



Elevated serum galectin-3 levels predict the incidence of type 2 diabetes mellitus in a Japanese general population: A 10-year follow-up study

Harumi Yoshimura-Takubo¹ , Mika Enomoto^{1,2*}, Ako Fukami^{1,3}, Nagisa Morikawa^{1,4} , Yume Nohara-Shitama¹, Hiromi Sato¹, Mayo Shimoyama-Yamamoto¹, Hisashi Adachi^{1,5}, Yoshihiro Fukumoto¹

¹Division of Cardio-Vascular Medicine, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan, ²Department of Sports Medicine and Science, Faculty of Human Health, Kurume University, Kurume, Japan, ³Preventive Health and Screening Center, Kurume University Hospital, Kurume, Japan, ⁴Department of Community Medicine, Kurume University School of Medicine, Kurume, Japan, and ⁵Keikokai, Hara Hospital, Fukuoka, Japan

Keywords

galectin-3, obesity, type 2 diabetes mellitus

*Correspondence

Mika Enomoto

Tel.: +81-942-43-4411

Fax: +81-942-43-4797

E-mail address:

emika@kurume-u.ac.jp

J Diabetes Investig 2026

doi: [10.1111/jdi.70326](https://doi.org/10.1111/jdi.70326)

ABSTRACT

Aims/Introduction: Although several studies have reported elevated serum galectin-3 levels in type 2 diabetes mellitus, its association with type 2 diabetes mellitus, in Japan, where obesity is relatively uncommon, remains unclear. We investigated whether serum galectin-3 levels can be a predictive marker for type 2 diabetes mellitus in a Japanese general population.

Materials and methods: A total of 433 participants who underwent a health check-up in Nagasaki between 2013 and 2014 were enrolled; of these, 307 participants completed follow-up by 2023. Participants were classified into quartiles based on serum galectin-3 levels measured by a sandwich enzyme immunoassay, and multivariate logistic regression analysis was performed.

Results: The serum galectin-3 levels were associated with type 2 diabetes mellitus prevalence ($P = 0.002$) in the regression analysis. Over the 10-year follow-up, the highest galectin-3 quartile had a higher type 2 diabetes mellitus incidence than the lowest galectin-3 quartile (adjusted odds ratio: 5.75; 95% confidence interval: 1.08–30.65). Subgroup analysis stratified by body mass index revealed that each 1-standard deviation increase in serum galectin-3 level was associated with a significantly increased risk of incident type 2 diabetes mellitus in the low body mass index group, but not in the high body mass index group.

Conclusions: The serum galectin-3 levels were significantly associated with type 2 diabetes mellitus prevalence and incidence in a general Japanese population, particularly among individuals without obesity. Galectin-3 may be a useful biomarker for identifying individuals at risk of type 2 diabetes mellitus.

INTRODUCTION

Galectin-3 is a multifunctional protein involved in various biological processes, including cell metastasis and apoptosis. Galectin-3 plays a role in inflammation^{1, 2}, fibrosis², and atherosclerosis³, thereby contributing to the pathogenesis of cardiac and renal diseases^{3, 4}. Recent evidence suggests that

galectin-3 plays a key role in insulin resistance⁵. Elevated galectin-3 levels have been observed in individuals with obesity⁶.

Type 2 diabetes mellitus (T2DM) is primarily caused by insulin resistance, which is induced by adipokines secreted from the visceral fat that is commonly increased by obesity⁷. Previous studies have shown that serum galectin-3 levels increase in the prediabetic stage⁸, however, the underlying mechanism remains

Received 12 November 2025; revised 23 December 2025; accepted 22 April 2026

unclear, and no studies to date have examined the association between galectin-3 and T2DM in Japan. Investigating the relationship between galectin-3 and T2DM may facilitate the timely detection of T2DM and the development of novel therapeutic strategies, potentially contributing to cardiovascular disease (CVD) prevention.

The association between galectin-3, T2DM, and obesity in general populations has been previously examined^{6, 9, 10}. However, galectin-3 is not routinely measured in clinical practice in Japan, and to the best of our knowledge, no study has evaluated the relationship between galectin-3 and T2DM in the Japanese general population. Notably, the Japanese population has a relatively low obesity prevalence, with only 27.2% of adults having a body mass index (BMI) of ≥ 25 kg/m²¹¹, as compared to the global population, where 43 and 16% of the adults have BMIs of 25–29 and ≥ 30 kg/m², respectively. In the present study, we aimed to investigate whether galectin-3 may serve as a predictive marker for the development of T2DM in a Japanese general population, where obesity is less prevalent.

MATERIALS AND METHODS

Study design, setting, and period

This study is a population-based study conducted between 2013 and 2014. Since 2002, we have been investigating the association between various biomarkers and CVD for more than 20 years. This involves annually screening approximately 200 randomly selected residents of Uku Island (population approximately 2,200), located in Nagasaki Prefecture in southwestern Japan. Our previous studies, for example, examined the relationships between serum proprotein convertase subtilisin/kexin type 9 and low-density lipoprotein cholesterol (LDL-c) and lipoprotein(a), as well as between plasma fetuin-A levels and metabolic syndrome^{12, 13}. Uku Island has a high aging rate and represents future demographic trends in Japan. Moreover, as an isolated island with minimal population inflow or outflow, it provides an ideal setting for longitudinal studies.

Study population

A total of 439 individuals underwent cardiovascular screening procedures and blood tests. Of these, 6 individuals with missing data were excluded. As a result, 433 individuals were included in the cross-sectional analysis, and 275 individuals who did not have diabetes at baseline among the 307 who underwent cardiovascular screening again by 2023 were included in the longitudinal analysis.

