Can J Diabetes 43 (2019) 201–206

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Adjustment for Waist Circumference Reveals a U-Shaped Association Between Glycated Hemoglobin Levels and Body Mass Index in Young Adults

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Key Messages

- Low body weight assessed by body mass index can also be associated with impaired glucose metabolism, which is commonly reflected in high glycated hemoglobin levels.
- Body mass index has rarely been adjusted for waist circumference as part of an analytic model for use in epidemiologic studies.
- Additional adjustment of body mass index for waist circumference revealed a latent association between low body weight and high glycated hemoglobin levels, particularly in young adults.

ARTICLE INFO

Article history:
Received 25 December 2017
Received in revised form
14 August 2018
Accepted 14 September 2018

Keywords:
body mass index
glycated hemoglobin levels
impaired glucose metabolism
low body weight
waist circumference
young adult

ABSTRACT

Objectives: Body mass index (BMI) is used to assess adiposity worldwide. However, additional adjustment for waist circumference (WC), a surrogate marker of abdominal fat, may be capable of revealing a latent relationship between low body weight and glycated hemoglobin (A1C) concentration. Here, we investigated the relationship between A1C and BMI in young adults, adjusting for WC.
Methods: We reviewed A1C, BMI, WC and other clinical data in a cross-sectional study of 26,475 apparently healthy Japanese people 20 to 39 years of age who were undergoing health check-ups.
Results: Although the values of most serum parameters were high in subjects with a high BMI in both younger (20 to 29 years of age, n=10,810) and older subjects (30 to 39 years of age, n=15,665), A1C had a J-shaped relationship with BMI category in younger subjects, regardless of sex. A traditional linear model via a generalized linear model showed that in younger subjects, an inverse association of A1C level with BMI category (19 to 26.9 kg/m^2 vs. ≤18.9 kg/m^2) was identified after adjustment for WC. This indicates positive associations between A1C and BMI categories of ≤18.9 (beta=0.06; p<0.0001), 19.0 to 20.9 (beta=0.03; p<0.01) and ≥27.0 kg/m^2 (beta=0.08; p<0.0001), in contrast to individuals with BMIs of 23.0 to 24.9 kg/m^2. Similarly, in older subjects, BMIs ≤18.9 kg/m^2 were associated with A1C levels but to a lesser extent (beta=0.04; p<0.05) than in younger subjects.
Conclusions: Additional adjustment of BMI for WC revealed a latent U-shaped association between A1C concentration and BMI, particularly in young adults; this deserves further investigation.

Mots clés :
indice de masse corporelle
concentrations de l'hémoglobine glyquée
détérioration du métabolisme du glucose
faible poids corporel
périmètre abdominal
jeune adulte

RÉSUMÉ

Objectifs : L'indice de masse corporelle (IMC) est utilisé dans le monde entier pour évaluer l'adiposité. Toutefois, l'ajustement supplémentaire sur le périmètre abdominal (PA), un marqueur de substitution de la graisse abdominale, est à même de révéler une relation latente entre le poids corporel faible et la concentration de l'hémoglobine glyquée (A1c). Ici, nous avons examiné la relation entre l'A1c et l'IMC chez les jeunes adultes après ajustement sur le PA.

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https://doi.org/10.1016/j.jcjd.2018.09.007

