Table 4 | Projected age- and sex-specific diabetes prevalence (%) in the Japanese population 2010–2030

Sex	Year	Age category (years)					
		20–29	30–39	40–49	50–59	60–69	≥70
Men	2010	0.76 (0.26–2.17)	1.71 (1.29–2.26)	5.56 (4.48–6.87)	12.00 (10.29–13.95)	17.81 (15.79–20.03)	20.13 (17.87–22.60)
	2015	0.71 (0.13–3.80)	1.50 (0.99–2.25)	5.11 (3.81–6.83)	11.50 (9.26–14.19)	18.68 (15.79–21.98)	21.77 (18.41–25.53)
	2020	0.67 (0.06–6.69)	1.31 (0.76–2.27)	4.71 (3.23–6.82)	11.02 (8.31–14.51)	19.59 (15.71–24.14)	23.50 (18.85–28.90)
	2025	0.63 (0.03–11.53)	1.15 (0.57–2.29)	4.33 (2.71–6.84)	10.56 (7.39–14.85)	20.53 (15.63–26.52)	25.32 (19.31–32.49)
	2030	0.59 (0.01–19.52)	1.01 (0.44–2.32)	3.98 (2.28–6.85)	10.12 (6.59–15.20)	21.51 (15.54–28.95)	27.23 (19.69–36.33)
Women	2010	0.59 (0.24–1.46)	0.78 (0.43–1.41)	2.40 (1.55–3.72)	5.56 (4.41–6.98)	10.65 (8.84–12.79)	12.12 (10.46–14.00)
	2015	0.55 (0.14–2.17)	0.67 (0.29–1.53)	2.18 (1.20–3.94)	5.24 (3.80–7.19)	10.75 (8.28–13.82)	12.08 (9.79–14.78)
	2020	0.52 (0.08–3.28)	0.57 (0.19–1.71)	1.98 (0.92–4.24)	4.93 (3.24–7.45)	10.86 (7.71–15.05)	12.03 (9.15–15.71)
	2025	0.48 (0.04–5.08)	0.49 (0.12–1.91)	1.80 (0.70–4.55)	4.65 (2.76–7.72)	10.96 (7.18–16.37)	11.99 (8.48–16.68)
	2030	0.45 (0.02–7.88)	0.42 (0.08–2.15)	1.64 (0.53–4.94)	4.37 (2.33–8.06)	11.06 (6.65–17.84)	11.95 (7.89–17.74)

Data are point estimates (95% confidence intervals) of prevalence.

Table 5 | Projected age-standardized diabetes prevalence in the Japanese population 2010–2030

Sex	Year	Standardization population						
		Japanese population of the corresponding year		World population of the corresponding year	2010 Japanese population	2010 world population	2030 Japanese population	2030 world population
			Number of cases (×1,000)					
Men	2010	9.86 (9.24–10.60)	4,988	6.43 (5.99–7.04)	9.86 (9.24–10.60)	6.43 (5.99–7.04)	11.38 (10.63–12.24)	7.67 (7.17–8.30)
	2015	10.63 (9.71–11.80)	5,354	6.69 (6.09–7.73)	10.10 (9.23–11.21)	6.40 (5.82–7.45)	11.75 (10.68–13.06)	7.71 (7.05–8.74)
	2020	11.41 (10.10–13.21)	5,683	7.05 (6.27–8.73)	10.36 (9.23–12.01)	6.39 (5.67–8.22)	12.16 (10.74–14.06)	7.79 (6.95–9.44)
	2025	12.26 (10.51–14.87)	5,989	7.51 (6.55–10.24)	10.67 (9.25–13.03)	6.40 (5.56–9.57)	12.61 (10.82–15.25)	7.89 (6.88–10.59)
	2030	13.10 (10.91–16.71)	6,228	8.02 (6.82–12.41)	11.00 (9.29–14.39)	6.44 (5.47–11.72)	13.10 (10.91–16.71)	8.02 (6.82–12.41)
Women	2010	6.06 (5.53–6.72)	3,307	3.71 (3.36–4.21)	6.06 (5.53–6.72)	3.71 (3.36–4.21)	7.04 (6.40–7.82)	4.50 (4.09–5.04)
	2015	6.28 (5.52–7.29)	3,423	3.76 (3.30–4.51)	5.96 (5.25–6.92)	3.59 (3.15–4.34)	6.94 (6.07–8.07)	4.38 (3.85–5.17)
	2020	6.43 (5.41–7.86)	3,478	3.85 (3.27–4.93)	5.87 (4.98–7.19)	3.49 (2.96–4.57)	6.85 (5.76–8.38)	4.28 (3.64–5.39)
	2025	6.57 (5.31–8.50)	3,501	3.97 (3.27–5.48)	5.79 (4.73–7.51)	3.39 (2.78–4.94)	6.77 (5.47–8.75)	4.18 (3.44–5.71)
	2030	6.69 (5.19–9.22)	3,486	4.10 (3.26–6.19)	5.72 (4.50–7.95)	3.30 (2.62–5.54)	6.69 (5.19–9.22)	4.10 (3.26–6.19)
Total	2010	7.89 (7.49–8.39)	8,295	5.06 (4.79–5.47)	7.89 (7.49–8.39)	5.06 (4.79–5.47)	9.11 (8.62–9.69)	6.08 (5.76–6.50)
	2015	8.37 (7.79–9.16)	8,777	5.22 (4.86–5.88)	7.95 (7.41–8.70)	4.99 (4.64–5.65)	9.24 (8.57–10.11)	6.04 (5.64–6.71)
	2020	8.81 (8.02–9.98)	9,161	5.44 (4.99–6.49)	8.03 (7.35–9.11)	4.93 (4.52–6.04)	9.38 (8.53–10.62)	6.03 (5.54–7.07)
	2025	9.29 (8.26–10.94)	9,490	5.74 (5.19–7.38)	8.14 (7.30–9.65)	4.89 (4.42–6.76)	9.56 (8.50–11.23)	6.03 (5.45–7.66)
	2030	9.75 (8.50–12.01)	9,714	6.05 (5.39–8.64)	8.26 (7.29–10.37)	4.86 (4.33–7.95)	9.75 (8.50–12.01)	6.05 (5.39–8.64)

Data are point estimates (95% confidence intervals) of prevalence.

We observed moderate heterogeneity among studies, particularly in age categories 40 years or older (Table S2). We therefore carried out a sensitivity analysis by repeating the meta-analysis and meta-regression steps excluding: (i) studies using OGTT for diabetes diagnosis[31–33]; and (ii) studies carried out in a single center[36,37]. Analyses excluding studies using OGTT for diabetes diagnosis (Table S3) and studies carried out in a single center (Table S4) showed similar patterns, with a higher diabetes prevalence in men than women and an increase in prevalence in men aged 70 years or more with time. Furthermore, we also examined sensitivity by including data from the national health surveys only. This resulted in a substantial reduction of heterogeneity and the corresponding trends in prevalence were higher than those estimated when using all studies (Table S5).

DISCUSSION

Here, we present the results of a comprehensive meta-regression analysis of studies carried out among the Japanese population in the past two decades. The present study included

161,087 individuals, allowing us to estimate sex- and age-specific trends in the prevalence of diabetes over the past two decades, and to present prevalence projections from 2010 until 2030. Furthermore, by combining these estimates with sex- and age-specific population distribution estimates, we also calculated age-standardized diabetes prevalence trends as well as expected numbers of adults with diabetes in Japan.