Study procedures

Anthropometric measurements

Height and weight were measured to calculate for the BMI [weight (kilograms) divided by the square of height (square meters)], which was utilized as an index of the presence or absence of obesity. Waist circumference was measured at the umbilical level in a standing position.

Vital signs

Blood pressure (BP) was measured twice in the sitting position at 3-min intervals using an upright standard sphygmomanometer. Hypertension (HT) was defined as a systolic BP of ≥ 140 mmHg, a diastolic BP of ≥ 90 mmHg, or current use of antihypertensive medications.

Laboratory tests

Laboratory measurements included high-sensitivity C-reactive protein (Hs-CRP), serum creatinine (Crea), fasting plasma glucose (FPG), insulin, glycated hemoglobin A1c (HbA_{1c}), LDL-c, triglycerides (TG), high-density lipoprotein (HDL-c), and galectin-3.

The estimated glomerular filtration rate (eGFR) was calculated using a formula for dietary modification in renal disease, applying Japanese coefficients based on serum creatinine levels, age, and sex¹⁴.

Fasting blood samples were drawn from the antecubital vein in the morning after a 12-h fast and centrifuged within 1 h of collection. Insulin resistance was assessed using the homeostasis model assessment index (HOMA-IR), calculated as FPG (mg/dL) \times insulin (μ U/mL)/405. Beta cell function was assessed using the homeostatic model assessment of beta cell function (HOMA- β), calculated as insulin (μ U/mL) \times 360/[FPG (mg/dL)-63]¹⁵. T2DM was defined as an FPG level of ≥ 7.0 mmol/L, HbA_{1c} level of ≥ 47 mmol/mol, or the current use of oral hypoglycemic agents or insulin therapy¹⁶.

Dyslipidemia (DL) was defined as having an LDL-c level of ≥ 3.62 mmol/L, TG level of ≥ 1.69 mmol/L, or an HDL-c level of ≤ 1.03 mmol/L, or as the use of lipid-lowering medications. Serum galectin-3 concentrations were measured at baseline only, using a sandwich enzyme immunoassay method (Immunobiology Laboratory, Gunma, Japan). The intra- and inter-assay coefficients of the galectin-3 level variations were $< 15\%$, as validated by a commercial laboratory (SRL Inc., Fukuoka, Japan)¹⁷.

Data collection

At both baseline and follow-up, the participants completed a self-administered questionnaire, underwent physical examinations, and provided fasting blood samples. The participants' medical history, smoking habits, and alcohol consumption were assessed using a questionnaire. Dietary intake was evaluated utilizing the Brief-type Self-Administered Diet History Questionnaire (BDHQ), which was adjusted for the traditional Japanese diet. Energy intake from fat, protein, and carbohydrate was calculated accordingly^{18, 19}.

Statistical methods

First, a box plot of serum galectin-3 levels was created to confirm its left skewness, after which the skewness correlation with age was examined. Baseline characteristics were summarized as mean (standard deviation) for continuous variables and number (percentage) for categorical variables, stratified by quartiles of

serum galectin-3 levels. Insulin, TG, galectin-3, Hs-CRP, HOMA-IR, and HOMA-β were log-transformed to correct for skewed distributions and then reconverted to antilogarithmic values for presentation in Tables 1 and 2. Between group differences across the four quartile groups were assessed using analysis of variance for continuous variables and the chi-squared test for categorical variables. Second, we performed univariate linear regression with serum galectin-3 levels as an objective variable and T2DM occurring at 10 years as the dependent variable. Finally, we performed multiple logistic regression analysis using galectin-3 quartiles with the lowest quartile as the reference, and another multiple logistic regression analysis for each 1-SD increase in galectin-3.

We performed subgroup analyses by BMI and waist circumference using a logistic regression analysis. We classified all participants into the following two groups: low (BMI <25 kg/m²) and high (BMI ≥25 kg/m²) BMI groups. We also used the metabolic syndrome criteria²⁰ to classify the participants into the low (waist circumference: men, <85 cm; women, <90 cm) and

high (men, ≥85 cm; women, ≥90 cm) waist circumference groups. In this analysis, to obtain reliable estimates in each subgroup, we modeled the serum galectin-3 levels as continuous variables with a unit of 1-SD (standard deviation) increment.

Statistical significance was defined as *P* < 0.05. All statistical analyses were performed using the SAS system (Release 9.4, SAS Institute, Cary, NC, USA).

RESULTS

Participant selection

Complete data were available for 433 participants (176 men and 257 women aged 40–90 years). Of these, 87, 15, and 24 participants were excluded due to the lack of follow-up examination, relocation, and died during the follow-up period, respectively. Consequently, 307 participants who underwent repeat health examinations over a 10-year period until 2023, of whom 275 participants without T2DM at baseline were included in the present analysis. A flowchart for selecting the study participants is presented in Figure 1.