Méthodes : Nous avons passé en revue l'A1c, l'IMC, le PA et les autres données cliniques d'une étude transversale auprès de 26 475 Japonais de 20 à 39 ans, apparemment en bonne santé, qui avaient subi des bilans de santé.
Résultats : Bien que les valeurs de la plupart des paramètres sériques fussent élevées chez les sujets plus jeunes (de 20 à 29 ans, n=10 810) et les sujets plus âgés (de 30 à 39 ans, n=15 665), dont l'IMC était élevé, l'A1c avait une relation en J avec la catégorie de l'IMC chez les sujets plus jeunes, quel que soit le sexe. Un modèle linéaire traditionnel via un modèle linéaire généralisé a montré que chez les sujets plus jeunes, une association inverse de la concentration de l'A1c a la catégorie de l'IMC (de 19 à 26,9 kg/m^2 *vs*≤18,9 kg/m^2) était établie après ajustement du PA. Cela indique des associations positives entre l'A1c et les catégories d'IMC≤18,9 (bêta=0,06; p<0,0001), de 19,0 à 20,9 (bêta=0,03; p<0,01) et≥27,0 kg/m^2 (bêta=0,08; p<0,0001), contrairement aux individus ayant des IMC de 23,0 à 24,9 kg/m^2. De même, chez les sujets plus âgés, des IMC≤18,9 kg/m^2 étaient associés aux concentrations de l'A1c, mais dans une moindre mesure (bêta=0,04; p<0,05) que chez les sujets plus jeunes.
Conclusions : L'ajustement supplémentaire de l'IMC sur le PA a révélé une association latente en U entre l'A1c et l'IMC, particulièrement chez les jeunes adultes. Ceci mérite des études plus approfondies.

Introduction

For a long time throughout the world, body mass index (BMI) has been used as an index of adiposity. In addition, during the past decade, waist circumference (WC) has been used as a surrogate marker of abdominal fat mass (1,2), mainly for screening for metabolic syndrome, in which visceral adiposity is a fundamental feature (3). Because BMI and WC are highly correlated, the predictive value of these indices for cardiometabolic disease has been thought to be very similar (2,4,5) and, therefore, BMI has rarely been adjusted for WC as part of an analytic model for use in epidemiologic studies investigating the relationship between abnormal body weight and cardiometabolic risk.

However, BMI and WC have been used together in some studies, a few of which have shown that people with high WCs and low BMIs are at high risk for death after myocardial infarction or in the presence of high blood pressure (6–8) and that the number of years during which individuals have both high BMIs and high WCs are a predictor of cardiovascular disease (9). However, others have reported that the use of both indices did not appear to improve substantially the predictive value for vascular events or intra-abdominal fat mass over the use of a single measure (10,11). Theoretically, using WC to adjust a person's BMI, for instance in multivariate logistic regression analysis (12), eliminates or reduces the effects of central adiposity, so the results generated indicate whether residual (peripheral) or ectopic adiposity remains as a potential contributor to the associations under investigation (13,14).

To date, however, no large clinical study has investigated the effects of such an adjustment for WC in the categorization of people with low body weight (LBW) using BMI. Individuals with LBW are common in Asia, including in the Japanese population, and such people can also develop impaired glucose metabolism, including impaired glucose tolerance (IGT) (15) and poor pancreatic beta-cell function (16,17), which may be a feature of the cause of malnutrition-induced diabetes mellites (18). This form of diabetes has been shown to occur in lean adults who are younger than 30 to 40 years of age, although this is rare (19–21). Additionally, in young adults who are close to adolescence in age (in their 20s), pubertal hormones, such as growth hormone and gonadal steroids, have been shown to contribute to the development of insulin resistance (22–25).

In this study, we investigated the association between glycated hemoglobin (A1C) levls, an index reflecting glycemia during the preceding few months, and low BMI, which was adjusted for WC in order to reveal any latent association, in a cross-sectional study of Japanese subjects 20 to 39 years of age.

Methods

This cross-sectional study is included in a series of long-standing observational research that was performed to explore the relationships between lifestyle-related diseases and cardiometabolic risk factors. The protocol of the original study is described in greater detail elsewhere (26). The current study involved 2 institutions in Kanagawa and Saitama, Japan: Kanagawa University of Human Services and the Saitama Health Promotion Corporation, a public interest corporation. The participants were residents and workers in Saitama Prefecture, near Tokyo. All the procedures followed were in accordance with the ethical standards dictated by the committee on human experimentation (Kanagawa University of Human Services, Japan) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients who were included in the study.

