



Seasonal variations and the influence of COVID-19 pandemic on hemoglobin A1c, glycoalbumin, and low-density lipoprotein cholesterol

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Abstract

Aim The purpose of the study was to investigate seasonal variations in HbA1c, GA and LDL-C and to examine the effects of the COVID-19 pandemic on these variations and on glycemic and lipid control themselves in patients with type 2 diabetes.

Patients and methods The subjects were outpatients with type 2 diabetes who had received standard treatment for glycemic control for more than 3 years. Data for patients who visited our hospital from January 2021 to March 2021 were retrospectively investigated based on electronic medical records.

Results HbA1c showed seasonal variation (high in winter–spring and low in summer–autumn), and this was similar during the COVID-19 pandemic. However, the mean HbA1c over 1 year was significantly elevated during the COVID-19 pandemic ($7.53 \pm 1.02\%$ in 2020) compared with the previous 2 years: (7.34 ± 0.91 in 2018, 7.39 ± 0.93 in 2019; 2020 vs. 2018; 0.19% , $P < 0.001$; 2020 vs. 2019; 0.14% , $P = 0.0013$) and the difference was larger in winter. GA showed no apparent seasonal variation, but mean GA during the COVID-19 pandemic was elevated compared with earlier years (2020 vs. 2018, $P < 0.001$; 2020 vs. 2019, $P < 0.001$). LDL-C did not show apparent seasonal variation and was unaffected by COVID-19 pandemic.

Conclusion The COVID-19 pandemic influenced mean HbA1c and GA levels over 1 year, but did not affect seasonal variations, while LDL-C was not affected by COVID-19. Observation of these levels over a longer period is warranted to determine the longer-term influence of the COVID-19 pandemic.

Keywords Seasonal variation · HbA1c · GA · LDL-C · COVID-19

Introduction

The main purpose of treatment of type 2 diabetes is to prevent progression of micro-angiopathies, such as neuropathy, retinopathy and nephropathy, and macro-angiopathies including peripheral arterial disease, ischemic heart disease and stroke. Intensive therapy for glycemic control is effective for prevention or delay of progression of these complications [1, 2]. Hemoglobin A1c (HbA1c) is a non-enzymatic glycation product of hemoglobin that reflects the average plasma glucose level in the previous 2–3 months [3] and is a marker for diagnosis and a target for treatment [4, 5].

However, the HbA1c value is also influenced by conditions, such as hemodialysis, age, genetic background, race/ethnicity, anemia and hemoglobinopathies [4]. HbA1c also shows seasonal variations in type 1 and type 2 diabetes, with higher levels in winter (cooler season) and nadir levels in summer (warmer season) [6–18], although different seasonal variations have also been suggested [19, 20]. Therefore, treatment in which seasonal variations are taken into consideration may be desirable to achieve good glycemic control.

The reasons for seasonal variations in HbA1c are unknown, but may involve differences in air temperature, the influence of seasonal changes in hormones such as vitamin D [21, 22], and possible changes of physical activities and food intake. Among these factors, patients in regions with a large difference in temperature between summer and winter have more apparent seasonal variations of HbA1c [11]. In Japan, there are four distinct seasons in most regions. Koshigaya City, Saitama Prefecture, where our hospital is located, has a very hot and humid

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summer (one of the hottest in Japan) with a maximum temperature that can exceed 40°C, while the winter is relatively cool and has a minimum temperature of about 0°C, but with many sunny days [23]. Thus, Koshigaya City has four particularly distinct seasons, which makes the region suitable to explore seasonal variations of HbA1c in patients with diabetes. Furthermore, the COVID-19 pandemic has changed lifestyles and caused considerable mental stress for many people since winter 2020. Therefore, it is of interest to investigate the effects of the pandemic on seasonal variation of HbA1c and glycemic control itself (i.e., mean HbA1c over 1 year).

Based on this background, in the current study, seasonal variations of HbA1c were evaluated in patients with type 2 diabetes who visited our hospital as outpatients, including during the COVID-19 pandemic. We also simultaneously evaluated glyco-albumin (GA) as a marker of glycemic control that reflects mean plasma glucose levels over the previous 2–4 weeks [24], and low-density lipoprotein cholesterol (LDL-C) as a marker of circulating lipids, which may also show seasonal variation [25].