Table 1 | Characteristics of study subjects in galectin-3 quartiles at baseline

Characteristics	Total (n = 433)	Quartile 1 (lowest) (n = 108)	Quartile 2 (n = 108)	Quartile 3 (n = 107)	Quartile 4 (highest) (n = 110)	<i>P</i> for trend
Galectin-3 (pg/mL) [†]	2,815.0 (586.0–9,750.0)	1,258.7 (586.0–2,270.0)	2,724.7 (2,280.0–3,140.0)	3,568.1 (3,150.0–4,090.0)	5,086.3 (4,100.0–9,750.0)	<0.0001
Age (years)	67.0 ± 9.5	62.8 ± 9.2	66.4 ± 8.2	67.3 ± 9.5	71.5 ± 9.0	<0.0001
Men % (n: yes)	176 (40.6)	30 (27.8)	49 (45.4)	46 (43.0)	51 (46.4)	0.02
Height (cm)	157.1 ± 8.6	156.6 ± 7.7	157.5 ± 9.3	157.6 ± 8.2	156.7 ± 9.3	0.8
Weight (kg)	58.3 ± 11.4	58.3 ± 11.3	59.5 ± 12.1	56.2 ± 9.5	59.2 ± 12.5	0.1
BMI (kg/m ²)	23.5 ± 3.5	23.7 ± 3.6	23.8 ± 3.3	22.6 ± 3.1	24.0 ± 3.7	0.01
Waist circumference (cm)	84.1 ± 9.8	83.4 ± 9.7	85.8 ± 9.8	81.9 ± 8.9	85.1 ± 10.5	0.02
Smoking % (n: yes)	42 (9.7)	12 (11.1)	16 (14.8)	8 (7.5)	6 (5.5)	0.1
Alcohol intake % (n: yes)	179 (41.3)	42 (38.9)	49 (45.4)	43 (40.2)	45 (40.9)	0.8
HT % (n: yes)	305 (70.4)	62 (57.4)	77 (71.3)	77 (72.0)	89 (80.9)	0.002
T2DM % (n: yes)	51 (11.8)	5 (4.6)	11 (10.2)	17 (15.9)	18 (16.4)	0.02
DL % (n: yes)	230 (53.1)	67 (62.0)	59 (54.6)	54 (50.5)	50 (45.5)	0.09
CVD % (n: yes)	69 (15.9)	7 (6.5)	17 (15.7)	19 (17.8)	26 (23.6)	0.006
Hs-CRP (mg/L) [†]	0.04 (0.002–5.26)	0.03 (0.005–1.64)	0.03 (0.003–0.49)	0.05 (0.002–0.94)	0.05 (0.006–5.26)	0.0009
Crea (μmol/L)	70.7 ± 26.5	61.9 ± 8.8	61.9 ± 17.7	70.7 ± 35.4	70.7 ± 26.5	<0.0001
eGFR (mL/min/1.73 m ²)	88.2 ± 15.8	94.3 ± 12.1	90.5 ± 12.4	87.4 ± 16.7	80.9 ± 18.2	<0.0001
FPG (mmol/L)	5.4 ± 0.9	5.3 ± 0.9	5.4 ± 0.7	5.4 ± 1.0	5.6 ± 0.9	0.03
HbA _{1c} (%)	5.6 ± 0.5	5.5 ± 0.5	5.6 ± 0.4	5.6 ± 0.5	5.7 ± 0.5	0.04
Insulin (pmol/L) [†]	25.2 (4.8–133.2)	24.0 (4.8–114.0)	26.4 (7.8–84.0)	24.0 (6.6–135.0)	26.4 (5.4–108.6)	0.3
HOMA-IR [†]	1.0 (0.2–9.4)	0.9 (0.2–6.5)	1.1 (0.3–4.7)	1.0 (0.3–9.4)	1.1 (0.2–5.1)	0.2
HOMA-β [†]	47.9 (7.9–200.7)	49.0 (11.8–200.7)	51.1 (11.6–173.5)	45.7 (7.9–191.5)	46.2 (10.7–186.2)	0.4

Data are mean ± standard deviation, range, or percent. The bold of *p* values was defined as *p* < 0.05. BMI, body mass index; Crea, creatinine; CVD, cardiovascular disease; DL, dyslipidemia; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin A_{1c}; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-β, homeostatic model assessment of beta cell function; Hs-CRP, high sensitive C-reactive protein; HT hypertension; T2DM, type 2 diabetes mellitus. [†]These variables are shown in the original scale after analysis using log (natural)-transformed values.

Table 2 | Univariate linear regression analyses with serum galectin-3 levels at baseline

Variables	β	SE	<i>P</i>
Age	0.018	0.003	<0.001
Men (women: 1)	-0.215	0.056	<0.001
Height	0.003	0.003	0.330
Weight	0.001	0.002	0.785
BMI	-0.003	0.008	0.696
Waist circumference	0.002	0.003	0.430
Smoking (yes: 1)	-0.089	0.094	0.342
Alcohol intake (yes: 1)	0.040	0.056	0.475
HT (yes: 1)	0.205	0.060	<0.001
T2DM (yes: 1)	0.260	0.085	0.002
DL (yes: 1)	-0.122	0.055	0.028
CVD (yes: 1)	0.210	0.075	0.006
Hs-CRP [†]	0.063	0.022	0.005
Crea	0.449	0.108	<0.001
eGFR	-0.009	0.002	<0.001
FPG	0.006	0.002	0.001
HbA _{1c}	0.153	0.056	0.006
Insulin [†]	0.046	0.047	0.335
HOMA-IR [†]	0.068	0.042	0.109
HOMA- β [†]	-0.075	0.050	0.137

The bold of *p* values was defined as *p* < 0.05. BMI, body mass index; Crea, creatinine; CVD, cardiovascular disease; DL, dyslipidemia; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin A_{1c}; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA- β , homeostatic model assessment of beta cell function; Hs-CRP, high sensitive C-reactive protein; HT hypertension; SE, standard error; T2DM, type 2 diabetes mellitus. [†]These variables are shown in the original scale after analysis using log (natural)-transformed values.