Subjects

Clinical data were obtained for 27,920 apparently healthy individuals 20 to 39 years of age, who underwent routine check-ups in Saitama Prefecture between April 2008 and March 2009. Inpatients, disabled individuals who could not move without assistance, those with acute inflammatory disease and women with diagnosed or self-reported pregnancy were not enrolled. Subjects who were taking any pharmacotherapy for diabetes, including insulin, were excluded from the study (n=85). Furthermore, subjects with A1C levels <4.0% or >10.0% were excluded because those values lay outside the reference range for individuals without diabetes (27) or they have a high likelihood of experiencing acute glycemic events (28,29), respectively. Subjects completed a questionnaire that recorded lifestyle factors, which was developed by the Japanese Ministry of Health, Labor, and Welfare in 2008, for the detection of unhealthy lifestyles (30). After also excluding individuals with incomplete clinical data (n=1,360), 26,475 subjects who were 20 to 39 years of age remained in the study. Subjects were divided into younger subjects (20 to 29 years of age, n=10,810) and older subjects (30 to 39 years of age, n=15,665), because people in their 20s may have causes close to those in adolescence (24,25), whereas people in their 30s may begin to have different causes, similar to those of middle age, in which the degree of BMI has a substantial effect on glucose homeostasis and beta-cell mass (31,32).

Anthropometry and laboratory assays

Anthropometric measurements and the collection of samples for laboratory analysis were carried out in the mornings. Height and body weight were measured objectively by trained staff using electronic scales. BMIs were calculated as body weight (kg) divided by height squared (m^2). WCs were measured (cm) to 1 decimal place at the level of the umbilicus using a measuring tape. Subjects were further divided into 6 BMI categories to investigate the detailed relationship between A1C levels and BMIs (≤18.9, 19.0 to 20.9, 21.0 to 22.9, 23.0 to 24.9, 25.0 to 26.9 and ≥27.0 kg/m^2), as in previous studies

(26,33). This was done for the possible reproducibility of our results showing fixed BMI values and to ensure that there were enough subjects in each BMI category to maintain the validity of the analyses. Because the prevalence of underweight among the subjects (BMI <18.5 kg/m^2) in their 30s was small (6.5%) compared with other BMI categories in this study, we defined the lowest BMI category as ≤18.9 kg/m^2. When we selected these BMI categories, we took into consideration that the World Health Organization has proposed that the BMI cutoff points for overweight and obesity in Asian populations should be ≥23.0 and ≥27.5 kg/m^2, respectively, which are lower than those in Western countries (34).

Serum triglyceride, high-density lipoprotein cholesterol, A1C and hemoglobin levels were measured by standard methods using Hitachi autoanalyzers (Tokyo, Japan) at the Saitama Health Promotion Corporation. A1C levels were measured in Japan Diabetes Society A1C units, which were converted to National Glycohemoglobin Standardization Program A1C units using the officially certified formula: A1C (National Glycohemoglobin Standardization Program) (%) = 1.02 × Japan Diabetes Society (%) + 0.25% (35).

Statistical analysis

Data are expressed as the mean ± SD, mean (range) or median (interquartile range), in tables. Significant differences in continuous and categorical variables among BMI categories were evaluated using analysis of variance (ANOVA) and the chi-square test, respectively. Differences in A1C levels between subjects with BMIs ≤18.9 kg/m^2 and other BMI groups were evaluated using a post hoc Dunnett test. A traditional linear model with an identity-link function via a generalized linear model was used to evaluate associations between A1C as a continuous variable and the 6 BMI categories, without or with adjustment for relevant confounders, which yielded crude and adjusted coefficients (beta) and 95% CIs. The possible confounders included age (continuous variable), sex, a history of cardiovascular disease (vs. no history), systolic blood pressure, serum HDL cholesterol, serum triglyceride, pharmacotherapy for hypertension or dyslipidemia, current smoking (vs. no current smoking), daily alcohol intake (vs. no daily alcohol intake) and regular exercise (vs. no regular exercise). Adjustment for WC (continuous variable) was conducted while treating it as a continuous variable. Blood hemoglobin was considered to be a potential confounding factor that could influence the measurement of A1C levels (36,37). A BMI of ≤18.9 kg/m^2 (LBW) was selected as the reference BMI category. However, the reference BMI was finally changed, as required, when there was a coefficient lower than 0 among the BMI categories. Statistical analyses were performed using Stat-view 5.0 (SAS Institute, Cary, North Carolina, United States) or using SAS-Enterprise Guide (SAS-EG 7.1) in SAS software, v. 9.4 (SAS Institute) for the generalized linear model. $p<0.05$ was considered to represent statistical significance.