The present findings suggest that diabetes prevalence in Japan will substantially increase in the next two decades, mainly as a result of population aging. The number of cases is expected to rise from 8.3 million in 2010 to 9.7 million in 2030. Thus, rapidly aging societies, such as Japan, Italy and Germany[1], could experience substantial increasing trends in diabetes prevalence during the next decades. Curbing this increase in these societies requires the identification of effective preventive strategies, such as promoting a healthy lifestyle and screening for people at high risk for diabetes[56]. With regard to sex- and age-specific prevalence estimates, we observed a marked difference between men and women: prevalence is expected to remain constant for women regardless of age category, but to steeply increase in older men.

A major strength of the present study was its use of the standard diagnostic criteria provided in the JDS recommendation[18]. This implies that the estimated trends might be attributed to real changes in the prevalence of diabetes in the Japanese population and not merely to changes in the criteria used to define diabetes.

Our present estimates substantially differ from those of several recent studies that estimated and projected diabetes prevalence worldwide, including the Japanese population[6,11–13]. The International Diabetes Federation provided diabetes prevalence estimates of 7.6% for 2013 and 8.2% for 2035[14], which are slightly lower than those in the present study and show a less pronounced increasing trend. This difference might be partly explained by the fact that data used to derive the International Diabetes Federation estimates used results from a single national health survey carried out in 2007[43]. Furthermore, the International Diabetes Federation estimates are based on a country-specific prevalence function that depends on sex, age and level of urbanization, but does not vary with year of assessment; as a result, these estimates reflect changes in the demographic structure of the country's population (population growth, aging, and urbanization), but take no account of possible trends in diabetes prevalence resulting from changes in the influence of factors, such as unhealthy diet, sedentary lifestyle (though this is partly taken into account through the urbanization variable) or other possibly unexplored societal factors.

A recent article by Danaei *et al.*[11] provided global and country-specific diabetes prevalence estimates up to 2008 using a Bayesian hierarchical modeling procedure that included the year of assessment as an explanatory covariate. Prevalence estimates for Japan were lower than those of the present study, but showed similar trends and differences between men and women (4.9 and 4.2% in 1990, 7.2 and 4.7% in 2008 for men and women respectively). However, the regression models used to calculate these estimates were based on FPG estimates, and the primary outcome was thus derived from studies that used different glycemic metrics from those in our present study.

The observed sex difference in diabetes prevalence in the Japanese population might be partly a result of the higher prevalence of obesity among Japanese men[20,57,58]. This sex difference could also result from a strong influence of lifestyle habits. Indeed, several studies have reported substantial sex differences in alcohol and tobacco consumption, physical activity, and levels of stress[59,60], which could directly or indirectly influence the development of diabetes.

The increase in diabetes prevalence along time in men aged 70 years or older might be partially explained by cohort effects; changes in lifestyle habits between birth cohorts, particularly changes in dietary intake since the Second World War[61], might be responsible for the trend. A possible decrease in mortality among Japanese individuals with diabetes over time might also explain the increasing prevalence in this age category. Alternatively, because of the use of wide age categories, residual confounding by age might also explain the observed trend. In contrast, we observed no evidence for such differences in diabetes prevalence between birth cohorts in women. The reasons for this sex difference are unclear, but the difference might possibly reflect differential shifts in lifestyle habits between men and women[59,60], or the effects of sex hormones on glucose metabolism[62].

The present study had several limitations. First, although the largest studies included in our analysis covered several calendar years, we summarized the diabetes prevalence of the corresponding population for a single point in time, namely the central year, because details about the precise year of diagnosis for each patient were not available. As a consequence, we might not have been able to accurately capture the temporal trend in diabetes prevalence. In particular, results from the sensitivity analysis using only national survey data, which did have year-specific prevalence estimates, showed that we might have substantially underestimated the projected prevalence for both sexes. Second, our use of wide age categories decreased the precision of our estimates of the effect of age on the prevalence of diabetes. However, we consider that this lack of precision is compensated for by the robustness of our estimates. Third, our projections assume that the trends estimated by meta-regression will remain constant during the next decades, which might not be correct. However, given that a sudden change in the incidence of diabetes is not expected, our predictions could appropriately describe what might happen in the absence of specific public health policies aimed at reversing this tendency. Finally, we observed moderate heterogeneity across studies in the prevalence estimates, particularly in age categories 40 years or older. The presence of heterogeneity, while unavoidable, could have altered the results of our meta-regression. In particular, studies carried out in a single center might not be representative of the overall Japanese population. The exclusion of such studies,

however, did not materially change prevalence estimates. Furthermore, the restriction of the analysis to data from the national health surveys, which have a very similar design and consequently exhibit much less heterogeneity, showed higher trends in prevalence. However, because participants in the national health surveys tend to be more cooperative and perhaps more health-conscious than the average, despite the random selection procedure used at the time of recruitment, these surveys might fail to encompass the Japanese population in all its diversity. For that reason, we believe that the estimates presented, based on all the studies included, might give a better reflection of the trends in diabetes prevalence in the Japanese population.

In conclusion, this comprehensive meta-regression analysis of the Japanese population shows that diabetes can be expected to substantially increase in the next few decades, and that this increase will be mainly a result of population aging. Because diabetes is preventable through diet and lifestyle modification, our findings support the need for public policies and health systems that promote a healthy diet and lifestyle.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Flow diagram of the study identification and selection process.
Figure S2 | Prevalence of diabetes mellitus in Japanese men according to year of assessment.
Figure S3 | Prevalence of diabetes mellitus in Japanese women according to year of assessment.
Table S1 | Coefficient associated with time in the linear meta-regression model.
Table S2 | Assessment of heterogeneity across studies.
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Table S5 | Sensitivity analysis using national surveys only.

発表論文

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ORIGINAL ARTICLE

Abdominal Fat Accumulation, as Measured by Computed Tomography, Increases the Risk of Ischemic Colitis: A Retrospective Case–Control Study

Tomonori Aoki · Naoyoshi Nagata · Kayo Sakamoto · Tomohiro Arai · Ryota Niikura · Takuro Shimbo · Masafumi Shinozaki · Katsunori Sekine · Hidetaka Okubo · Kazuhiro Watanabe · Toshiyuki Sakurai · Chizu Yokoi · Junichi Akiyama · Mikio Yanase · Masashi Mizokami · Mitsuhiko Noda · Naomi Uemura

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Abstract
Background and Aim Visceral fat contributes to insulin resistance and atherosclerosis. We retrospectively investigated whether abdominal fat accumulation, as measured by computed tomography, is a risk of ischemic colitis and related clinical outcomes.
Materials and Methods Outpatient-onset ischemic colitis patients ($n = 58$) and age- and sex-matched controls ($n = 58$) underwent colonoscopy and computed tomography. Associations between body mass index, visceral adipose tissue area, subcutaneous adipose tissue area, and ischemic colitis were estimated using odds ratios adjusted for hypertension, diabetes mellitus, and dyslipidemia.
Results In multivariate analysis, ischemic colitis was significantly associated with subcutaneous adipose tissue area (P for trend 0.030) and marginally associated with visceral adipose tissue area (P for trend 0.094), but was not associated with body mass index (P for trend 0.460). The adjusted odds ratios for the highest quartile of subcutaneous and visceral adipose tissue in ischemic colitis were

T. Aoki · N. Nagata (✉) · R. Niikura · K. Sekine · H. Okubo · K. Watanabe · T. Sakurai · C. Yokoi · J. Akiyama · M. Yanase
Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan
e-mail: nnagata_ncgm@yahoo.co.jp