Participant characteristics by quartiles of serum galectin-3 levels

The mean serum galectin-3 level at baseline was 2,815.0 pg/mL (range: 586.0–9,750.0 pg/mL) (Figure 2a). The serum galectin-3 levels were significantly positively correlated with age (*r* = 0.3, *P* < 0.0001) (Figure 2b). The baseline characteristics of the participants stratified by quartiles of serum galectin-3 levels are shown in Table 1. Increased serum galectin-3 levels were significantly associated with increasing age (*P* < 0.0001), male sex (*P* = 0.02), higher BMI (*P* = 0.01), greater waist circumference (*P* = 0.02), HT prevalence (*P* = 0.002), T2DM prevalence (*P* = 0.02), a history of CVD (*P* = 0.006), higher Hs-CRP (*P* = 0.0009), Crea (*P* < 0.0001), FPG (*P* = 0.03), and HbA_{1c} (*P* = 0.04), and lower eGFR (*P* < 0.0001).

Baseline assessments

Table 2 presents the results of the univariate linear regression analyses illustrating the correlation between the baseline patient characteristics and serum galectin-3 levels. Significant positive associations were observed between age, male sex, presence of HT or T2DM, history of CVD, and Hs-CRP, Crea, FPG, and

HbA_{1c} levels and serum galectin-3 levels in the univariate analysis. Conversely, significant negative associations were observed between the presence of DL and eGFR and serum galectin-3 levels. No significant associations were observed between insulin, HOMA-IR, or HOMA- β and serum galectin-3 levels.

Univariate and multivariate logistic regression analyses illustrating the relationship between the quartiles of serum galectin-3 levels and T2DM prevalence at baseline are shown in Table 3. In the highest quartile of serum galectin-3 levels, the odds ratio of developing T2DM was significantly higher compared to the lowest quartile (odds ratio: 4.03 [95% confidence interval [CI]: 1.44–11.29]), but this significance disappeared after multivariate adjustment.

Follow-up assessments

Among the 307 participants who were followed up longitudinally, 32 (10.4%) had T2DM at baseline. Among the remaining 275 participants without T2DM at baseline, 27 (9.8%) developed new-onset T2DM over the 10-year follow-up period. Individuals in the highest quartile of the baseline serum galectin-3 levels had a significantly higher incidence of T2DM than those in the lowest quartile, even after adjusting for confounding factors (adjusted odds ratio: 5.75 [95% CI: 1.08–30.65]) (Table 4). Furthermore, the odds ratio for the incidence of T2DM per 1-SD increase in serum galectin-3 levels showed a trend toward higher values, although not statistically significant, after adjusting for confounding factors including age, sex, baseline BMI, and FPG consistent with the findings (adjusted odds ratio: 1.49 [95% CI: 0.89–2.49], *P* = 0.13).

Subgroup analysis

In the follow-up assessment, the odds of incident T2DM for each 1-SD increase in serum galectin-3 level were associated with significantly higher odds ratio of incident T2DM (adjusted odds ratio: 2.48 [95% CI: 1.13–5.47]) within the low BMI group. Contrarily, in the high BMI group, there was no association between the serum galectin-3 levels and the incidence T2DM.

In the low waist circumference group, each 1-SD increase in serum galectin-3 level was associated with higher odds of incident T2DM and was significantly elevated (adjusted odds ratio: 2.59 [95% CI: 1.27–5.28]). However, in the high waist circumference group, there was no association between the serum galectin-3 levels and T2DM.

The forest plots as odds ratios for the incidence of T2DM stratified by BMI and waist circumference are shown in Figure 3a,b.

DISCUSSION

In the present cohort study involving a general Japanese population, the mean serum galectin-3 level was 2,815.0 pg/mL, which is comparable to the value reported in a prior Japanese study involving a small general population²¹. Contrarily, a population-based study from the Netherlands reported a higher

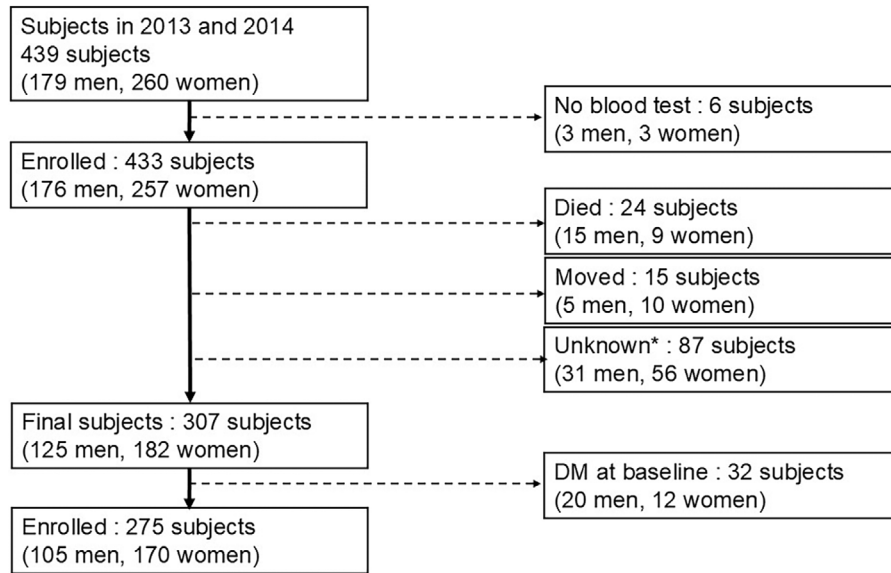


Figure 1 | Flowchart of the selection of study participants. *: still alive but has not undergone the second cardiovascular screening procedure and blood tests since baseline