Results

The clinical characteristics of younger and older subjects are shown in Table 1 and Table 2, respectively. Most continuous parameters, including A1C levels and the prevalence of most categorical findings, increased with increasing BMI in both age groups (all $p<0.0001$, ANOVA or chi-square test), with the exception of high-density lipoprotein cholesterol, which decreased. The proportion of subjects doing regular exercise was lowest in younger subjects with BMIs ≤18.9 kg/m^2 (11.7%).

Figure 1 shows the relationship between A1C level and BMI category according to age and sex. A consistent increase in A1C was observed with increasing BMI in men in the older group, but a J-shaped relationship was observed in the younger group and in women in the older group. In these groups, significant differences in A1C levels between subjects with BMIs ≤18.9 kg/m^2 and subjects with higher BMIs (25.0 to 26.9 and ≥27.0 kg/m^2) were observed (Dunnett test). In men in the older group, significant differences in A1C levels between BMIs of ≤18.9 kg/m^2 and the other categories, except for the BMI 19.0 to 20.9 kg/m^2 group, were observed.

Table 3 shows the results of a traditional linear model. In the younger group, an unadjusted BMI of ≥27.0 kg/m^2 only was significantly associated with A1C levels relative to the reference BMI of ≤18.9 kg/m^2. This finding remained when BMI was adjusted for all the confounders except WC. After additional adjustment for WC, the association between BMI ≥27.0 kg/m^2 and A1C levels disappeared; however, BMIs of 19.0 to 20.9, 21.0 to 22.9, 23.0 to 24.9 and 25.0 to 26.9 kg/m^2 were significantly inversely associated with A1C levels, independent of confounding factors, including hemoglobin concentration. Finally, when the reference BMI category used was changed to 23.0 to 24.9 kg/m^2, BMIs of ≤18.9 kg/m^2, 19.0 to 20.9 kg/m^2 and ≥27.0 kg/m^2 were significantly associated with A1C levels.

Table 1
Characteristics of younger subjects (<30 years of age)

BMI categories (kg/m^2)	≤18.9 (LBW)	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	≥ 27.0
N (% of total)	1,372 (12.7)	2,573 (23.8)	2,943 (27.2)	1,872 (17.3)	962 (8.9)	1,088 (10.1)
Age	25.4±2.4	25.3±2.4	25.4±2.5	25.5±2.5	25.7±2.5	25.8±2.6
Men, n (%)	472 (34.4)	1,362 (52.9)	2,047 (69.6)	1,476 (78.8)	784 (81.5)	885 (81.3)
BMI (kg/m^2)	18.0±0.8	20.0±0.6	21.9±0.6	23.9±0.6	25.8±0.6	30.0±2.8
Waist circumference (cm)	67.3±4.0	71.4±4.0	75.7±4.2	80.2±4.5	85.1±4.7	95.5±8.0
Systolic blood pressure (mmHg)	108±11.1	112±11.6	115±11.8	119±11.9	123±12.8	128±13.7
Triglyceride (mg/dl)	56 (42–77)	61 (45–87)	72 (50–106)	82 (58–123)	96.5 (64–148)	124 (84–189)
HDL cholesterol (mg/dL)	68.2±13.5	65.0±13.7	61.6±12.7	58.4±12.6	56.0±11.8	51.8±11.7
Hemoglobin (g/dL)*	13.7±1.4	14.1±1.4	14.4±1.4	14.8±1.3	15.0±1.3	15.2±1.3
A1C (%)	5.20±0.27	5.19±0.26	5.20±0.27	5.20±0.28	5.22±0.34	5.33±0.41
(range)	(4.02–6.68)	(4.02–6.17)	(4.02–6.47)	(4.33–7.29)	(4.23–9.33)	(4.33–9.94)
Current smokers, n (%)	356 (25.9)	813 (31.6)	1021 (34.7)	698 (37.3)	385 (40.0)	453 (41.6)
Alcohol drinkers, n (%)†	770 (56.1)	1,624 (63.1)	1,957 (66.5)	1,260 (67.3)	610 (63.4)	657 (60.4)
Regular exercisers, n (%)‡	160 (11.7)	533 (20.7)	869 (29.5)	556 (29.7)	262 (27.2)	233 (21.4)

Data are presented as the mean ± standard deviation, median (interquartile range) [triglyceride], mean ± standard deviation (range) [A1C] or n (%).