T. Aoki
e-mail: iitomo_1020@yahoo.co.jp

R. Niikura
e-mail: rniikura@triton.ocn.ne.jp

K. Sekine
e-mail: hawaiiantuberider@gmail.com

H. Okubo
e-mail: h.okubo.john@gmail.com

K. Watanabe
e-mail: c12pagani@yahoo.co.jp

T. Sakurai
e-mail: tsakurai@hosp.ncgm.go.jp

C. Yokoi
e-mail: chizzzucchi@gmail.com

J. Akiyama
e-mail: akiyama@fc4.so-net.ne.jp

M. Yanase
e-mail: myanase@hosp.ncgm.go.jp

K. Sakamoto · T. Arai · M. Shinozaki
Department of Diagnostic Radiology, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan
e-mail: ksakamo@hosp.ncgm.go.jp

T. Arai
e-mail: depository.of.mail@gmail.com

M. Shinozaki
e-mail: shmasafu@hosp.ncgm.go.jp

T. Shimbo
Department of Clinical Research and Informatics, International Clinical Research Center Research Institute, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan
e-mail: tshimbo@ohta-hp.or.jp

M. Mizokami
The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Kohnodai Hospital, 1-7-1 Kohnodai, Ichikawa City, Chiba 272-8516, Japan
e-mail: mizokami0810@gmail.com

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3.48 (1.06–11.4) and 2.43 (0.74–8.00), respectively, compared with the lowest quartile. When body mass index was considered simultaneously, ischemic colitis remained associated with subcutaneous adipose tissue (*P* for trend 0.016) and visceral adipose tissue (*P* for trend 0.077). No significant differences were noted between any of the obesity indices and the distribution type of colitis, blood transfusion requirement, or length of hospital stay.

Conclusion Abdominal fat accumulation measured by computed tomography, but not body mass index, was associated with outpatient-onset ischemic colitis. Ischemic colitis remained associated with abdominal fat, even when body mass index was simultaneously considered. However, clinical outcomes of ischemic colitis were not associated with abdominal fat accumulation.

Keywords Abdominal visceral fat · Metabolic syndrome · Acute large bowel ischemia · Computed tomography · Body mass index

Abbreviations

IC	Ischemic colitis
NCGM	National Center for Global Health and Medicine
NSAIDs	Nonsteroidal anti-inflammatory drugs
SAT	Subcutaneous adipose tissue
VAT	Visceral adipose tissue

Introduction

Ischemic colitis (IC) is considered to have a multifactorial pathogenesis [1–7]. In particular, metabolic factors involving hypertension, diabetes mellitus, and dyslipidemia are causes of atherosclerosis, which is the fundamental risk factor for IC. The accumulation of abdominal visceral fat, as measured by computed tomography (CT), is known to underlie hypertension, diabetes mellitus, and dyslipidemia by virtue of insulin resistance. A previous study also suggested that mucosal inflammation due to abdominal visceral fat increases the risk of Crohn's disease (CD) [8]. Thus, abdominal visceral fat accumulation is a potential risk of IC development due to its association with atherosclerosis and inflammation. However, the effect on IC of abdominal fat accumulation as measured directly by CT has never been studied.

Thus, we conducted an age- and sex-matched case–control study of subjects who underwent both colonoscopy and CT, because the incidence of IC differs between men and women [9]. In addition, because the risks between outpatient- and inpatient-onset IC differ [10], we focused on outpatient-onset IC. The objective was to elucidate the effect of abdominal fat accumulation on IC development and IC-related clinical outcomes such as blood transfusion requirement and prolonged hospital stay.

Materials and Methods

Patient Selection

This retrospective, hospital-based, case–control study was conducted between January 2008 and June 2013 at the National Center for Global Health and Medicine (NCGM), Japan. The NCGM is one of the largest territorial emergency hospitals (900 beds) in the Metropolitan Tokyo area.

Cases

During the study period, we included patients with clinically suspected IC and patients who underwent endoscopy. From these patients, we excluded those who did not fulfill the following diagnostic criteria. Patients with mild to moderate abdominal pain, diarrhea, or lower gastrointestinal bleeding with abdominal tenderness were investigated for clinically suspected IC. We applied the following strict diagnostic criteria of IC in addition to previously published findings for colon ischemia [11]. Endoscopic findings suggestive of IC were the presence of edema with hemorrhagic infiltration and/or scattered ulcers or bluish discoloration of the mucosa with ulceration. Histologic findings suggestive of IC included loss of epithelium, mucosal edema with hemosiderosis, and fibrosis in the deeper mucosal layers. Patients with a previous history of inflammatory bowel disease, recent use of antibiotics, or with IC that was not newly diagnosed were excluded. We also excluded patients with infectious colitis based on the findings of microscopy, culture, polymerase chain reaction, and histologic examination of specimens obtained from endoscopy, aspiration, or biopsy [12]. Fulfillment of all the clinical, endoscopic, and histologic criteria as well as the exclusion of infectious colitis was required to confirm the diagnosis of IC.

M. Noda
Departments of Diabetes Research, Diabetes Research Center, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan
e-mail: mnoda@hosp.ncgm.go.jp

N. Uemura
Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Kohnodai Hospital, 1-7-1 Kohnodai, Ichikawa City, Chiba 272-8516, Japan
e-mail: nuemura@hospk.ncgm.go.jp

After confirmation of IC diagnosis, we excluded patients who did not undergo CT, those with inpatient-onset IC, and those with unknown baseline characteristics. The remaining outpatient-onset IC patients were selected as cases. They underwent CT within 48 h from admission but before endoscopy, and endoscopy was then performed within 1 week of admission.

Controls

The control subjects in this study comprised patients undergoing colorectal adenoma/cancer screening or surveillance for polyps at the same time as MDCT. They had requested MDCT primarily for the screening of cancer in other organs than for the purposes of the present study. They underwent CT within 6 months of colonoscopy. Of them, we excluded subjects whose information was not recorded in our prospective database [13]. We then excluded patients with colorectal cancer, adenoma, or diverticulosis because these diseases are known to be associated with intra-abdominal fat [14, 15]. To minimize confounding effects, controls were randomly selected from the individuals matched for decennial age and sex with a case-to-control ratio of 1:1.

This study was approved by the ethics committee of NCGM (No. 1012).

Measurement of IC-Related Clinical Outcomes

IC-related clinical outcomes were the location of colitis, the need for blood transfusion during hospitalization, and the length of hospital stay. We classified the location of colitis into two types: right-sided (ascending colon involvement) and left-sided, because right-sided IC has been reported to be associated with poor outcomes [16]. Blood transfusion was indicated for patients whose hemoglobin level fell below 7.0 g/dL (or 8.0 g/dL in those with unstable vital signs) [17]. After spontaneous cessation of bleeding with conservative treatment or hemostasis, all patients were started on a liquid diet and gradually progressed to a solid diet over 3 days, before being discharged.

Exposure Measurements

Subjects were asked by questionnaire on the same day as pre-colonoscopy about alcohol and smoking status, medication use, height, weight, and medical history of diabetes mellitus, dyslipidemia, and hypertension. IC patients' data were collected from the medical records for unanswered questionnaire items to avoid omissions. Smoking status was classified as current (daily or occasionally), ever, or never. Hypertension, diabetes mellitus, and dyslipidemia were considered to be present in patients taking specific drugs for these conditions. The use of any oral drugs approved in Japan was assessed by questionnaire with photographs of each drug provided. Use of a drug was defined as intermittent or regular oral administration within 2 weeks before colonoscopy. Patients were asked about their use of nonsteroidal anti-inflammatory drugs, low-dose aspirin, non-aspirin anti-platelet drugs, anticoagulants, and acetaminophen. BMI was calculated as weight divided by height squared (kg/m^2). Subjects were categorized according to Western BMI [18] (<20.0, 20.0–24.9, 25.0–29.9, and ≥ 30.0) and Asian BMI [19] (<18.5, 18.5–22.9, 23.0–27.4, and ≥ 27.5) standards.