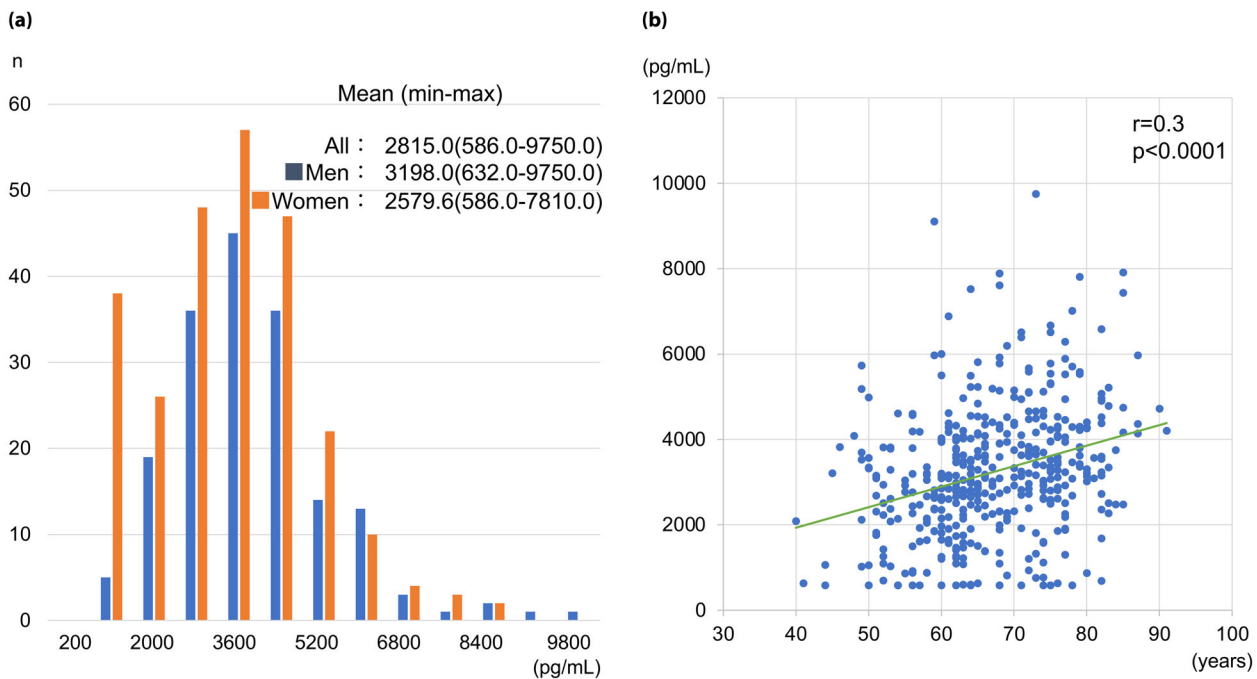


Figure 2 | Serum galectin-3 levels of a Japanese general population. (a) Distribution of serum galectin-3 levels in men and women. (b) Correlation between age and serum galectin-3 levels.

mean serum galectin-3 level of 10,900 pg/mL²². Given that galectin-3 is associated with obesity, and the obesity rate is 14.98% in the Netherlands compared with 5.57% in Japan²³,

the difference in mean serum galectin-3 levels may be attributable to differences in obesity prevalence. Galectin-3 has also been reported to correlate with obesity, especially subcutaneous

Table 3 | Odds ratio of T2DM prevalence at baseline

Quartiles of galectin-3				
	Quartile 1 (lowest) (586.0–2,270.0) <i>n</i> = 108	Quartile 2 (2,280.0–3,140.0) <i>n</i> = 108	Quartile 3 (3,150.0–4,090.0) <i>n</i> = 107	Quartile 4 (highest) (4,100.0–9,750.0) <i>n</i> = 110
<i>n</i> (%)	5 (4.6)	11 (10.2)	17 (15.9)	18 (16.4)
Crude	Reference	2.34 (0.78–6.97)	3.89 (1.38–10.97)	4.03 (1.44–11.29)*
Model 1	Reference	2.00 (0.66–6.08)	3.51 (1.22–10.13)	3.64 (1.24–10.70)
Model 2	Reference	3.30 (0.66–16.65)	6.25 (1.22–32.05)	3.15 (0.63–15.76)

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, BMI, and FPG. Odds ratio (95% C.I.). **P* < 0.01 vs Q1.

Table 4 | Odds ratio of T2DM incidence in 10-year follow-up

Quartiles of galectin-3				
	Quartile 1 (lowest) (586.0–2,100.0) <i>n</i> = 68	Quartile 2 (2,140.0–2,940.0) <i>n</i> = 69	Quartile 3 (2,960.0–3,940.0) <i>n</i> = 70	Quartile 4 (highest) (3,950.0–9,750.0) <i>n</i> = 68
<i>n</i> (%)	2 (2.9)	8 (11.6)	5 (7.1)	12 (17.7)
Crude	Reference	4.33 (0.88–21.18)	2.54 (0.48–13.56)	7.07 (1.52–32.94)
Model 1	Reference	4.01 (0.81–19.92)	2.60 (0.48–14.06)	7.39 (1.54–35.59)
Model 2	Reference	3.93 (0.74–20.91)	3.81 (0.64–22.72)	5.75 (1.08–30.65)

Model 1; adjusted for age and sex. Model 2; adjusted for age, sex, BMI and FPG. Hazard ratio (95% C.I.).