Patients and methods

Outpatients with type 2 diabetes who had received regular treatment for glycemic control from the same doctor (K.T.) for more than 3 years (visits from prior to March 2018) and visited the hospital from January 2021 to March 2021 were first identified from a retrospective evaluation of electronic medical records. Patients with repeated severe anemia due to chemotherapy for cancer or due to gastrointestinal bleeding caused by digestive system diseases were excluded before analyses based on the judgment of the physician in charge (K.T.). Patients with type 1 diabetes were also excluded to permit a focus on type 2 diabetes.

Data for HbA1c, GA and LDL-C from March 2018 to February 2021 were obtained from electronic medical records. The intervals between each visit were mostly 2–3 months (range 1–3 months). The four seasons of spring, summer, autumn and winter were defined as March–May, June–August, September–November, and December–February, respectively, and the years 2018, 2019 and 2020 were defined from March 2018–February 2019, March 2019–February 2020, and March 2020–February 2021. The 2020 year was also defined as the COVID-19 pandemic period because the serious effects of COVID-19 started in Japan in about March 2020 and have continued to the present time (i.e., April 2021) and most patients had not received the COVID-19 vaccine by the end of February 2021.

Measurements of HbA1c, GA, and LDL-C

HbA1c was evaluated by an enzymatic assay using protease in the initial reaction and fructosyl-peptide oxidase (FPOX) and peroxidase (POD) in the second reaction (Nordia[®]N HbA1c, Sekisui Medical Inc., Tokyo, Japan). GA was measured using a Lucica GA-L kit (Asahi Kasei Pharma Co., Ltd, Tokyo, Japan). Serum LDL-C was measured by an enzymatic assay in a Cholestest LDL[®] kit (Daiichi Pure Chemicals Co., Ltd, Tokyo, Japan).

Ethical considerations

The Institutional Ethics Committee at Dokkyo Medical University Saitama Medical Center approved the study with a 6-month opt-out period (Approval no. 21014/ approval day: 4/26/2021).

Statistical methods

Differences of HbA1c, GA, and LDL-C among the four seasons in 2018, 2019 and 2020 (as defined above) and among the 3 years were evaluated using repeated measures analysis of variance (ANOVA) with a post hoc Holm test. Correlations between two variables were examined using Pearson's correlation analysis. All statistical analyses were performed using BellCurve for Excel software (Social Survey Research Information Co., Ltd, Tokyo, Japan). A *P* value of less than 0.05 was estimated as indicating statistical significance (two-sided).

Results

Clinical characteristics and laboratory data in the 290 registered patients at baseline (first visit after March 2018) are summarized in Table 1

The mean values for HbA1c ($n=290$), GA ($n=267$) and LDL-C ($n=280$) per year (Fig. 1A–C) in 2018, 2019 and 2020 were 7.34 ± 0.91 , 7.39 ± 0.93 , $7.53 \pm 1.02\%$; 18.64 ± 3.88 , 19.25 ± 3.98 , $19.87 \pm 4.35\%$; and 111.98 ± 28.63 , 110.80 ± 29.38 , 110.52 ± 28.38 mg/dL, respectively. HbA1c was significantly higher in 2020 than in 2018 (change of 0.19%, $P < 0.001$) and 2019 (0.14%, $P = 0.0013$). Similarly, GA was significantly higher in 2020 compared with 2018 and 2019 (both $P < 0.001$) and in 2019 compared to 2018 ($P < 0.001$). In contrast, LDL-C did not differ significantly among the 2018, 2019 and 2020 years.

The mean HbA1c, GA and LDL-C levels per month and for each season in 2018, 2019 and 2020 are shown in Figs. 2A–C and 3A–C, respectively. The differences

Table 1 Clinical features and laboratory data at baseline in patients with type 2 diabetes

No. (male/female)	290(166/124)
Age (year)	70.1 ± 10.9
<i>Duration of diabetes (n)</i>	
Year	
0–4	13
5–9	74
10–14	79
> 15	124
BMI (kg/m ²)	24.7 ± 4.4
HbA1c (%)	7.4 ± 1.1
GA (%)	19.2 ± 4.4
LDL-C (mg/dL)	111.3 ± 30.1
eGFR (ml/min/1.73 m ²)	63.6 ± 18.1
<i>Diabetic therapy (n)</i>	
Sulfonylureas and glinides	132
Metformin	111
Pioglitazone	18
αGI	76
DPP4-I	150
SGLT2-I	18
GLP-1RA	21
Insulin	69
<i>Statins (n)</i>	
	76