Measurement of Abdominal Adipose Tissue Areas by Multidetector CT

The technique used for measuring the adipose tissue area on CT images has been previously standardized and validated [20] and has only negligible interobserver variation [21]. Subjects were assessed in the supine position with a 320-row area detector CT scanner (Aquilion ONE; Toshiba Medical Systems, Japan). All CT examinations were performed using helical scanning with the following parameters: 64 × 0.5 mm collimation, 120 kV, 0.83 autoexposure control beam pitch (table feed per gantry, 53 mm; collimation beam width, 64 mm), 0.5-s gantry rotation time, 512 × 512 matrix, and 350- to 500-mm field of view. All images were reconstructed using a standard reconstruction algorithm with a section thickness of 5 mm. The cross-sectional surface area (cm^2) of different abdominal fat compartments was automatically calculated at the iliac crest, corresponding to the L4/5 level and the level of the umbilicus level, using commercially available CT software (Aquilion ONE; Toshiba Medical Systems) in order to electronically determine the adipose tissue area by setting attenuation values within the range of −150 to −30 Hounsfield units for a region of interest. The visceral adipose tissue (VAT) area was defined as intra-abdominal fat bound by the parietal peritoneum or transversalis fascia, excluding the vertebral column and paraspinal muscles. The subcutaneous adipose tissue (SAT) area was defined as fat superficial to the abdominal and back muscles. A region of interest drawn around the external margin of the dermis was used to calculate the total adipose tissue area. The SAT area was obtained by subtracting the VAT area from the total adipose tissue area.

Statistical Analysis

Patient characteristics were compared between cases and controls using Pearson's Chi-squared test or Fisher's exact test as appropriate. We used logistic regression analysis to

estimate the association between IC and BMI, VAT area, and SAT area by computing odds ratios. The Cochrane–Armitage test between the proportion of IC and quartiles of SAT and VAT showed P values <0.1, in a departure from trend, which indicates nonlinearity; therefore, we selected qualitative variables (quartiles) to evaluate the relationship between obesity and IC. The lowest quartiles of the VAT area and SAT area were selected as reference groups prior to analysis. Multivariate analysis was conducted after adjusting for hypertension, diabetes mellitus, and dyslipidemia, which are known risk factors for IC [1–3] (Model 1). We then conducted multivariate analysis including the BMI index in addition to hypertension, diabetes mellitus, and dyslipidemia (Model 2) to determine the association between abdominal fat accumulation and IC development. We also determined the association between the clinical outcomes of IC (i.e., location of colitis, blood transfusion requirement, and length of hospital stay) and BMI, VAT area, and SAT area. The odds ratio and 95 % confidence interval were estimated for each factor, and $P < 0.05$ was considered significant. All statistical analysis was performed using Stata version 10 software (StataCorp, College Station, TX, USA).

Results

Patients

Cases

During the study period, 120 patients who underwent endoscopy had suspected IC. After excluding patients who did not undergo CT and those who did not fulfill the diagnostic criteria of IC, 62 patients were diagnosed with IC. Of them, four with inpatient-onset IC or unknown baseline characteristics were excluded, leaving 58 outpatient-onset IC patients for enrollment and analysis.

Controls

During the same period, 2,949 adults underwent colonoscopy and CT for cancer screening in the colorectal region or other organs. Of them, 2,060 subjects with no data recorded in the prospective database were excluded, and we then excluded 466 patients diagnosed with colorectal tumor or diverticulosis. Finally, age- and sex-matched controls were randomly selected, and data from a total of 116 subjects (58 IC patients, 58 controls) were analyzed.

The baseline characteristics of the total 116 subjects enrolled are shown in Table 1. Dyslipidemia was significantly associated with IC. Mean VAT area and total adipose tissue level were significantly higher in cases than in controls, while mean SAT area was marginally higher in cases. No significant differences were found in the other factors between cases and controls. Men had a higher VAT area and lower SAT area than women, and VAT area increased significantly with age ($P < 0.001$) (Table 2). Pearson's correlation test revealed correlations between the following obesity indices: BMI and VAT area ($r = 0.40$, $P < 0.001$); BMI and SAT area ($r = 0.55$, $P < 0.001$); and VAT area and SAT area ($r = 0.47$, $P < 0.001$).

Abdominal Fat and IC

In univariate analysis, IC was positively associated with VAT and SAT areas for trend but was not associated with BMI or the VAT-to-SAT ratio (Table 3). In multivariate analysis (Model 1), IC was not associated with Western BMI scores, Asian BMI scores, or the VAT/SAT ratio (P for trend 0.460, 0.205, and 0.867, respectively); however, it was marginally associated with VAT area (P for trend 0.094) and significantly associated with SAT area for both categorical data and trend (P for trend 0.030). When BMI was simultaneously considered (Model 2), IC remained marginally associated with VAT area for trend (P for trend 0.077) and significantly associated with SAT area (P for trend 0.016). The highest quartile of SAT area was associated with a 5.9-fold risk of IC compared with that of the lowest quartile. Analysis was not conducted separately by sex because no significant interactions were found between sex and VAT area ($P = 0.59$), sex and SAT area ($P = 0.54$), or sex and BMI ($P = 0.41$).

Effect of Abdominal Fat on Clinical Outcomes in Patients with IC

IC was left-sided in 55 cases (95 %) and right-sided in three cases (5 %). For 55 cases (95 %), admission was required, for a median length of 8 days (interquartile range 6–11). Two cases (3 %) required blood transfusion. No significant differences were noted between any of the obesity indices and the distribution type of colitis, blood transfusion, or length of hospital stay (Table 4).

Discussion

To our knowledge, this is the first age- and sex-matched case–control study to show that outpatient-onset IC is associated with higher VAT and SAT area values as measured by CT, but not with BMI. The location of colitis, blood transfusion requirements, and the length of hospital stay were not associated with any of the obesity indices.

The development of IC is associated mainly with atherosclerosis, thromboembolic disease, hypoperfusion

Table 1 Subject characteristics for cases (patients with ischemic colitis) and sex- and age-matched controls

	Cases ($n = 58$)	Controls ($n = 58$)	P value
Age (years)	61.5 ± 17.3	61.5 ± 16.9	0.989
Age ≥65 (years)	28 (48.3)	31 (53.5)	0.577
Male sex	20 (34.5)	20 (34.5)	1.000
Lifestyle factors			
Current smoker	11 (19.0)	11 (19.0)	1.000
Ever smoker	13 (22.4)	12 (20.7)	0.821
Never smoker	34 (58.6)	35 (60.3)	0.850
Current drinker	30 (51.7)	26 (44.8)	0.457
Chronic disease and medication			
Hypertension	22 (37.9)	21 (36.2)	0.848
Diabetes mellitus	7 (12.1)	9 (15.5)	0.590
Dyslipidemia	23 (39.7)	9 (15.5)	**0.004**
Use of NSAIDs[a]	9 (15.5)	4 (6.90)	0.238[d]
Use of low-dose aspirin[b]	10 (17.2)	9 (15.5)	0.802
Use of non-aspirin anti-platelets[c]	7 (12.1)	6 (10.3)	0.769
Use of anticoagulants	4 (6.9)	3 (5.2)	1.000[d]
Use of acetaminophen	1 (1.7)	1 (1.7)	1.000[d]
Measures of obesity			
Height	158.4 ± 9.4	157.1 ± 9.9	0.418
Weight	54.5 ± 10.0	54.6 ± 14.0	0.724
BMI (kg/m^2)	21.6 ± 3.0	22.0 ± 4.5	0.699
VAT area (cm^2)	107.3 ± 68.1	80.2 ± 59.1	**0.025**
SAT area (cm^2)	134.4 ± 50.4	121.2 ± 82.7	0.085
VAT/SAT ratio	0.87 ± 0.60	0.87 ± 0.86	0.466
Total adipose tissue area (cm^2)	241.0 ± 95.5	201.4 ± 128.2	**0.038**