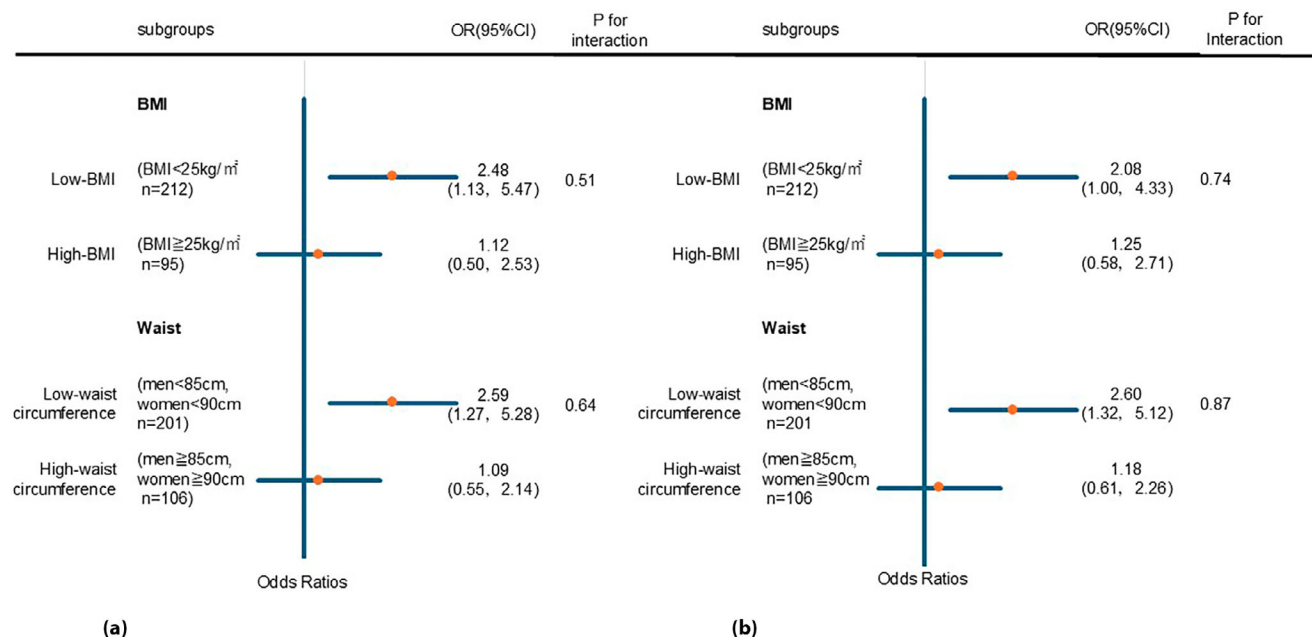


Figure 3 | (a) Adjusted odds ratio of incident T2DM among the participants stratified by BMI and waist circumference adjusted for age, sex, baseline BMI, and FPG as confounding factors (b) Adjusted odds ratio of incident T2DM as a sensitivity analysis adjusted for age, sex, baseline BMI, and HOMA-IR.

fat mass^{10, 24}. Subcutaneous obesity is more prevalent in Western countries, whereas visceral obesity predominates in Asian populations²⁵. In the present study, the serum galectin-3 levels were significantly higher in men. This finding differs from a study conducted in China, where no significant sex differences were observed²⁶, whereas in a Western study, the serum galectin-3 level was significantly higher in women. Women also tend to accumulate more subcutaneous fat than men. There are sex and racial differences in the serum galectin-3 levels, which may be due to body fat distribution.

In our study, the serum galectin-3 levels were significantly associated with the prevalence of T2DM, FPG, and HbA_{1c} in the univariate analysis. Multivariate logistic regression analyses revealed that serum galectin-3 levels were significantly associated with both prevalent T2DM in the cross-sectional study and incident T2DM in the prospective study. These findings are consistent with previous reports linking serum galectin-3 with glucose metabolism parameters and with the prevalence and incidence of diabetes^{9, 10}. However, in our study, of the 27 participants who developed new-onset T2DM over the 10-year follow-up period, 17 participants were receiving antidiabetic medications. We attempted to reanalyze the data after excluding these 17 participants to minimize any potential influence of pharmacotherapy on galectin-3 concentrations. However, after exclusion, no incident T2DM cases remained in the reference group with the lowest serum galectin-3 levels. Therefore, we could not completely rule out the influence of pharmacotherapy.

Also, no significant correlations were found between the serum galectin-3 and baseline insulin levels, HOMA-IR, or HOMA- β . This finding is in contrast with previous studies examining the associations between serum galectin-3 levels and insulin resistance^{5, 27–29}. In those studies, the populations were not clearly defined or were restricted to specific groups, such as reproductive-age or postmenopausal women, which may account for the discrepant results. By contrast, a previous study reported an inverse association between serum galectin-3 levels and insulin resistance. However, this study focused on patients with T2DM, including patients receiving current use of oral hypoglycemic agents³⁰. Moreover, HOMA-IR is known to fluctuate with pharmacologic interventions³¹. To minimize confounding, we therefore analyzed 394 individuals not receiving T2DM treatment from among the 433 baseline participants and again found no significant association between serum galectin-3 levels and HOMA-IR. We also extracted 240 participants who did not have insulin resistance at baseline and investigated whether baseline serum galectin-3 levels were a predictive marker for future acquisition of insulin, but again, no significant association was found.