* Available n=10,759 total.

† Including social drinkers.

‡ Regular exercise was defined as≥30 min at least twice a week.

All continuous and categorical variables showed significant differences by ANOVA or χ^2 test, with P<0.0001 across the 6 BMI groups.

A1C, glycated hemoglobin; *BMI*, body mass index; *HDL cholesterol*, high-density lipoprotein cholesterol; *LBW*, low body weight.

Fewer than 5 subjects per BMI group were taking pharmacotherapy for hypertension or dyslipidemia (data not shown); therefore, statistical analysis was not conducted.

Fewer than 20 subjects across all BMI groups had cardiovascular disease (P=0.95, ANOVA, data not shown).

Table 2
Characteristics of older subjects (≥30 years of age)

BMI categories (kg/m^2)	LBW ≤18.9	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	≥ 27.0
N (% of total)	1,539 (9.8)	3,118 (19.9)	3,833 (24.5)	3,084 (19.7)	1,842 (11.8)	2,249 (14.4)
Age	34.6±2.8	34.8±2.8	34.8±2.8	35.0±2.8	35.0±2.8	35.1±2.8
Men, n (%)	502 (32.6)	1,580 (50.7)	2,734 (71.3)	2,460 (79.8)	1,544 (83.8)	1,845 (82.0)
BMI (kg/m^2)	18.0±0.8	20.0±0.6	22.0±0.6	23.9±0.6	25.9±0.6	29.5±2.7
Waist circumference (cm)	67.8±4.1	72.5±4.2	77.2±4.4	82.3±4.5	86.8±4.7	96.2±7.7
Systolic blood pressure (mmHg)	109±11.7	112±12.4	116±12.8	120±12.9	124±13.3	130±15.2
Triglyceride (mg/dl)	58 (45–80)	64 (48–92)	79 (55–119)	99 (65–154)	116 (77–183)	148 (98–225)
HDL cholesterol (mg/dl)	69.9±14.6	67.3±14.5	62.3±14.0	57.8±13.3	54.2±12.3	50.0±11.2
Hemoglobin (g/dl)*	13.5±1.5	13.9±1.6	14.4±1.5	14.8±1.4	15.0±1.3	15.2±1.3
A1C (%)	5.25±0.28	5.26±0.29	5.30±0.32	5.32±0.31	5.39±0.39	5.52±0.56
(range)	(4.02–6.37)	(4.23–8.21)	(4.02–9.23)	(4.02–9.53)	(4.13–9.63)	(4.33–9.94)
Current smokers, n (%)	423 (27.5)	1,008 (32.3)	1,395 (36.4)	1,272 (41.2)	815 (44.2)	945 (42.0)
Alcohol drinkers, n (%)†	795 (51.7)	1,902 (61.0)	2,495 (65.1)	2,063 (66.9)	1,241 (67.4)	1,343 (59.7)
Regular exercisers, n (%)‡	163 (10.6)	591 (19.0)	900 (23.5)	740 (24.0)	418 (22.7)	445 (19.8)

Data are presented as the mean ± standard deviation, median (interquartile range) [triglyceride], mean ± standard deviation (range) [A1C], or n (%).
* Available n=15,524 total.
† Including social drinkers.
‡ Regular exercise was defined as ≥30 min at least twice a week.
All continuous and categorical variables showed significant differences by ANOVA or χ^2 test, with P<0.0001 across the 6 BMI groups.
A1C, glycated hemoglobin; *BMI*, body mass index; *HDL cholesterol*, high-density lipoprotein cholesterol; *LBW*, low body weight.
Fewer than 15 subjects in each BMI group were taking pharmacotherapy for hypertension or dyslipidemia, except for the BMI≥27.0 kg/m^2 group (data not shown), therefore statistical analysis was not conducted. Fewer than 30 subjects across all BMI groups had cardiovascular disease (P=0.12, ANOVA); therefore, the numbers of subjects are not given.

