Original Article

Characterized factors of subjects who were first time diagnosed as hyperglycemia more than 126 mg/dl during annual or biannual medical checkups: a case-control study in Japan

Miwako Minami,[1,2] Tomohiro Imamura,[1,2,*] Ayako Takamori,[3] Hiromu Minagawa,[1,2] Rina Matsuo,[2] Junko Miyakawa,[2] Kenichi Izumi,[2] Shoichiro Ohta,[1,2] Kohei Yamanouchi,[1,2] Nobuya Souta,[2] Kyosuke Yamamoto,[2] Sadatosi Tsuji,[2] Tsukuru Umemura,[1,2] Keizo Anzai,[1,2] Yuji Hirai,[1,2] Kazuma Fujimoto,[1,2] and Takuya Kishi[1]

[1]International University of Health and Welfare Graduate School of Medicine, Okawa, Fukuoka 831-8501, Japan
[2]Preventive Medical Center, the Kouhou-kai Takagi Hospital, Okawa, Fukuoka 831-0016, Japan
[3]Clinical Research Center, Saga University Hospital, Saga, Saga 849-0937, Japan

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The present study examined factors in subjects diagnosed with hyperglycemia during periodic medical checkups. In total, 9,324 subjects (males: 4,532, females: 4,792) visited the Takagi Hospital for medical checkups in 2019. Eighty-two subjects (59 males) whose fasting blood glucose exceeded 126 mg/dl for the first time during the annual or biannual follow-up were included. Sex- and age-matched controls were used. Data from cases with hyperglycemia were compared to data from themselves one or two years before hyperglycemia. Body mass index (BMI), waist circumference, fatty liver, and blood pressure were higher in cases than in controls. Fasting blood glucose and hemoglobin A1c were higher in cases. Blood test results indicated that triglyceride, low-density lipoprotein (LDL) cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (γ-GTP), were significantly enhanced in cases. Multiple logistic regression analysis revealed that BMI, waist circumference, blood pressure, triglyceride, ALT, and γ-GTP were significant independent risk factors for cases with hyperglycemia. These risk factors were already enhanced in the cases of themselves in one or two years before hyperglycemia. In conclusion, BMI, waist circumference, blood pressure, and fatty liver indicated by ALT and γ-GTP were exacerbated concomitant with hyperglycemia, and increases in these factors preceded hyperglycemia.

***Key Words*: metabolic syndrome, hyperlipidemia, fatty liver, hypertension, medical staff**

It is well known that the prevalence of type 2 diabetes mellitus (DM) with obesity, which is caused by excessive food intake and an irregular lifestyle, has been rapidly increasing worldwide in recent years, including in Japan.[1–3] Type 2 DM might induce several severe complications, including cardiovascular and cerebrovascular disorders, in addition to typical complications of DM.[4–9] Obesity and type 2 DM-related clinical pathological conditions commonly observed are characterized as metabolic syndrome, which is characterized by elevated blood glucose and lipid levels and increased blood pressure and waist circumference.[10–13]

In Japan, the threshold of obesity for metabolic disorders such as type 2 DM and metabolic syndrome might be lower than that in Western countries, and the diagnostic criteria for obesity in the clinical practice guidelines of the Japan Society for the Study of Obesity is more than 25 of body mass index (BMI).[13] Various therapeutic interventions have been applied to obesity in Japan, including pharmacotherapy,[14,15] laparoscopic surgery,[16–18] and nutritional and lifestyle improvement therapy.[19–23] These therapeutic approaches may not necessarily yield adequate therapeutic outcomes. Therapeutic approaches to improve nutrition and lifestyle have undergone extensive trial and error over an extended period but have not yielded satisfactory results.[19–24] In addition, few studies in Japan have evaluated hyperglycemia and metabolic syndrome risk factors in longitudinal follow-up.

Periodic annual medical checkups have been widely carried out in Japan, especially workplace health checkups.[24] In addition, specific health checkups with health guidance intervention started in 2008 for metabolic syndrome, including obesity with type 2 DM.[24–27] The present study aimed to evaluate the risk factors for newly developed hyperglycemia among subjects who received periodic (annual or biannual) health checkups at the Preventive Medical Center of the Kouhou-kai Takagi Hospital, a regional core hospital in Japan.