In Japan, obesity—the primary driver of insulin resistance—is less prevalent than in Western countries, and insulin deficiency is more frequently observed³². To our knowledge, no previous studies have investigated the association between HOMA- β , an index of insulin secretion, and serum galectin-3

levels. Therefore, we examined this relationship in our study but found no significant association.

A subgroup analysis showed that higher serum galectin-3 levels were significantly associated with the incidence of T2DM in the low BMI and low waist circumference group. Conversely, no significant association with the incidence of T2DM was observed in the high BMI and high waist circumference groups. These results suggest that galectin-3 may contribute to T2DM development via mechanisms independent of obesity. Similar findings across both BMI- and waist-based subgroupings—waist circumference being more directly related to insulin resistance—further support the absence of a meaningful relationship between serum galectin-3 levels and HOMA-IR. Additionally, a sensitivity analysis adjusted for baseline HOMA-IR yielded consistent results (Figure 3b), indicating that the serum galectin-3 levels may promote T2DM independently of insulin resistance. However, the interaction term was not statistically significant, and no clear interaction effects based on BMI and waist circumference were identified. Further investigation is required to address these issues.

We also found that the serum galectin-3 levels were significantly associated with Hs-CRP, a marker of systemic inflammation. Given that inflammation is a well-known contributor to T2DM pathogenesis, the association between serum galectin-3 levels and Hs-CRP supports a potential inflammation-mediated mechanism.

Taken together, these findings suggest that elevated serum galectin-3 levels may predict T2DM onset through a pathway independent of obesity or insulin resistance. Individuals with high serum galectin-3 levels may be at a high risk of developing T2DM, even in the absence of obesity. In such individuals, traditional preventive strategies, including weight control and exercise, may be less effective than in others. Further investigation into the roles of galectin-3 levels and inflammation in T2DM pathogenesis could uncover novel disease mechanisms and inform the development of new preventive therapies targeting nonclassical pathways.

Furthermore, serum galectin-3 concentrations were associated with renal function indicators in our study, consistent with findings from a previous study in patients with T2DM³³. That study demonstrated that elevated serum galectin-3 levels were associated with poor renal prognosis. Although treatment with sodium-glucose cotransporter-2 inhibitors did not affect serum galectin-3 levels, higher baseline serum galectin-3 levels were associated with greater renal benefit from therapy. Taken together, our findings suggest that serum galectin-3 concentration may serve not only as a risk stratification marker for the incidence of T2DM but also as a potential early indicator for identifying individuals who may benefit from timely interventions to prevent future renal dysfunction.

Study strengths and limitations

A major strength of the present study is its longitudinal design, with 10 years of follow-up allowing for the assessment of

incident T2DM. Furthermore, the analyses were adjusted for multiple known confounders, enhancing the robustness of the observed associations between the serum galectin-3 levels and T2DM.

However, some limitations of this study must be acknowledged. First, dietary intake was assessed using the BDHQ, which was based on unpublished observations³⁴. Information on medical history, smoking habits, and alcohol consumption was self-reported, which may introduce recall or reporting bias. Second, the serum galectin-3 levels were only measured at baseline, precluding the evaluation of longitudinal changes. Third, the small number of T2DM cases resulted in wide confidence intervals in the logistic regression analysis. Finally, the possibility of residual confounding cannot be completely ruled out.

CONCLUSION

In this prospective cohort study involving a general Japanese population, elevated serum galectin-3 levels were significantly associated with incident T2DM, especially among individuals with low BMI and waist circumference, suggesting that galectin-3 may promote the development of T2DM through non-obesity-mediated mechanisms. Serum galectin-3 may serve as a useful biomarker for identifying individuals at risk for developing T2DM who might not be determined by using conventional risk factors, thereby offering a novel target for future preventive strategies.

ACKNOWLEDGMENTS

We are grateful to the members of the Japan Medical Association of Sasebo, Nagasaki, the elected officials and residents of Uku City, and the team of physicians who helped perform the health examinations. This study was partly supported by a grant from the Noboru Kimura Foundation, Fukuoka, and by a grant from Kurume University for the Promotion of Female Researchers.

DISCLOSURE

The authors declare no conflicts of interest associated with this manuscript.

Approval of the research protocol: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. The Research Ethics Committee of the Kurume University School of Medicine (No. 20186) approved this study.