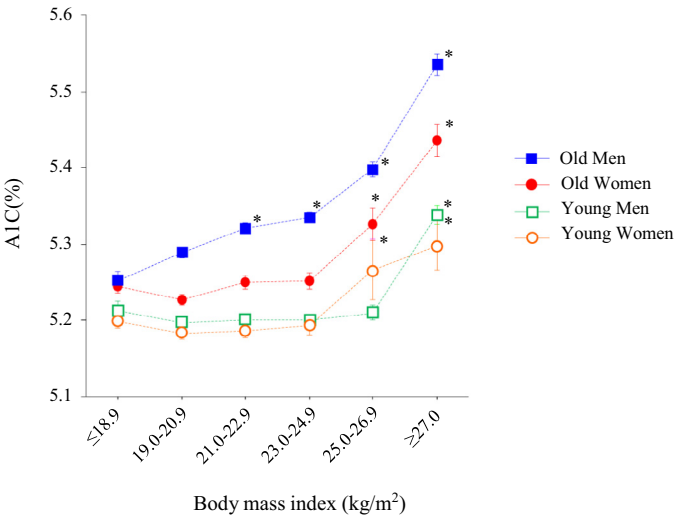

Figure 1. Relationship between glycated hemoglobin (A1C) levels and body mass index (BMI) according to age and sex. The symbol in the middle of each bar is the mean A1C level of the subjects. The vertical bar represents the SEM. *p<0.05 vs. BMI ≤18.9 kg/m^2 (Dunnett test) within each age and sex group. N=472, 1,362, 2,047, 1,476, 784 and 885 (young men); 900, 1,211, 896, 396, 178 and 203 (young women); 502, 1,580, 2,734, 2,460, 1,544 and 1,845 (older men); and 1,037, 1,538, 1,099, 624, 298 and 404 (older women) in the BMI categories of ≤18.9, 19.0 to 20.9, 21.0 to 22.9, 23.0 to 24.9, 25.0 to 26.9 and ≥27.0 kg/m^2, respectively.

In older subjects, the unadjusted coefficients for A1C levels with respect to each BMI category increased with increasing BMI. However, after adjustment, particularly for WC, inverse but weak associations were observed between A1C levels and BMIs of 19.0 to 20.9 and 23.0 to 24.9 kg/m^2 relative to the reference BMI category of ≤18.9 kg/m^2. When the reference BMI category was changed to 23.0 to 24.9 kg/m^2, a BMI of ≤18.9 kg/m^2 was significantly associated with A1C levels but to a lesser extent relative to younger subjects. Unlike in younger subjects, regardless of additional adjustment for WC, the significant association between A1C levels and BMIs of ≥27.0 kg/m^2 persisted.

Discussion

This study has demonstrated that people in their 20s with LBW are more likely to have higher A1C levels than subjects with normal or slightly high BMIs, especially when WC is taken into consideration, such that there is a latent U-shaped relationship between A1C level and BMI. Similarly, subjects in their 30s with LBW, corrected for WC, had higher A1C levels than their counterparts with normal or higher BMIs, although the strength of this relationship was less than it was in the younger group. Therefore, the recommendation that lower BMI is always better may not necessarily be applicable, particularly in the case of postadolescent individuals, with respect to A1C levels—a finding that is consistent with that of previous studies (15–17). In the analysis, the reference BMI category finally had to be changed from a lower to a higher BMI category for Japanese people, suggesting that young people with LBW may still have higher A1C levels in the absence of the other problems investigated in this study. Of note, Ito (15) has shown that in 15,238 Japanese patients with glycosuria, the lowest proportion of patients with IGT was observed when BMIs were 19.0 to 19.9 kg/m^2 (23.3% for men and 19.7% for women), whereas those with BMIs <17.0 kg/m^2 (28.3% for men and 23.3% for women) had a higher prevalence. However, relevant confounding factors were not considered, and statistical analysis was not conducted in this study.