Methods

Nine thousand three hundred twenty-four subjects (males: 4,532, females: 4,792) visited the Preventive Medical Center of the Takagi Hospital, a regional core hospital in Japan,[28–30] for medical checkups, including specific health checkups in 2019. From January 1, 2019, to December 31, 2019, subjects whose fasting blood glucose exceeded 126 mg/dl for the first time during the annual or biannual follow-up period were picked up for evaluation. In total, 82 subjects (59 males and 23 females) exceeded 126 mg/dl of fasting blood glucose for the first time. Sex- and age-matched controls were selected from subjects without hyperglycemia, and two controls were selected in each case. From medical checkup data, height, BMI, waist circumference, body fat percentage, blood pressure, pulse, and fatty liver were evaluated in both cases and controls. Regarding fasting blood samples, fasting blood glucose, hemoglobin A1c, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpepti-

*To whom correspondence should be addressed.
E-mail: imamura_tomohiro@iuhw.ac.jp

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Table 1. Characteristics of subjects who was first time diagnosed with hyperglycemia (fasting blood glucose >126 mg/ml) in 2019 during annual or biannual medical checkups

	Hyperglycemia (n = 82)	Controls (n = 164)	p value
Males:females	59:23	118:46	
Age (year)	54.8 ± 9.8	54.8 ± 9.7	
BMI (kg/m^2)	27.0 ± 4.7	23.1 ± 3.4	<0.001**
Height (cm)	165.5 ± 8.7	166.9 ± 7.8	
Body weight (kg)	74.2 ± 15.6	64.7 ± 12.5	
Waist circumference (cm)	93.0 ± 10.9	87.0 ± 14.3	<0.001**
Body fat percentage	30.2% ± 8.6%	25.1% ± 7.1%	<0.001**
Blood pressure (mmHg)			
Systolic	128.1 ± 14.3	118.9 ± 15.4	<0.001**
Diastolic	83.5 ± 10.6	78.2 ± 10.8	<0.001**
Pulse rate (/min)	72.3 ± 11.8	67.3 ± 9.9	<0.001**
Echo- or CT-detected fatty liver	51/82 (62.2%)	39/164 (23.8%)	<0.001**

**p<0.01. Data are mean ± SD. BMI, body mass index.

Table 2. A fasting blood test of subjects who was first time diagnosed with hyperglycemia (fasting blood glucose >126 mg/ml) in 2019 during annual or biannual medical checkups

	Hyperglycemia (n = 82)	Controls (n = 164)	p value
Fasting blood glucose (mg/ml)	139.8 ± 33.8	97.2 ± 8.3	<0.001**
Hemoglobin A1c	6.6% ± 1.0%	5.6% ± 0.3%	<0.001**
HDL cholesterol (mg/dl)	60.6 ± 35.6	62.4 ± 13.5	0.57
LDL cholesterol (mg/dl)	138.1 ± 33.8	129.7 ± 27.4	0.04*
Triglyceride (mg/dl)	204.2 ± 251.9	105.6 ± 53.5	<0.001**
AST (U/ml)	32.3 ± 21.4	23.0 ± 8.4	<0.001**
ALT (U/ml)	42.2 ± 32.9	23.1 ± 15.7	<0.001**
γ-GTP (IU/L)	80.6 ± 96.1	37.5 ± 33.9	<0.001**
Blood urea nitrogen (mg/dl)	14.5 ± 3.5	14.6 ± 3.6	0.91
Creatinine (mg/dl)	0.79 ± 0.22	0.80 ± 0.17	0.87
Uric acid (mg/dl)	6.4 ± 1.6	5.6 ± 1.4	<0.001**

*p<0.05, **p<0.01. Data are mean ± SD. HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase.

dase (γ-GTP), blood urea nitrogen, creatinine, and uric acid were evaluated. Body fat percentage was estimated by biomedical impedance analysis using the body composition monitor (TANITA, Tokyo, Japan).[31,32] Fatty liver was evaluated by ultrasonic echo examination and/or Computed Tomography (CT) using previous studies' criteria.[22,33,34] In addition, data of cases when fasting glucose level was >126 mg/dl were compared with data from themselves just before hyperglycemia (one or two years before). The present study complied with the Declaration of Helsinki, and the protocol was approved by the Ethics Committees of the Takagi Hospital (21-KR-13) and the International University of Health and Welfare (21-Ifh-044).

The data were compared between cases with hyperglycemia and controls without hyperglycemia using the Student's t test for continuous variables and the *chi*-squared test for categorical variables. Regarding these cases and controls, we applied the multiple logistic regression model considering explanatory variables with significance levels (univariate p value <0.05 on statistical tests). The model did not consider blood glucose, hemoglobin A1c, diastolic blood pressure, echo- and/or CT-detected fatty liver, and AST due to their high correlation (Spearman or Pearson) with other factors. To investigate the differences between before and after data among the cases, the paired t test for continuous variables and McNemar the test for categorical variables were conducted. Odds ratios and 95% confidence intervals are presented in the tables. JMP Pro 16 (SAS Institute Inc., Cary, NC) was used for all analyses, and statistical significance was defined as p<0.05.