Values presented with a plus/minus sign are mean ± SD

Bold values indicate $P < 0.05$

NSAIDs nonsteroidal anti-inflammatory drugs, *BMI* body mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue

[a] NSAIDs include loxoprofen, diclofenac, naproxen, etodolac, zaltoprofen, meloxicam, lornoxicam, and celecoxib

[b] Low-dose aspirin includes enteric-coated aspirin (100 mg) and buffered aspirin (81 mg)

[c] Non-aspirin anti-platelets include ticlopidine, clopidogrel, cilostazol, dipyridamole, sarpogrelate hydrochloride, ethyl icosapentate, dilazep, limaprost, and beraprost

[d] Analyzed using Fisher's exact test

Table 2 Distribution of obesity index by age and sex

Obesity index	Sex	Value	P value*	Regression coefficient of age[a]	P value[‡]
BMI (kg/m^2)	Male	22.3 ± 4.0		−0.01	0.665
	Female	21.6 ± 3.7	0.276		
VAT (cm^2)	Male	116.3 ± 73.6		1.26	**<0.001**
	Female	81.9 ± 56.8	**0.011**		
SAT (cm^2)	Male	104.1 ± 54.3		0.58	0.122
	Female	140.2 ± 72.1	**0.004**		

Values presented with a ± sign are mean ± SD

Bold values indicate $P < 0.05$

BMI body mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue

* P values for differences between the sexes were calculated using the Mann–Whitney U test

[a] Denotes β coefficient and refers to an increase in the variables (obesity indices) with an increase in age of 1 year

[‡] P value from simple linear regression analysis

states, and hypercoagulable disorders [22, 23]. On the basis of our results, we posit that the main mechanism of IC development is atherosclerosis caused by abdominal visceral fat accumulation. This suggestion is based on the following reasoning. Firstly, cytokines such as interleukin-6 and TNF-α, various metabolites, and hormones from abdominal visceral fat can cause, directly or hepatically, systemic inflammation and increase clotting factors or adhesion molecules, leading to atherosclerosis [24]. Secondly, abdominal visceral fat increases the levels of plasminogen activator inhibitor 1, a rapid inhibitor of tissue plasminogen activator, and therefore makes abdominal visceral fat a potential risk factor for thrombosis of mesenteric feed arteries. Thirdly, insulin resistance due to

Table 3 Effect of BMI and intra-abdominal fat accumulation on the risk of ischemic colitis in cases and controls

Obesity index	Cases	Controls	Crude OR	*P* value	Adjusted OR Model 1[a]	*P* value	Adjusted OR Model 2[b]	*P* value
Western BMI category (kg/m^2)								
<20	15 (25.9)	21 (36.2)	1.00		1.00			
20–24.9	34 (58.6)	25 (43.1)	1.90 (0.82–4.41)	0.133	1.99 (0.83–4.80)	0.124		
25–29.9	8 (13.8)	9 (15.5)	1.24 (0.39–3.97)	0.712	1.20 (0.34–4.29)	0.780		
≥30	1 (1.72)	3 (5.17)	0.47 (0.44–4.93)	0.526	1.16 (0.89–15.1)	0.912		
P for trend				0.346		0.460		
Asian BMI category (kg/m^2)								
<18.5	8 (13.8)	10 (17.2)	1.00		1.00			
18.5–22.9	29 (50.0)	30 (51.7)	1.21 (0.42–3.49)	0.727	1.48 (0.47–4.58)	0.501		
23.0–27.4	20 (34.5)	11 (19.0)	2.27 (0.69–7.44)	0.175	2.52 (0.72–8.91)	0.150		
≥27.5	1 (1.72)	7 (12.1)	0.18 (0.02–1.77)	0.141	0.28 (0.03–3.13)	0.303		
P for trend				0.109		0.205		
VAT (cm^2)								
Quartile I (≤45.8)	8 (13.8)	21 (36.2)	1.00		1.00		1.00	
Quartile II (45.9–79.0)	17 (29.3)	12 (20.7)	3.72 (1.24–11.2)	**0.019**	3.31 (1.06–10.3)	**0.040**	3.60 (1.12–11.6)	**0.032**
Quartile III (79.1–127.5)	18 (31.0)	11 (19.0)	4.30 (1.42–13.0)	**0.010**	4.14 (1.26–13.6)	**0.019**	4.55 (1.34–15.4)	**0.015**
Quartile IV (≥127.6)	15 (25.9)	14 (24.1)	2.81 (0.94–8.39)	0.064	2.43 (0.74–8.00)	0.145	2.96 (0.79–11.1)	0.108
P for trend				**0.048**		0.094		0.077
SAT (cm^2)								
Quartile I (≤79.4)	7 (12.1)	22 (37.9)	1.00		1.00		1.00	
Quartile II (79.5–119.9)	18 (31.0)	11 (19.0)	5.14 (1.65–16.0)	**0.005**	4.27 (1.32–13.9)	**0.016**	4.62 (1.40–15.3)	**0.012**
Quartile III (120.0–166.2)	19 (32.8)	10 (17.2)	5.97 (1.90–18.8)	**0.002**	5.80 (1.69–19.9)	**0.005**	8.38 (2.12–33.1)	**0.002**
Quartile IV (≥166.3)	14 (24.1)	15 (25.9)	2.93 (0.96–8.99)	0.060	3.48 (1.06–11.4)	**0.039**	5.92 (1.38–25.5)	**0.017**
P for trend				**0.010**		**0.030**		**0.016**
VAT/SAT ratio								
Quartile I (≤0.457)	15 (25.9)	14 (24.1)	1.00		1.00		1.00	
Quartile II (0.458–0.673)	17 (29.3)	12 (20.7)	0.76 (0.27–2.13)	0.598	0.66 (0.22–1.96)	0.453	0.66 (0.22–1.96)	0.455
Quartile III (0.674–1.032)	13 (22.4)	16 (27.6)	1.32 (0.47–3.70)	0.600	0.98 (0.33–2.96)	0.975	0.99 (0.33–2.97)	0.979
Quartile IV (≥1.033)	13 (22.4)	16 (27.6)	1.32 (0.47–3.70)	0.600	0.84 (0.27–2.64)	0.763	0.84 (0.27–2.64)	0.761
P for trend				0.853		0.867		0.868

The numbers in parenthesis represent the 95 % confidence interval

Bold values indicate $P < 0.05$

OR odds ratio, *CI* confidential interval, *BMI* body mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue

[a] Adjusted for hypertension, diabetes, and dyslipidemia (Model 1)

[b] Adjusted for hypertension, diabetes, dyslipidemia, and BMI (Model 2)

abdominal visceral fat causes metabolic syndrome consisting of hypertension, diabetes mellitus, and dyslipidemia, which are well-known risk factors for atherosclerosis [25, 26].

Another possible mechanism of IC development is colonic mucosal inflammation in response to inflammatory cytokines. Pierre et al. found that the ratio of the abdominal visceral fat area to total abdominal fat area in 21 non-operated patients with CD was higher than that in 13 healthy volunteers matched for age, height, weight, and BMI [8]. Their findings suggested that abdominal visceral fat accumulation causes colonic mucosal inflammation.