Data are expressed mean ± standard deviation

Baseline: first visit after March 2018

n: number of the patients

BMI body mass index, *HbA1c* hemoglobin A1c, *GA* glycoalbumin, *LDL-C* low-density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate

Diabetic therapy: *αGI* α glucosidase inhibitors, *DPP4-I* dipeptidyl peptidase 4 inhibitors, *SGLT2-I* Sodium Glucose cotransporter 2 inhibitors, *GLP-1RA* glucagon-like peptide (GLP)-1 receptor agonists. In therapies, most patients were receiving combination therapy for diabetes

between the maximum and minimum monthly mean HbA1c were 0.33%, 0.37% and 0.7% in 2018, 2019 and 2020, respectively. Comparisons of these variables among four seasons were performed in each year. In 2018 and 2019, HbA1c was significantly higher in spring and winter than in summer and autumn, while in 2020, HbA1c was significantly higher in winter compared to spring, summer and autumn (all $P < 0.001$). Thus, in the non-COVID-19 period, HbA1c was higher in the winter–spring season and lower in the summer–autumn season, but in the COVID-19 period, the winter HbA1c was higher than all other seasons. In the winter seasons in 2018, 2019, and 2020, HbA1c was 7.47 ± 1.11 , 7.52 ± 1.08 , and $7.7 \pm 1.24\%$, respectively; and the winter HbA1c in 2020 was significantly higher than the values in 2018 (change 0.23%, $P < 0.001$) and 2019 (0.18%, $P = 0.0048$).

GA was significantly higher in winter compared to spring in 2018 ($P = 0.0029$) and significantly higher in spring compared to autumn in 2019 ($P = 0.0389$), indicating no clear seasonal variation in GA. LDL-C was significantly higher in winter compared to spring ($P = 0.0186$) and summer ($P < 0.001$) in 2018 and significantly higher in spring compared to summer in 2020 ($P = 0.0113$).

In sub-analyses for HbA1c, patients ($n = 129$) with no change in dose or type of anti-diabetes drugs over the 3-year study period showed similar seasonal patterns to those for all patients, although comparison of the spring value with those in summer and autumn in 2018 did not reach statistical significance (Fig. 4A). Patients ($n = 69$) receiving insulin therapy with or without other anti-diabetes drugs also had similar seasonal patterns of HbA1c compared to those for all patients, although again a significant difference was not obtained in 2018 (Fig. 4B).

HbA1c showed significant positive correlations with GA ($r = 0.5961$, $P < 0.001$) and LDL-C ($r = 0.1140$, $P = 0.0175$) at baseline (first visit after March 2018). Correlations of monthly HbA1c, GA, and LDL-C with temperature or hours of sunlight in Koshigaya City were examined based on data from the website of the Japan Meteorological Agency (26). HbA1c was significantly negatively correlated with temperature in 2018 ($r = -0.6048$, $P = 0.0372$), 2019 ($r = -0.7615$,

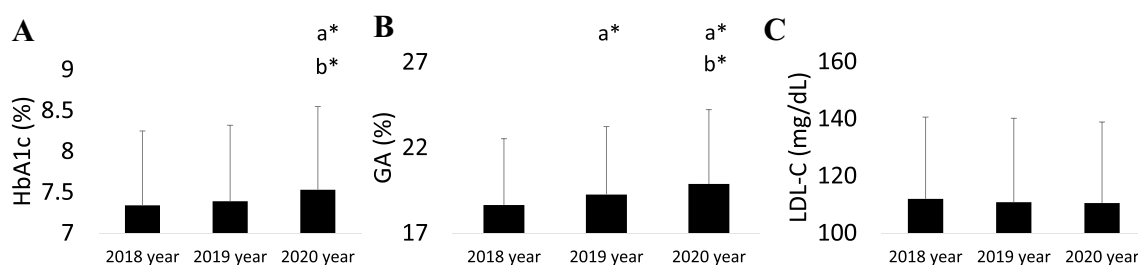


Fig. 1 Comparisons of mean hemoglobin A1c (HbA1c) (A), glycoalbumin (GA) (B), and low-density lipoprotein cholesterol (LDL-C) (C) in 2018, 2019 and 2020. a vs. 2018, b vs. 2019, * $P < 0.001$