Results

The patient characteristics of cases whose fasting blood glucose was elevated for the first time to more than 126 mg/ml in 2019 during annual or biannual medical checkups were compared with age- and sex-matched controls in Table 1. Among the 82 subjects with hyperglycemia, the hemoglobin A1c of 39 subjects (males: 24, females: 9) exceeded 6.5%. The number of cases of hyperglycemia in males (59 cases) was 2-fold more than in females (23 cases). In contrast, the number of subjects who visited the Takagi Hospital Preventive Medical Center was almost the same for both genders (males: 4,532 subjects, females: 4,792 subjects). BMI, waist circumference, and echo- and/or CT-detected fatty liver percentage were higher in cases than in controls (p<0.001 in each). Systolic and diastolic blood pressure and pulse rate were high in the cases (p<0.001).

Table 2 compares blood test results between cases and controls. Fasting blood glucose and hemoglobin A1c levels were significantly higher in cases than controls (p<0.001). Regarding

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Table 3. The multivariate analysis compared cases with hyperglycemia to age-and sex-matched controls without hyperglycemia

Subjects vs controls	Odd ratio	95% confidential interval	*p* value
BMI	1.36	1.13–1.62	<0.001**
Waist circumference	0.94	0.86–0.99	0.03*
Body fat percentage	1.05	0.98–1.11	0.16
Systolic blood pressure	1.04	1.01–1.06	0.008**
Pulse rate	1.03	0.98–1.07	0.07
LDL cholesterol	1.00	0.99–1.02	0.64
Triglyceride	1.01	1.00–1.01	0.007**
ALT	1.04	1.00–1.07	0.04*
γ-GTP	1.01	1.00–1.02	0.001**
Uric acid	1.12	0.84–1.49	0.44

*p<0.05, **p<0.01. We analyzed factors of p values less than 0.05 in univariate analysis except blood glucose, hemoglobin A1c, diastolic blood pressure, echo-detected fatty liver and AST. BMI, body mass index; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase.

Table 4. Characteristics of subjects who first time experienced hyperglycemia (fasting blood glucose >126 mg/ml) in 2019 during annual or biannual medical checkups: comparison with the corresponding data one or two year before without hyperglycemia

	Hyperglycemia	Before	*p* value
BMI (kg/m^2)	27.0 ± 4.7	26.8 ± 4.2	0.73
Waist circumference (cm)	93.0 ± 10.9	87.0 ± 14.3	0.47
Body fat percentage	30.2% ± 8.6%	29.3% ± 7.7%	0.73
Blood pressure (mmHg)			
Systolic	128.1 ± 14.3	130.7 ± 16.3	0.28
Diastolic	83.5 ± 10.6	83.7 ± 12.1	0.67
Pulse rate (/min)	72.3 ± 11.8	69.1 ± 9.4	0.11
Echo- and/or CT-detected fatty liver	51/82 (62.2%)	35/66 (53.0%)	0.82

Data are mean ± SD. BMI, body mass index.

blood lipid examination, triglyceride and LDL cholesterol increased in cases (p<0.001 and p = 0.04), whereas HDL cholesterol levels did not differ between cases and controls. AST, ALT, and γ-GTP were significantly enhanced in cases with hyperglycemia compared to controls (p<0.001). Renal function evaluated by blood urea nitrogen and creatinine level did not differ between cases and controls, and uric acid significantly increased in cases (p<0.001).

Table 3 presents the results of the multiple logistic regression analysis regarding explanatory variables with significance levels (univariate p value <0.05) except blood glucose and hemoglobin A1c (correlation of glucose and Hemoglobin A1c: r = 0.69). Blood pressure was represented by systolic blood pressure (correlation between systolic and diastolic pressure: r = 0.75). Fatty liver was represented by ALT and γ-GTP (correlation of echo- and/or CT-detected fatty liver and ALT: r = 0.44; correlation of AST and ALT: r = 0.77). Multivariate analysis revealed that BMI (p<0.001), waist circumference (p = 0.03), systolic blood pressure (p = 0.008), blood triglyceride (p = 0.007), ALT (p = 0.04), and γ-GTP (p = 0.001) were significant independent risk factors for cases with hyperglycemia.