Informed consent: Informed consent was obtained from the participants.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Stojanovic BS, Stojanovic B, Milovanovic J, *et al.* The pivotal role of Galectin-3 in viral infection: A multifaceted player in host-pathogen interactions. *Int J Mol Sci* 2023; 24: 9617.
2. Bouffette S, Botez I, De Ceuninck F. Targeting galectin-3 in inflammatory and fibrotic diseases. *Trends Pharmacol Sci* 2023; 44: 519–531.
3. Wang F, Zhou L, Eliaz A, *et al.* The potential roles of galectin-3 in AKI and CKD. *Front Physiol* 2023; 14: 1090724.
4. Cheng Z, Cai K, Xu C, *et al.* Prognostic value of serum Galectin-3 in chronic heart failure: A meta-analysis. *Front Cardiovasc Med* 2022; 9: 783707.
5. Li P, Liu S, Lu M, *et al.* Hematopoietic-derived Galectin-3 causes cellular and systemic insulin resistance. *Cell* 2016; 167: 973–984.e12.
6. Menini S, Iacobini C, Blasetti Fantauzzi C, *et al.* Role of Galectin-3 in obesity and impaired glucose homeostasis. *Oxidative Med Cell Longev* 2016; 2016: 9618092.
7. Unamuno X, Gómez-Ambrosi J, Rodríguez A, *et al.* Adipokine dysregulation and adipose tissue inflammation in human obesity. *Eur J Clin Invest* 2018; 48: e12997.
8. Saad MEME, El Mancy IM, Bayomy IM, *et al.* Evaluation of serum level of Galectin-3 in prediabetic and Type-2 diabetic patients with and without vascular complications. *Al-Azhar Int Med J* 2024; 5. doi: [10.58675/2682-339X.2389](https://doi.org/10.58675/2682-339X.2389).
9. Atalar MN, Abuşoğlu S, Ünlü A, *et al.* Assessment of serum galectin-3, methylated arginine and Hs-CRP levels in type 2 diabetes and prediabetes. *Life Sci* 2019; 231: 116577.
10. Vora A, de Lemos JA, Ayers C, *et al.* Association of Galectin-3 with diabetes mellitus in the Dallas heart study. *J Clin Endocrinol Metab* 2019; 104: 4449–4458.
11. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: A pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* 2017; 390: 2627–2642.
12. Hamamura H, Adachi H, Enomoto M, *et al.* Serum proprotein convertase subtilisin/Kexin type 9 (PCSK9) is independently associated with insulin resistance, triglycerides, lipoprotein(a) levels but not low-density lipoprotein cholesterol levels in a general population. *J Atheroscler Thromb* 2021; 28: 329–337.
13. Obuchi A, Adachi H, Enomoto M, *et al.* High plasma fetuin-a levels are associated with metabolic syndrome among males but not females in a Japanese general population. *Diabetes Res Clin Pract* 2014; 106: 128–135.
14. Matsuo S, Imai E, Horio M, *et al.* Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; 53: 982–992.
15. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; 27: 1487–1495.
16. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014; 37(Suppl): S81–S90.

17. Inohara H, Segawa T, Miyauchi A, *et al.* Cytoplasmic and serum galectin-3 in diagnosis of thyroid malignancies. *Biochem Biophys Res Commun* 2008; 376: 605–610.
18. Kobayashi S, Honda S, Murakami K, *et al.* Both comprehensive and brief self-administered diet history questionnaires satisfactorily rank nutrient intakes in Japanese adults. *J Epidemiol* 2012; 22: 151–159.
19. Kobayashi S, Murakami K, Sasaki S, *et al.* Comparison of relative validity of food group intakes estimated by comprehensive and brief-type self-administered diet history questionnaires against 16 d dietary records in Japanese adults. *Public Health Nutr* 2011; 14: 1200–1211.
20. Definition and the diagnostic standard for metabolic syndrome—committee to evaluate diagnostic standards for metabolic syndrome. *Nippon Naika Gakkai Zasshi* 2005; 94: 794–809.
21. Shimura T, Shibata M, Gonda K, *et al.* Significance of circulating Galectin-3 in patients with pancreaticobiliary cancer. *Anticancer Res* 2017; 37: 4979–4986.
22. de Boer RA, van Veldhuisen DJ, Gansevoort RT, *et al.* The fibrosis marker galectin-3 and outcome in the general population. *J Intern Med* 2012; 272: 55–64.
23. Collaboration NCDRF. Worldwide trends in underweight and obesity from 1990 to 2022: A pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet* 2024; 403: 1027–1050.
24. Fryk E, Rodrigues Silva VR, Strindberg L, *et al.* Metabolic profiling of galectin-1 and galectin-3: A cross-sectional, multi-omics, association study. *Int J Obes* 2024; 48: 1180–1189.
25. Kadowaki T, Sekikawa A, Murata K, *et al.* Japanese men have larger areas of visceral adipose tissue than Caucasian men in the same levels of waist circumference in a population-based study. *Int J Obes* 2006; 30: 1163–1165.
26. Liu L, Zhen J, Liu S, *et al.* Association between sleep patterns and galectin-3 in a Chinese community population. *BMC Public Health* 2024; 24: 1323.
27. Zhang Z, Kang X, Guo Y, *et al.* Association of circulating galectin-3 with gestational diabetes mellitus, progesterone, and insulin resistance. *J Diabetes* 2021; 13: 54–62.
28. Chen Y, Das S, Zhuo G, *et al.* Elevated serum levels of galectin-3 binding protein are associated with insulin resistance in non-diabetic women after menopause. *Taiwan J Obstet Gynecol* 2020; 59: 877–881.
29. Alves MT, de Souza IDP, Ferreira CN, *et al.* Galectin-3 is a potential biomarker to insulin resistance and obesity in women with polycystic ovary syndrome. *Gynecol Endocrinol* 2020; 36: 760–763.
30. Ohkura T, Fujioka Y, Nakanishi R, *et al.* Low serum galectin-3 concentrations are associated with insulin resistance in patients with type 2 diabetes mellitus. *Diabetol Metab Syndr* 2014; 6: 106.
31. Mather KJ, Verma S, Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. *J Am Coll Cardiol* 2001; 37: 1344–1350.
32. Fukushima M, Suzuki H, Seino Y. Insulin secretion capacity in the development from normal glucose tolerance to type 2 diabetes. *Diabetes Res Clin Pract* 2004; 66(Suppl): S37–S43.
33. Haller PM, Wiviott SD, Berg DD, *et al.* Galectin-3 and kidney function in type 2 diabetes treated with dapagliflozin: Analysis from DECLARE-TIMI 58. *ESC Heart Fail* 2025; 12: 3981–3986.
34. Ogawa K, Tsubono Y, Nishino Y, *et al.* Validation of a food-frequency questionnaire for cohort studies in rural Japan. *Public Health Nutr* 2003; 6: 147–157.