In this study, we found a significant association between SAT and IC. Pou et al. [27] demonstrated that CT-measured SAT was positively related to levels of inflammatory biomarkers such as C-reactive protein, interleukin-6, and tumor necrosis factor receptor-2 as well as VAT. Tordjman et al. [28] recently observed that SAT has an inflammatory profile (i.e., IL-6 gene and macrophage accumulation) similar to that of VAT in nonalcoholic steatohepatitis subjects. Further, a literature review by Patel and Abate [29] indicated that SAT plays a role in insulin resistance and metabolic disorders different from that of VAT. These data support our findings of an

Table 4 Effect of obesity on the location of colitis, blood transfusion requirement, and length of hospital stay in cases with ischemic colitis ($n = 58$)

	BMI (kg/m^2)	*P* value	VAT (cm^2)	*P* value	SAT (cm^2)	*P* value
Location						
Left ($n = 55$)	21.8 ± 3.0		107.4 ± 68.6		136.5 ± 50.2	
Right ($n = 3$)	19.0 ± 1.1	0.053	107.1 ± 70.9	0.958	95.1 ± 45.4	0.155
Transfusion						
None ($n = 56$)	21.8 ± 2.9		107.9 ± 69.2		135.3 ± 50.9	
Requirement ($n = 2$)	17.5 ± 0.49	0.084	90.7 ± 0.28	0.725	109.7 ± 35.9	0.476
Hospital stay[a]						
≤8 days ($n = 29$)	21.8 ± 2.5		94.6 ± 63.4		130.3 ± 48.1	
≥9 days ($n = 26$)	21.3 ± 3.6	0.519	118.4 ± 68.8	0.189	136.0 ± 55.6	0.679

Values presented with a plus/minus sign are mean ± SD. *P* values were derived from the Mann–Whitney *U* test

BMI body mass index, *VAT* visceral adipose tissue area, *SAT* subcutaneous adipose tissue area

[a] Excluding patients without hospitalization ($n = 3$)

association between SAT and IC via systemic inflammation and insulin resistance.

Although BMI is a major indicator of obesity, it was not associated with IC in the present study. This may be due to the scarcity of obese patients (BMI ≥30) in our sample (3 %), although it reflects the general population in Japan [30]. However, BMI might be a better predictor of IC in Western countries. To date, as only scant data are available on the direct relationship between obesity and IC, further studies are desirable.

In this study, we examined the relationship between abdominal fat accumulation and poor outcomes of IC such as right-sided IC [4, 16], blood transfusion requirement, and length of hospital stay, but found no associations. In a study of 50 patients with CD, Bara et al. reported that the ratio of the visceral fat area to the subcutaneous fat area might be a biomarker of complicated CD [31], so abdominal visceral fat accumulation would appear to worsen intestinal inflammation through inflammatory cytokines. Given that the mechanism of IC is the same as that of CD, we postulated that abdominal visceral fat is associated with poor IC outcomes. Our negative findings for this may be due to few cases of poor clinical outcomes in our sample.

The strengths of the present study are that we applied strict IC diagnostic criteria, excluding patients with infectious colitis, and distinguished outpatient-onset from inpatient-onset IC, because the etiology and clinical outcomes between them are quite different [10]. On the other hand, this study also has limitations. First, information was not collected on potential risk factors such as chronic obstructive pulmonary disease, atrial fibrillation, constipation, and the use of antibiotics or female hormones [2, 3]. We also did not collect data on possible confounding factors such as waist circumference and waist-to-hip ratio. Second, although we conducted an age- and sex-matched case–control study, the sample population was relatively small, which may have resulted in the marginal significance observed for the association between IC and VAT. Third, the case–control design of the study itself is a limitation when clarifying the risks of IC. Further prospective cohort studies with a large number of subjects are needed to address this issue. Fourth, we did not perform sample estimation because our study was based on a descriptive and exploratory design.

In conclusion, abdominal fat accumulation as measured by CT, but not BMI, is associated with outpatient-onset IC, suggesting a significant role of abdominal fat accumulation in the development of IC through inflammation or atherosclerosis. However, no associations were found between the clinical outcomes of IC and abdominal fat accumulation.

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Conflict of interest None.

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発表論文

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ORIGINAL ARTICLE

Possible discrepancy of HbA1c values and its assessment among patients with chronic renal failure, hemodialysis and other diseases

Kaori Inoue[1,3] · Atsushi Goto[2,3] · Miyako Kishimoto[1] · Tetsuro Tsujimoto[1] · Ritsuko Yamamoto-Honda[1] · Hiroshi Noto[1] · Hiroshi Kajio[1] · Yasuo Terauchi[3] · Mitsuhiko Noda[2]

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Abstract
Background Glycated hemoglobin (HbA1c) and glycated albumin (GA) are frequently used as glycemic control markers. However, these markers are influenced by alterations in hemoglobin and albumin metabolism. Thus, conditions such as anemia, chronic renal failure, hypersplenism, chronic liver diseases, hyperthyroidism, hypoalbuminemia, and pregnancy need to be considered when interpreting HbA1c or GA values. Using data from patients with normal albumin and hemoglobin metabolism, we previously established a linear regression equation describing the GA value versus the HbA1c value to calculate an extrapolated HbA1c (eHbA1c) value for the accurate evaluation of glycemic control. In this study, we investigated the difference between the measured HbA1c and the eHbA1c values for patients with various conditions.
Methods Data sets for a total of 2461 occasions were obtained from 731 patients whose HbA1c and GA values were simultaneously measured. We excluded patients with missing data or changeable HbA1c levels, and patients who had received transfusions or steroids within the previous 3 months. Finally, we included 44 patients with chronic renal failure (CRF), 10 patients who were undergoing hemodialysis (HD), 7 patients with hematological malignancies and a hemoglobin level of less than 10 g/dL (HM), and 12 patients with chronic liver diseases (CLD).
Results In all the groups, the eHbA1c values were significantly higher than the measured HbA1c values. The median difference was 0.75 % (95 % CI 0.40–1.10 %, P for the difference is <0.001) in the CRF group, 0.80 % (95 % CI 0.30–1.65 %, P for the difference is 0.041) in the HD group, 0.90 % (95 % CI 0.90–1.30 %, P for the difference is 0.028) in the HM group, and 0.85 % (95 % CI 0.40–1.50 %, P for the difference is 0.009) in the CLD group.
Conclusions We found that the measured HbA1c values were lower than the eHbA1c values in each of the groups.

Keywords Glycated hemoglobin · Glycated albumin · Chronic renal failure

Introduction

Glycated hemoglobin (HbA1c) and glycated albumin (GA) are frequently used as glycemic control markers. HbA1c is used as the gold standard index of glycemic control in clinical practice for diabetes treatment [1]. Since the lifespan of erythrocytes is approximately 120 days, HbA1c reflects the plasma glucose levels over the past few months. The metabolic turnover of albumin is faster than hemoglobin, with a lifespan of approximately 17–23 days. Accordingly, GA is used as an index of short-term glycemic control [2].

Although these glycemic control markers are well correlated with blood glucose levels, HbA1c is influenced by alterations in hemoglobin metabolism and GA is influenced by alterations in albumin metabolism. In clinical practice,

✉ Mitsuhiko Noda
mnoda@hosp.ncgm.go.jp

1 Department of Endocrinology, Diabetes, and Metabolism, Center Hospital, National Center for Global Health and Medicine, Tokyo 162-8655, Japan

2 Department of Diabetes Research, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan

3 Department of Endocrinology and Metabolism, Yokohama City University Graduate School of Medicine, Yokohama 236-0004, Japan

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conditions such as anemia, chronic renal failure, hypersplenism, chronic liver diseases, hyperthyroidism, hypoalbuminemia, and pregnancy need to be considered when interpreting HbA1c or GA values.