The patient characteristics and blood tests of cases with hyperglycemia were compared with data recorded just before hyperglycemia one or two years before during annual or biannual medical checkups. As shown in Table 4, the patient characteristics, including risk factors for hyperglycemia, were not significantly different before and after hyperglycemia of more than 126 mg/dl, suggesting these risk factors might be established before hyperglycemia. As shown in Table 5, the blood tests except fasting blood glucose and hemoglobin A1c did not differ between data with hyperglycemia and data of themselves without hyperglycemia just before hyperglycemia in annual or biannual medical checkups.

Discussion

The present retrospective longitudinal study in the Takagi hospital, a regional core hospital in Japan, indicated that i) 82 subjects (around 0.9%) might annually develop hyperglycemia of more than 126 mg/dl in approximately 9,000 subjects who received periodic (annual or biannual) medical checkups; ii) ratio of male-subjects (1.3%) who developed hyperglycemia was more than two hold higher compared to females (0.5%); iii) Hemoglobin A1c increased in subjects with hyperglycemia; iv) multiple logistic regression analysis revealed that BMI, waist circumference, blood pressure, triglyceride, fatty liver represented by ALT and γ-GTP were significant independent risk factors for cases with newly developed hyperglycemia compared to controls; and iv) these risk factors were already enhanced in the cases of themselves in one or two years before hyperglycemia.

The present study indicated that the annual newly developed hyperglycemia of more than 126 mg/dl was approximately 0.9% (males: 1.3%, females: 0.5%) during periodic medical checkups of middle-aged subjects. The National Health and Nutrition Survey in Japan estimated that the annual incidence of type 2 DM was 0.6–0.8%/year in 1997, and the prevalence of Japanese patients who were strongly suspected of having type 2 DM was

Table 5. A blood test of subjects who first time experienced hyperglycemia (fasting blood glucose >126 mg/ml) in 2019 during annual or biannual medical checkups: comparison with the corresponding data one or two year before without hyperglycemia

	Subjects with hyperglycemia	Before	*p* value
Fasting blood glucose (mg/ml)	139.8 ± 33.8	115.7 ± 9.2	<0.001**
Hemoglobin A1c	6.6% ± 1.0%	6.1% ± 0.3%	0.02*
HDL cholesterol (mg/dl)	60.6 ± 35.6	54.7 ± 11.7	0.16
LDL cholesterol (mg/dl)	138.1 ± 33.8	133.1 ± 31.6	0.63
Triglyceride (mg/dl)	204.2 ± 251.9	229.3 ± 331.7	0.78
AST (U/ml)	32.3 ± 21.4	28.2 ± 15.6	0.47
ALT (U/ml)	42.2 ± 32.9	37.2 ± 22.9	0.84
γ-GTP (IU/L)	80.6 ± 96.1	78.8 ± 100.5	0.93
Blood urea nitrogen (mg/dl)	14.5 ± 3.5	14.8 ± 3.9	0.81
Creatinine (mg/dl)	0.79 ± 0.22	0.82 ± 0.21	0.51
Uric acid (mg/dl)	6.4 ± 1.6	6.4 ± 1.5	0.69

**$p<0.01$. Data are mean ± SD. HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase.

19.7% in males and 10.8% in females in 2019.[35] Our results regarding medical checkups of incidence in annually developed hyperglycemia in males and females might be supported by the data on the incidence and prevalence of DM in Japan's national survey.

A well-established close relationship exists between type 2 DM and metabolic syndrome.[10–13] This study indicated that risk factors for hyperglycemia included BMI, waist circumference, blood pressure, triglyceride, and fatty liver. Waist circumference, blood pressure, and triglyceride levels were risk factors for metabolic syndrome worldwide, including in Japan.[10–13] Several studies in Japan demonstrated that increased BMI and fatty liver were the most severe exacerbated factors for type 2 DM.[7,24,36–40] The BMI threshold for type 2 DM was just over 25, as indicated in the present study (mean BMI in hyperglycemia subjects: 27.0 kg/m^2).[13] The present study suggested that these risk factors, including increased waist circumference, hypertension, hyperglycemia, increased BMI, and fatty liver, might precede hyperglycemia for at least one or two years, which warrants further exploration.

Several limitations were present in the present retrospective study with longitudinal observation, including a limited examination period during one year, 2019, a limited number of subjects around 10,000 in a single institution, and no follow-up evaluation. Only a few epidemical studies focus on healthy subjects with detailed longitudinal clinical examinations, and studies with medical checkups in Japan might facilitate related clinical research.

In conclusion, increased blood glucose in healthy subjects who underwent medical checkups in Japan was more common in males with increased BMI, waist circumference, blood pressure, triglycerides, and fatty liver exacerbation. These risk factors for hyperglycemia might precede hyperglycemia.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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