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Seasonal Variation of Glucose Variability in Rather Elderly Patients with Type 2 Diabetes (T2D) Treated by Vildagliptin and Metformin (EquMet)

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Abstract

Background: Seasonal variation of HbA1c has been in focus.

Patients and Methods: The protocol included type 2 diabetes (T2D) patients (n=26, 71.4±10.2 years) on vildagliptin and metformin (EquMet) and HbA1c changes in 4 seasons for 6 years.

Results: HbA1c values ranged 6.9-7.5%, and tend to show highest in winter, and rather lower in autumn.

Discussion & Conclusion: Rather elderly T2D cases can tolerate EquMet with fair control. Previous reports showed a similar tendency. Some factors may be involved in the variation, such as temperature, climate, carbohydrate intake, Ramadan, and others. Furthermore, blood pressure and cardiovascular disease (CVD) can also influence them.

Keywords

Seasonal variation of HbA1c, Type 2 Diabetes, Cardiovascular Disease, EquMet, Ramadan

Abbreviations

T2D: Type 2 Diabetes; CVD: Cardiovascular Disease

Introduction

Diabetes mellitus has become a crucial disease to be managed from various points of view worldwide [1]. For decade, several effective pharmacological agents for type 2 diabetes (T2D) have been introduced in the medical practice, such as sodium–glucose cotransporter 2 inhibitor (SGLT2i) and glucagon-like-peptide 1 receptor agonist (GLP1-RA) [2,3]. In the case of elderly patients with T2D, adequate glycaemic goals would be set associated with several factors including environmental temperature, seasons, QOL, ADL, and medication [4].

For years, T2D control situations and prevalence have had a close relationship associated with seasonal variation [5]. From these perspectives, a study was conducted to clarify the mutual relationships between blood glucose and ambient temperature. As a result,

non-linear associations were found between fasting plasma glucose (FPG) and temperature, and then, T2D control ratio and prevalence seemed to be involved in these factors.

T2D patients show seasonal changes in HbA1c values. It becomes lower in summer-autumn and higher in winter-spring [6]. A latest report revealed the comparison of non-intervention groups (usual care, UC) and diet education groups (DE) by providing nutritional lectures for starting in different seasons. The results showed that the UC group had stable HbA1c, whereas the DE group had reduced HbA1c as 6.8 to 6.2%. Consequently, nutritional lectures with continuing the same medication would be effective irrespective of starting in any season.

Authors and colleagues have continued clinical practice and research on T2D for seasonal influence and pharmacological treatment [7,8]. Recently, we have focused on the protocol that includes rather elderly T2D patients and a common combination of vildagliptin and metformin among various combinations of treatments [9]. In this study, we present current research concerning seasonal influence for diabetic control.

Subjects and Methods

The subjects in this study were 26 patients with T2D. They were treated with vildagliptin and metformin during 2016 to 2021, which were combined oral hypoglycemic agents (OHA) as the brand name EquMet. The patients have visited Kanaiso Hospital, where the authors have worked for years. Concerning the diagnosis, type 1 diabetes (T1D) and other special types of diabetes were excluded in the current investigation.

As regards to the methods, the authors have accumulated various data in diabetic patients for a long time. We have applied the calculation method for HbA1c in 4 seasons, which are winter, spring, summer, and autumn. The details of the calculation for winter would be the average data for Dec, Jan, and Feb (12-1-2). Similarly, average data of three seasons were 3-4-5, 6-7-8, 9-10-11, respectively. Using these methods, HbA1c seasonal variations were investigated from 2016 to 2021.

The characteristic aspect of Kanaiso hospital would be the average-scale private hospital with 50 beds and a dialysis center covering 100 patients with chronic renal failure (CRF). It is not a University hospital, or municipal hospital, but a standard Japanese hospital covering many patients in the community.

Ethical Considerations

The current study was fundamentally performed in compliance with suitable ethical principles, that was based on the Declaration of Helsinki. Further, there was some commentary on the Ethical Research Guidelines for Human subjects and Good Clinical Practice (GCP). As to the protection of human rights, an ongoing consideration was observed. In addition, “Ethical Guidelines for Epidemiology Research” has been applied for the related guideline. These principles were made by the Ministry of Education, Culture, Sports, Science, Japan and Technology, and also by the Ministry of Health, Labor and Welfare, Japan.

Concerning this study, the authors established an ethical committee in the Kanaiso Hospital of Tokushima, including the director of the hospital, pharmacist, the head-nurse of the nursing department, director of the administration, and expert in the legal profession. We have fully discussed and came to the confirmation that current study would be adequate and agreed with all members without any problems.

Results

Basic Data:

Table-1: The characteristics of the subjects

Age (years)	71.4 ± 10.2 y.o.
Number (M/F)	13/13 M/F
Body height	157.0 ± 9.1 cm
Body weight	66.2 ± 12.5 kg
Body mass index	26.6 ± 4.4 kg/m^2
ABD.circumference	91.0 ± 11.1 cm
Thigh circumference	41.3 ± 4.9 cm

The subjects in this study were 26 cases of T2D. The anthropometry and fundamental data were summarized in **Table-1**. Their detail was male/female

=13/13 and their average age was 71.4 ±10.2 years (mean ± SD). The median age was 71 years old. Among them (n=26), three oldest cases were 94, 89, 89 years old. Body mass index (BMI) showed 26.6 ± 4.4 kg/m^2 and the median BMI was 27.0 kg/m^2.