In a previous study, we developed a linear regression equation describing the GA value versus the HbA1c value among participants without altered albumin metabolism or hemoglobin metabolism, to calculate an extrapolated HbA1c (eHbA1c) value for the accurate evaluation of glycemic control [3].

We often encounter patients with conditions affecting the turnover of either HbA1c or GA. In such patients, the measured HbA1c and GA values are likely to diverge from the equation. Earlier studies have evaluated the associations between mean blood glucose levels, HbA1c values, and GA values in patients on dialysis or patients with chronic liver diseases or hemolytic anemia [4–6]. However, the impact of each condition affecting the turnover of either HbA1c or GA on the direction and magnitude of the discrepancy between the measured HbA1c and eHbA1c, which is the equation developed in patients who were free of such conditions is not well understood. In this study, we investigated the differences between the measured HbA1c and the eHbA1c values in patients with various conditions.

Materials and methods

A flow diagram depicting this study is shown in Fig. 1. We retrospectively analyzed the medical charts of patients attending the National Center for Global Health and Medicine (Tokyo, Japan) during 2011, and selected data sets for a total of 2461 occasions from 731 patients (including non-diabetes patients) whose HbA1c and GA values were simultaneously measured. If these values were measured in a single patient on more than one occasion, we selected the data set containing the smallest HbA1c value.

We excluded patients whose previous HbA1c values were missing or whose HbA1c levels were changeable and selected 550 patients. We then excluded patients without albumin, hemoglobin or eGFR data, and patients who had been treated with transfusions or steroids within the previous 3 months. Finally, we included 44 predialysis patients with an eGFR of less than 30 mL/min/1.73 m^2 chronic renal failure (CRF), 10 patients who were undergoing hemodialysis (HD), 7 patients with hematological malignancies and their hemoglobin level of less than 10 g/dL (HM), and 12 patients with chronic liver diseases (CLD). We further excluded patients who had combinations of these diseases, since the aim of this study was to investigate the impact of each condition on the turnover of either HbA1c or GA, as well as the direction and magnitude of the discrepancy. We did not include patients who were pregnant or who had hyperthyroidism because the data was insufficient for an analysis.

HbA1c was measured using high-performance liquid chromatography (HPLC) (ARKRAY ADAMS-A1C HA-8160; Kyoto, Japan) and was corrected to the National Glycohemoglobin Standardization Program (NGSP) values [7]. GA was measured using an enzymatic method with albumin-specific proteinase, ketoamine oxidase, and an albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) using an autoanalyzer (Hitachi 770; Hitachi Instruments Service Co., Tokyo, Japan). Each patient was assessed for clinical features such as age, sex, height, body weight, body mass index, blood and urine sample data, history and duration of diabetes mellitus, medications, and complications based on the data contained in the medical records.

This study was approved by the institutional ethical committee of the National Center for Global Health and Medicine (approval number: 1141) and was performed in accordance with the Declaration of Helsinki.

Statistical analysis

We performed the statistical analyses using Stata/IC 11. Data for the patient characteristics are shown as the mean ± SD. To investigate the difference between the eHbA1c and measured HbA1c values, we calculated 95 % confidence intervals (CI) of the median of the difference using a bootstrap method (2000 bootstraps), and determined the *P* values for the difference using the Wilcoxon signed-rank test.

Results

The clinical characteristics in each group are shown in Table 1. Patients in the HM group were less likely to have diabetes than patients in the other groups. The HbA1c, GA, hemoglobin, albumin, and eHbA1c levels were lower in the HM group than the other groups. The eGFR levels in the CRF and HD groups were lower than the other groups. Patients in the CRF and HD groups tended to have proteinuria and require erythropoietin or iron preparations.

In our previous study, we established the following equation: $eHbA1c = 0.216 \times GA + 2.978$ [3]. Figure 2 shows scatter plots for the HbA1c values versus the GA values for each group with a line for the equation.

In all the groups, the eHbA1c values (i.e., the line for the equation in Fig. 2) tended to be higher than the measured HbA1c levels. We further analyzed the medians of the differences between the eHbA1c and measured HbA1c values, and calculated the corresponding 95 % CI and *P* values for each group (Table 2). In all the groups, the

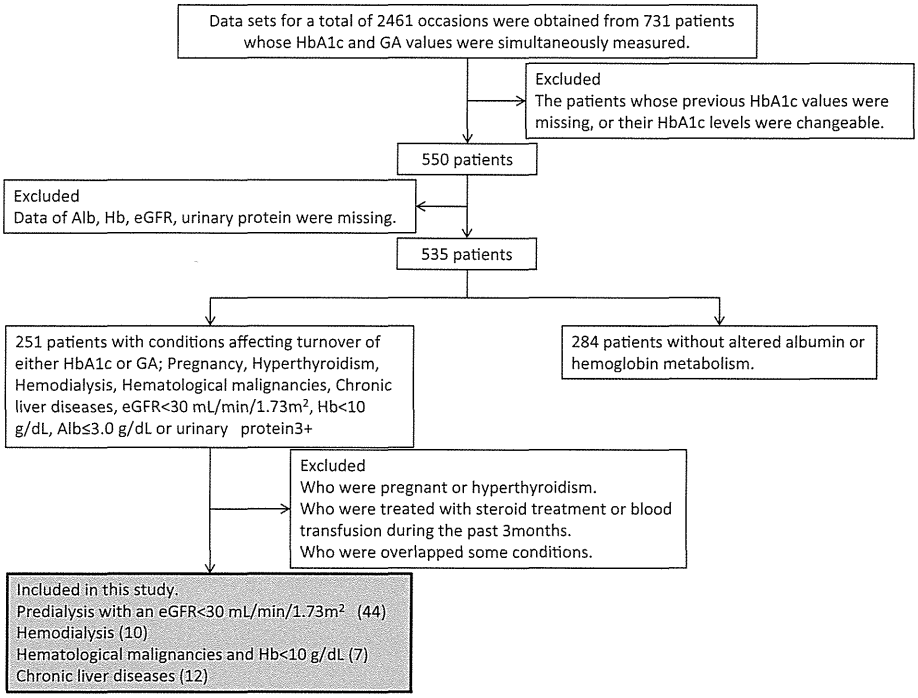

Fig. 1 Flow diagram depicting the study. Data sets for a total of 2461 occasions were obtained from 731 patients (including non-diabetes patients) whose HbA1c and GA values were simultaneously measured. If these values were measured in the patients on more than one occasion, the data set containing the smallest HbA1c value was selected. We then excluded patients whose previous HbA1c values were missing or whose HbA1c levels were changeable, selecting 550 patients. We excluded patients without albumin, hemoglobin or eGFR data, and patients who had been treated with transfusions or steroids within the previous 3 months. Finally, we included 44 predialysis patients with an eGFR of less than 30 mL/min/1.73 m^2 (CRF), 10 patients who were undergoing hemodialysis (HD), 7 patients with hematological malignancies and their hemoglobin level of less than 10 g/dL (HM), and 12 patients with chronic liver diseases (CLD). We further excluded patients who had combinations of these diseases, since the aim of this study was to investigate the impact of each condition affecting the turnover of either HbA1c or GA on the direction and magnitude of the discrepancy

eHbA1c values were significantly higher than the measured HbA1c levels. The median of the difference was 0.75 % (95 % CI 0.40–1.10 %, *P* for the difference is <0.001) in the CRF group, 0.80 % (95 % CI 0.30–1.65 %, *P* for the difference is 0.041) in the HD group, 0.90 % (95 % CI 0.90–1.30 %, *P* for the difference is 0.028) in the HM group, 0.85 % (95 % CI 0.40–1.50 %, *P* for the difference is 0.009) in the CLD group.