In older subjects, the association of BMI with A1C level may become stronger, almost linearly, bcause BMI increases in an unadjusted model. The association between the highest BMI category of ≥27.0 kg/m^2 and A1C level remained significant even after additional adjustment for WC, probably because besides visceral obesity, residual (peripheral) or ectopic adiposity, potentially accompanied by fatty liver and pancreas (14), predispose to high A1C levels in the most obese group. In contrast, in younger subjects, the association of BMI with A1C level may not become stronger in a linear relationship as BMI increases; it is a J- or U-shaped relationship. In the case of younger subjects with LBW, a plausible explanation for the latent association with A1C levels is that leanness, which might reflect lower muscle mass in the limbs, may contribute to the cause of impaired glucose metabolism. Therefore, detailed anthropometric measurements, such as midarm muscle circumference and body fat distribution, may help to determine the mechanism underlying our current findings (38–40). Sakurai et al (16) have

Table 3
Beta coefficients and 95% CIs for glycated hemoglobin in each BMI category

BMI categories (kg/m^2)	LBW ≤18.9	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	≥27.0
Younger subjects						
Unadjusted	0 (reference)	−0.014 (−0.035 to 0.007)	−0.007 (−0.027 to 0.014)	−0.005 (−0.027 to 0.018)	0.02 (−0.006 to 0.046)	0.141 (0.115 to 0.166)**
Adjusted, except WC*	0 (reference)	−0.015 (−0.036 to 0.006)	−0.014 (−0.034 to 0.008)	−0.017 (−0.040 to 0.007)	−0.002 (−0.029 to 0.026)	0.107 (0.079 to 0.135)**
Adjusted, including WC*	0 (reference)	−0.027 (−0.049 to −0.006)§	−0.039 (−0.063 to −0.016)¶	−0.057 (−0.084 to −0.029)**	−0.057 (−0.091 to −0.022)¶	0.018 (−0.026 to 0.062)
Adjusted, including for WC, and hemoglobin†	0 (reference)	−0.029 (−0.050 to −0.008)§	−0.047 (−0.070 to −0.024)**	−0.063 (−0.090 to −0.035)**	−0.057 (−0.092 to −0.023)¶	0.016 (−0.027 to 0.059)
Adjusted, including for WC, and hemoglobin‡	0.063 (0.035 to 0.090)**	0.033 (0.012 to 0.055)¶	0.016 (−0.003 to 0.035)	0 (reference)	0.005 (−0.020 to 0.030)	0.079 (0.049 to 0.109)**
Older subjects						
Unadjusted	0 (reference)	0.012 (−0.012 to 0.035)	0.057 (0.035 to 0.080)**	0.078 (0.054 to 0.102)**	0.152 (0.126 to 0.178)**	0.29 (0.265 to 0.315)**
Adjusted, except WC*	0 (reference)	−0.005 (−0.029 to 0.018)	0.02 (−0.004 to 0.043)	0.02 (−0.005 to 0.045)	0.077 (0.049 to 0.105)**	0.193 (0.165 to 0.221)**
Adjusted, including WC*	0 (reference)	−0.025 (−0.049 to −0.001)§	−0.018 (−0.044 to 0.008)	−0.038 (−0.068 to −0.009)§	0.00 (−0.035 to 0.035)	0.076 (0.033 to 0.118)¶
Adjusted, including for WC, and hemoglobin†	0 (reference)	−0.028 (−0.052 to −0.004)§	−0.021 (−0.047 to 0.004)	−0.037 (−0.066 to −0.007)§	0.004 (−0.031 to 0.039)	0.077 (0.035 to 0.120)¶
Adjusted, including for WC, and hemoglobin‡	0.037 (0.007 to 0.066)§	0.009 (−0.014 to 0.031)	0.016 (−0.003 to 0.035)	0 (reference)	0.041 (0.019 to 0.064)¶	0.114 (0.087 to 0.141)**