Fig. 2 Variations per month over 3 years for hemoglobin A1c (HbA1c) (A), glycoalbumin (GA) (B), and low-density lipoprotein cholesterol (LDL-C) (C)

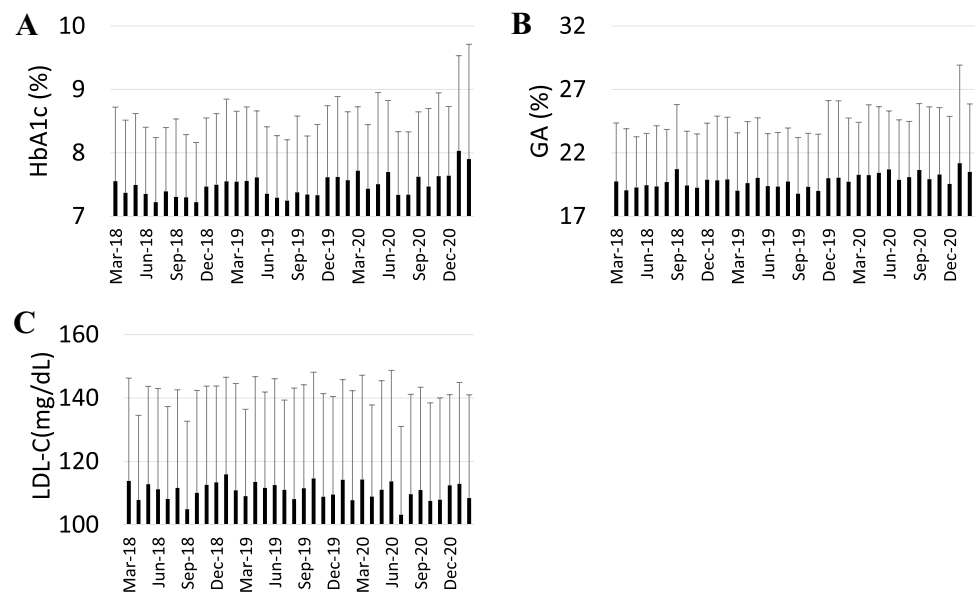
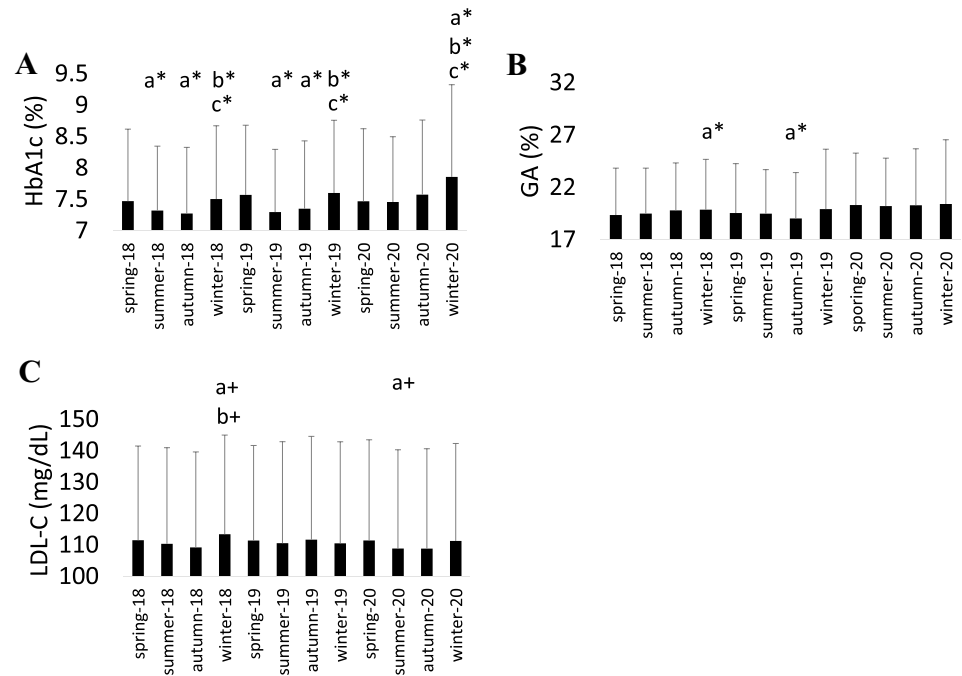