Discussion

In this study, we calculated the eHbA1c value using an equation for each of the several groups of patients suffering from various diseases, and investigated the difference from the measured HbA1c values. Few studies have investigated the difference between estimated values and actual measurements of HbA1c.

The patients were classified into 4 groups as follows: 44 patients with chronic renal failure, 10 patients undergoing hemodialysis, 7 patients suffering from hematological malignancies and who had a hemoglobin level of less than 10 g/dL, and 12 patients who were suffering from chronic liver diseases. In all of the groups, the eHbA1c values were significantly higher than the measured HbA1c values. These results suggested that the measured HbA1c values in these groups may be underestimated in clinical practice.

In cases with chronic renal failure, renal anemia lowers the HbA1c values because the lifespan of the erythrocytes is shortened. The HbA1c and eGFR values are reportedly correlated with the lifespan of the erythrocytes in patients with diabetic nephropathy [8]. It has also been reported that the values of HbA1c are underestimated in patients with diabetic nephropathy undergoing peritoneal dialysis or hemodialysis [9]. Furthermore, the HbA1c values in patients who were treated with erythropoietin were lower than those patients who were not treated, since the life span of the erythrocytes is shortened [10]. Because renal anemia is unlikely to affect the GA value, GA may be useful in patients with renal anemia. Although HbA1c has been commonly measured, several professional societies (e.g., the Japanese Society for Dialysis Therapy [11]) now recommend GA measurements for such patients. Our findings further suggest that eHbA1c may be a useful marker for the

Table 1 Clinical characteristics in each groups

	Predialysis with an eGFR <30 mL/min/1.73 m^2 (n = 44)	Hemodialysis (n = 10)	Hematological malignancies and Hb <10 g/dL (n = 7)	Chronic liver diseases (n = 12)
Men (n)	35	8	5	6
Age (years)	66.8 ± 12.0	67.8 ± 11.7	69.3 ± 18.2	71.5 ± 10.3
HbA1c (%)	6.8 ± 1.3	6.4 ± 0.9	5.7 ± 0.5	7.1 ± 0.8
GA (%)	20.8 ± 5.7	19.7 ± 4.5	16.1 ± 2.0	22.9 ± 4.4
Hb (g/dL)	11.3 ± 1.8	10.9 ± 1.6	8.7 ± 0.8	12.1 ± 1.6
Alb (g/dL)	3.7 ± 0.5	3.6 ± 0.9	2.9 ± 0.7	3.7 ± 0.4
eHbA1c (%)	7.5 ± 1.2	7.3 ± 1.0	6.4 ± 0.4	7.9 ± 1.0
eGFR (mL/min/1.73 m^2)	16.6 ± 7.8	–	123.3 ± 104.1	69.0 ± 14.4
Diabetes (n)	43	9	2	11
Urinary protein3+ (n)	13	4	0	0
Using erythropoietin (n)	19	6	0	0
Using iron preparation (n)	7	2	0	1
				Mean ± SD

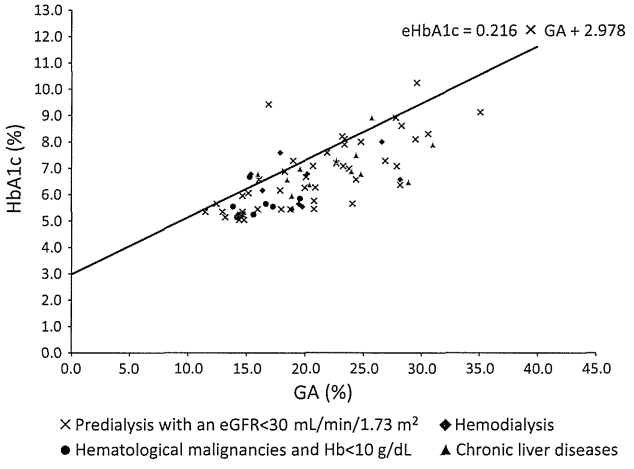

Fig. 2 Scatter plots for HbA1c values versus GA values in each group. In our previous study, we established the following equation: eHbA1c = 0.216 × GA + 2.978. Scatter plots for the HbA1c values versus the GA values are shown for each group with a line for the equation. In all the groups, the eHbA1c values tended to be higher values than the measured HbA1c levels

Table 2 The medians of the difference between eHbA1c and measured HbA1c values in each groups

	The median of the difference between eHbA1c and measured HbA1c values (%)	95 % CI	P values
Predialysis with an eGFR <30 mL/min/1.73 m^2 (n = 44)	0.75	0.40–1.10	<0.001
Hemodialysis (n = 10)	0.80	0.30–1.65	0.041
Hematological malignancies and Hb <10 g/dL (n = 7)	0.90	0.90–1.30	0.028
Chronic liver diseases (n = 12)	0.85	0.40–1.50	0.009

evaluation of glycemic control in patients with CRF or HD. However, a careful consideration is required in patients with diabetic nephropathy with marked proteinuria. The GA values are affected by the increased turnover of albumin metabolism and tend to decrease independent of glycemic state in patients with marked proteinuria [12], indicating their possible limited ability to evaluate glycemic control in such patients. Because the number of patients with marked proteinuria was relatively small in the present study, further studies are needed to clarify whether eHbA1c or GA is more useful than HbA1c in such patients.

In this study, we investigated 7 patients who were suffering from hematological malignancies and who had a hemoglobin level of less than 10 g/dL. Both the measured HbA1c and the eHbA1c levels in the HM group were lower than those in the other groups. The lower frequency of patients with diabetes in the HM group may explain the lower GA and eHbA1c levels. HbA1c values are known to be low, relative to the glucose levels in patients with hemolytic anemia because the lifespan of the erythrocytes is shortened in patients with this condition [6]. Moreover, in patients with iron deficiency anemia, the HbA1c values tend to be higher than in healthy individuals but decrease after iron treatment [13]. Although the mechanisms remain to be investigated, the altered lifespan of erythrocytes may partially explain the difference between the measured HbA1c and eHbA1c levels in the HM group observed in this study.

In chronic liver diseases, such as chronic hepatitis and liver cirrhosis, hypersplenism lowers the HbA1c values because of the shortened lifespan of the erythrocytes,

whereas, it raises the GA values because of reduced albumin synthesis and the prolonged half-life of serum albumin [5, 14]. Although neither marker reflects the plasma glucose control status accurately, we found the eHbA1c values were significantly higher than the measured HbA1c values in the CLD group.

Our study had several limitations. First, we retrospectively selected patients in whom simultaneous HbA1c and GA measurements had been obtained. Thus, a selection bias may exist. We excluded the patients, whose previous HbA1c values were missing or their HbA1c levels were changeable, but we couldn't exclude the patients who had become good control over past few weeks. Second, as the data were collected from a single hospital and the GA values were not standardized, the present results might not be directly applicable to other hospitals. Third, the small sample size might limit the applicability of the findings. In clinical situation, patients with various conditions affect the GA values, so we should take consideration to use the equation of the eHbA1c.

In conclusion, we found that the measured HbA1c values were lower than the eHbA1c values in groups of patients with chronic renal failure, who were undergoing hemodialysis, suffering from hematological malignancies and had a hemoglobin level of less than 10 g/dL, and who had chronic liver diseases.

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Conflict of interest None of the authors have any potential conflicts of interest associated with this research.

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