Data are presented as crude or adjusted β coefficients (95% CI).
BMI, body mass index; *LBW*, low body weight; *WC*, waist circumference.
* Adjusted coefficients were calculated with adjustment for sex, age (continuous variable), past history of cardiovascular disease (vs. no history), systolic blood pressure, serum HDL-cholesterol and triglyceride, pharmacotherapy for hypertension and dyslipidemia, current smoking (vs. no current smoking), daily alcohol intake (vs. no daily alcohol intake), and taking regular exercise (vs. no regular exercise).
† Available n=10,759 for younger and n=15,240 for older subjects.
‡ Reference BMI was changed to BMI of 23.0 to 24.9 kg/m^2.
§ P<0.05.
¶ P<0.001.
** P<0.0001.

shown that pancreatic beta-cell function is low in very lean Japanese people. Because insulin plays a crucial anabolic role in muscle (41,42), lower secretion of insulin may result not only in a higher risk for diabetes but also in lower lean body mass, including that of skeletal muscle. The fact that subjects in their 20s with LBW were less likely to do regular exercise than any other group (Table 1) may be consistent with this hypothesis. Heavy alcohol consumption is the leading cause of chronic pancreatitis, which often accompanies secondary diabetes and malnutrition (43). However, in this study, the prevalence of alcohol intake was lowest in the younger subjects with LBW; hence, chronic pancreatitis due to alcohol consumption is unlikely to contribute to the observed association.

There are also several other possible explanations. A proportion of young lean people may consume an inadequate amount of protein and total energy, which would predispose them to weight loss. Khardori et al (44) reported that in a primate model of protein malnutrition, fasting plasma glucose is lower as a consequence of the depletion of glycogen stores and hepatic dysfunction. Nevertheless, IGT was observed because of low insulin levels, hepatic dysfunction and lower glucose disposal. Furthermore, animal studies have shown that a low-protein diet causes low beta-cell mass, IGT and long-lasting changes in liver mitochondria (45,46).

Alternatively, as several studies have shown (25), insulin resistance caused by high levels of pubertal hormones can lead to a transient mild increase in A1C levels that resolves after puberty. Even in lean children, there is a modest increase in insulin resistance as they progress through puberty (24). In addition to these possibilities, hyperthyroidism due to Graves disease might affect the data presented here; however, thyroid function was not measured in this study. Hyperthyroidism, including subclinical hyperthyroidism, is common in young women and causes weight loss and abnormal glucose metabolism (47–49).

Several limitations in the current study must be mentioned. Some of the mechanisms described may have contributed to the marginally higher A1C levels in young people with LBW. This was a cross-sectional study; therefore, a future prospective study should be conducted that includes assessment of insulin secretion, IGT, anthropometric data and food intake to corroborate the present findings and determine the mechanisms underlying them. Although poorly controlled diabetes often accompanies malnutrition, especially in elderly people (50,51), the relatively higher A1C levels identified in young subjects with LBW were probably not the result of malnutrition-induced diabetes, as previously discussed by Chattopadhyay et al (20), because subjects taking pharmacotherapy for diabetes were excluded, and the maximum level of A1C levels measured in the group was 6.7% (Table 1). Furthermore, the study population consisted of mostly nonobese individuals who were not in treatment for diabetes, so the current findings may not be applicable to patients who are taking pharmacotherapy for diabetes or to people with higher body weights.

Conclusion

The results of this study suggest that young adults with LBW, particularly those in their 20s, may have a higher prevalence of impaired glucose metabolism, compared with individuals with a higher BMI, especially when WC is incorporated into the assessment. However, the mechanism that underlies the association between LBW and A1C levels remains to be determined, as does whether these relatively higher A1C levels resolve or worsen with advancing age.

Acknowledgments

We thank Mark Cleasby, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Author Disclosures

Conflicts of interest: None.

Author Contributions

HR and NK designed the study and analyzed the data; SK identified eligible subjects from the database at Saitama Health Promotion Corporation and confirmed validation of the measurements and methods; IT prepared the manuscript, including literatures and discussion; NK wrote the draft of the manuscript; all authors read and approved the final manuscript.

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