Fig. 3 Seasonal variation over 3 years for hemoglobin A1c (HbA1c) (A), glycoalbumin (GA) (B), and low-density lipoprotein cholesterol (LDL-C) (C). a vs. spring, b vs. summer, c vs. autumn, * $P < 0.001$, + $P < 0.05$

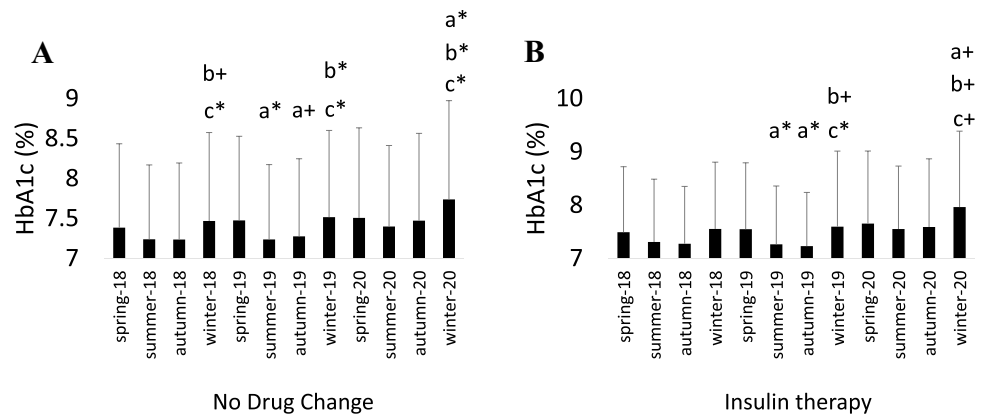


$P = 0.0040$), and 2020 ($r = -0.7043$, $P = 0.0106$). In contrast, GA and temperature showed no correlation in any year, and LDL-C was significantly negatively correlated with temperature only in 2018 ($r = -0.5944$, $P = 0.0415$). There were no correlations of HbA1c, GA, or LDL-C with hours of sunlight in each year. There were also no differences in the mean yearly temperatures (calculated as the mean of monthly temperatures) in comparisons of 2018, 2019 and 2020 (all $P = 1.0$).

Discussion

The results of the study showed differences in maximum and minimum monthly HbA1c in 2018 and 2019 of 0.33% and 0.37%, respectively. These findings are similar to those in previous studies showing differences of about 0.2–0.5% [6–8, 15, 16, 20]. HbA1c was higher in winter–spring and reached a nadir in summer–autumn in both years, which is also consistent with previous studies showing a higher HbA1c in cooler seasons and a nadir in hotter seasons

Fig. 4 Seasonal variation over 3 years for hemoglobin A1c (HbA1c) in patients with no change in dose or type of anti-diabetes drugs over the 3-year period (A) and in patients who received insulin therapy with or without other anti-diabetes drugs (B). a vs. summer, b vs. summer, c vs. autumn, * $P < 0.001$, + $P < 0.05$



[6–17]. The relatively high HbA1c in spring and the relatively low value in autumn are due to a time lag because HbA1c reflects glycemic control for the previous 2–3 months [3]. Sakamoto et al. found similar results for HbA1c of a lower value in summer–autumn and a higher value in winter–spring [12]. The difference in maximum and minimum monthly HbA1c in 2020 (the COVID-19 period) of 0.7% was larger, during a period in which there may have been changes in lifestyles. Higher values in winter–spring were maintained in 2020, although the mean HbA1c in spring 2020 was relatively low. This may also be due to a time lag since the effects of the COVID-19 pandemic on HbA1c may only have started in about May 2020 in Japan. The results for all 3 years were similar for all patients, for patients without a change in diabetes treatment during the study period, and even for patients treated with insulin, in whom variation of glycemic control is likely to be larger because of a possible decrease in endogenous insulin secretion capacity. Therefore, the observation of seasonal variation of HbA1c in the entire cohort is not biased by changes of drugs and appears to be robust.

