiological disturbances such as intermitted hypoxia, sleep fragmentation, and an increase in autonomic tone associated with insulin resistance [19]. Insulin resistance is correlated with reduced lipoprotein lipase (LPL) activity which results in hypertriglyceridemia and decreased synthesis of HDL-cholesterol [20].

We also found that the positive association between TG-HDL and sleep apnea syndrome is limited to participants with a BMI <25 kg/m^2. Although we did not record insulin data, fasting blood sugar was available. Since insulin resistance should positively correlate with fasting blood sugar, the correlation between fasting blood sugar and 3 % ODI may partly indicate the correlation between insulin resistance and 3 % ODI. Additional analyses showed that fasting blood sugar correlates with 3 % ODI in participants with a BMI <25 kg/m^2 but not a BMI ≥25 kg/m^2. This partially supports a mechanism in which insulin resistance is significantly associated with 3 % ODI only among participants with a BMI <25 kg/m^2. Therefore, compared to participants with a BMI <25 kg/m^2, those with a BMI ≥25 kg/m^2 might have a higher risk of sleep apnea syndrome independent of insulin resistance—even stronger insulin resistance is observed in those with a BMI ≥25 kg/m^2 than those with a BMI <25 kg/m^2. In fact, participants in this study with a BMI ≥25 kg/m^2 showed significantly higher values for fasting blood sugar and TG-HDL than those with a BMI <25 kg/m^2.

Thus, the former group may be masked by these risk factors that are independent of TG-HDL.

Potential limitations in this study warrant consideration. Although 3 % ODI is considered to be an initial diagnostic test for sleep apnea syndrome, it should not on its own be considered as conclusive evidence of sleep apnea syndrome in subjects with a BMI below 25 kg/m^2 [21]. However, the diagnostic sensitivity of each of the 3 % ODI thresholds for sleep apnea syndrome increased with BMI, while at the same time, the specificity of ODI for sleep apnea syndrome fell [21]. This study is compatible with our additional analysis with our study population of 219 subjects (82 for BMI <25 kgm^2 and 137 for BMI ≥25 kg/m^2) who had received overnight recordings of both PULSOX-Me300 and standard polysomnography (PSG). The sensitivity and specificity were 62 and 63 % for subjects with BMI <25kg/m^2 and 77 and 50 % for subjects with BMI ≥25kg/m^2) for detecting an AHI of 20 ≥ events/h by PSG using a cut-off threshold of 3 % ODI = 15. Although the correlation between TG-HDL and sleep apnea syndrome was shown to be independent of the traditional risk

factors, we did not adjust for other potential confounding factors whose values were associated with sleep apnea syndrome [22] and dyslipidemia [23] such as advanced glycation end-products. Further investigation using data from advanced glycation end-products is necessary.

Because this study was a cross-sectional, no causal relationships were able to be established.

In conclusion, an independent positive association between the TG-HDL levels and the risk of sleep apnea syndrome was observed in participants with a BMI of <25 kg/m^2 but not for participants with a BMI ≥ 25 kg/m^2. TG-HDL levels could be an efficient tool to estimate the risk of sleep apnea syndrome in non-overweight, but not in overweight, Japanese men. Since Japanese subjects with sleep apnea syndrome are reported to have a lower BMI than Caucasian subjects, our findings might be particularly applicable to the former group [24].

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Human and animal rights and informed consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Ethics Committee for Human Use of Nagasaki University obtained ethical approval.

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