The reasons for seasonal variations of HbA1c are still not fully apparent. However, temperature, changes of physical activity or food intake, and hormonal variation such as vitamin D, which can affect circulating glucose levels and insulin resistance [21, 22], may be associated with seasonal variation. A significant negative correlation between monthly mean HbA1c and monthly mean temperature has been shown [8, 10], and we found a similar strong negative correlation between these variables, suggesting that a relatively low temperature is associated with worsened HbA1c. Interestingly, despite the seasonal variation persisting in 2020 during the COVID-19 pandemic, the mean HbA1c was significantly larger than those in 2018 and 2019 (differences of 0.19% and 0.14%, respectively) and was particularly larger in winter (0.23% and 0.18%, respectively). In contrast, the mean temperatures in 2018, 2019 and 2020 did not differ significantly. Therefore, the worsened glycemic control assessed by HbA1c in 2020 appears to be due to reasons

other than temperature. The effects of COVID-19 pandemic included self-imposed limitations on going out and promotion of telework at home, which may have resulted in lack of exercise and increased food intake, including a probable increase of snacks. Thus, particularly careful attention to glycemic control is needed if the COVID-19 period continues into the winter of 2021.

Seasonal variations of GA were also evaluated as another marker of glycemic control. However, we found no apparent seasonal variation of GA in all 3 years and no correlation between monthly mean GA and monthly mean temperature in each year, as also found in the only previous study of this effect [10]. The reasons for these negative findings are unclear. GA reflects shorter-term glycemic control compared with HbA1c [24] and is negatively influenced by body fat mass and visceral adipose tissues, unlike HbA1c [27]. However, it is unclear whether these differences influence the results for seasonal variation. The mean GA level was significantly elevated in the COVID-19 period (2020) compared with those in 2018 and in 2019, similarly to HbA1c. This suggests that GA may have a different clinical utility compared with that of HbA1c as a marker of glycemic control, since GA is not affected by seasonal variation.

Seasonal variation of LDL-C levels was also investigated. LDL-C has previously been shown to have seasonal variation, with higher levels in cooler seasons and lower levels in warmer seasons [25]. LDL-C levels in our patients were slightly lower in summer–autumn and slightly higher in winter–spring in 2018 and 2020, but did not differ between seasons in 2019. There was a weak but significant correlation between monthly mean LDL-C and monthly mean temperature only in 2018. Based on these findings, we concluded that there was no apparent seasonal variation on LDL-C. Interestingly, the mean yearly LDL-C levels were quite similar in 2018, 2019, and 2020, which suggests that LDL-C was not influenced by the COVID-19 pandemic. The different results for HbA1c and LDL-C are difficult to explain, but speculatively, the possible increase of food intake (snacks) at home in the COVID-19 periods may have increased intake

of carbohydrates rather than lipids although the results may be different in Europe and the US, where eating habits and types of snacking are different compared with those in Japan. In addition, lack of exercise would generally influence HbA1c rather than LDL-C. However, a more detailed investigation is needed to explain these results more fully.

In the current study, seasonal variations of HbA1c and GA as markers of glycemic control, and LDL-C as a lipid marker were evaluated over a 3-year period. The limitations of the study include this relatively short period and the small number of patients. Furthermore, we could not accurately evaluate the change of body weight due to the nature of the retrospective observational study; the descriptions of body weight were mainly based on the patients' self-report and there were partially missing descriptions on electronic medical records. This is important limitation in this study. However, the study period also included 1 year of the COVID-19 pandemic, in which lifestyles changed compared to those under normal conditions. Other advantages of the study were its performance in patients examined by a single doctor at one center, which eliminates bias from different treatment policies, and the standard measurements used for HbA1c, GA and LDL-C.

In conclusion, HbA1c showed seasonal variation, with a high level in winter-spring and a low level in summer-autumn, and this variation was similar in the non-COVID-19 and COVID-19 periods. However, mean yearly HbA1c was significantly elevated during the COVID-19 period compared with the previous 2 years, and the difference was larger in winter. In contrast, GA did not show apparent seasonal variation, but mean GA during the COVID-19 period was significantly elevated compared with the non-COVID-19 years. LDL-C did not show an apparent seasonal variation, and was not influenced by COVID-19 pandemic. The observed effects of the COVID-19 pandemic on HbA1c and GA warrant further longer-term studies of these variables.

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Declarations

Conflict of interest All authors have no conflict of interest to declare.

Research involving human participants or animals The study with human subjects

Informed consent The information of this retrospective study was posted during 6-month opt-out period. Name of institutional committee: the institutional ethics committee at Dokkyo Medical University Saitama Medical Center: Approval no. 21014/ approval day: 4/26/2021.

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