Seasonal HbA1c Changes:

Seasonal changes in HbA1c levels during 2016-2021 are shown in **Fig-1**. The transvers axis reveals four seasons, which are winter, spring, summer and autumn. Each data represents the average of each month for 12-2, 3-5, 6-8. 9-11, respectively. HbA1c values for 4 seasons showed the range of 6.9-7.5%, and tend to show highest in winter, and rather lower in autumn. This general situation can be found during 6 years.

Discussion

Some reports have been found concerning the seasonal variation of diabetic control. HbA1c changes for different seasons were investigated for T2D patients throughout 11 years [10]. It was a retrospective cohort study including 61187 HbA1c data from 2860 T2D cases. The tendency of HbA1c was observed as spring peak and autumn trough. The lowest level was Oct-Nov, and the highest was March or August, associated with 0.17-0.31% (2-4 mmol/mol) of difference. For a possible explanation for hot periods, people tend to decrease physical activity, to change the meal pattern, leading to diabetic imbalance. Recognition of seasonal HbA1c variations may help physicians and patients for better diabetic control and care. Another study included 26 thousand respondents with 4 health surveys for 9 years [5]. Based on WHO criteria, these cases were categorized into newly diagnosed T2D, previously diagnosed T2D, and normal fasting glucose (NFG). As a result, non-linear associations were found between FPG and temperature in different subgroups. Then, T2D control ratio and prevalence seemed to be involved in the relationship of temperature and FPG.

Concerning East Asian countries, seasonal variations related to Ramadan have been reported. Search for seasonal glucose variations were performed for 32 reviews and 7 meta-analyses [11]. Among oral hypoglycemic agents (OHAs), DPP-4i such as vildagliptin with metformin would be a choice for those who are fasting during Ramadan. Results of meta-analysis showed reduced hypoglycemic risk in DPP-4i compared with sulphonylurea (SU) with an odd ratio of 0.38. By electronic search on Google Scholar and PubMed, eligible studies of randomized controlled trials (RCT) for 12 years were conducted for diabetic patients who are involved in the fasting of Ramadan [12]. The results showed that better effects for glucose

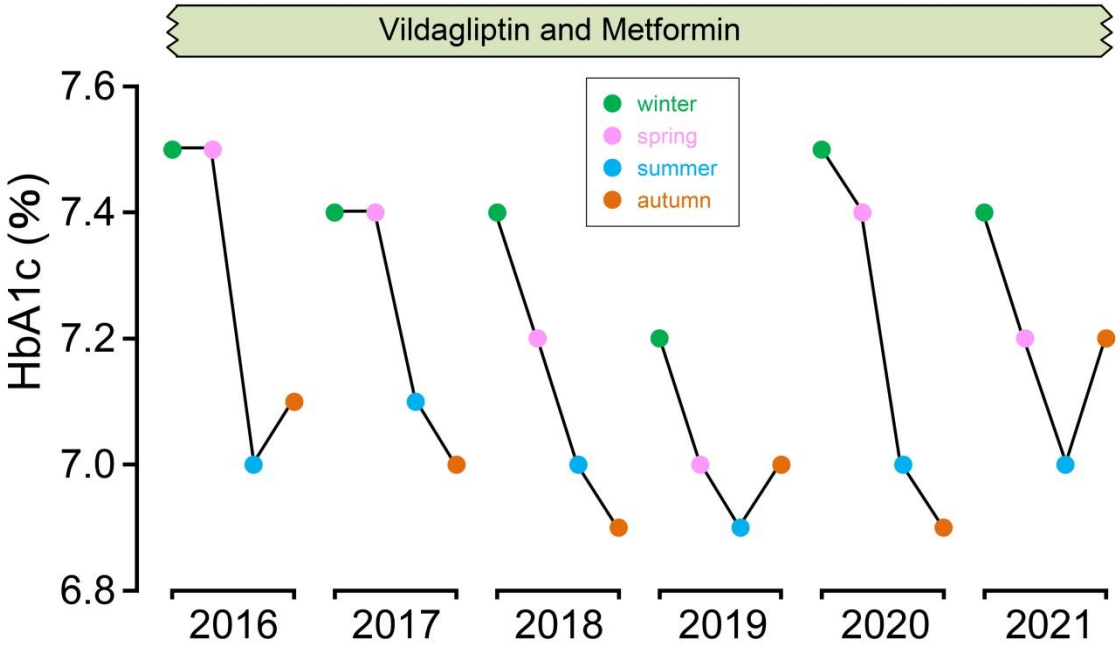

Fig-1: Seasonal HbA1c of T2D patients during 2016-2021

variability and weight control were found in OHAs of incretin mimetics and SGLT2i and novel insulin analogues in comparison with previous SU. Among SU, gliclazide has been a relatively safer agent.

Seasonal alterations in HbA1c were analyzed from 86 thousand samples of electronic medical records of Istanbul Univ. Hospital [13]. As a result, unexpected results were found. The data of HbA1c was 0.3% higher in summer compared with winter. A possible explanation would be from the occurrence of Ramadan in the summer. Unstable meal situations of feasting and fasting are included in several cultures and religions. During these opportunities, fluid and food intake are remarkably changed, associated with a higher risk of developing complications [14]. In Particular, intake of carbohydrates, and fasting in contrast may exacerbate diabetes.

Related to diabetes, blood pressure and cardiovascular disease (CVD) also have seasonal variations with temperature and other factors. For T2D patients, seasonal variations in home BP and the relationship of room temperature were investigated. The protocol included 41 T2D cases, and triplicate BP measurements at least 5 days a month for 1 year [15]. The results showed that the lowest BP was 126/70 in August, and highest BP was 140/77 in January. The root mean squared error of systolic BP and room temperature was 6.5 mmHg. Consequently, seasonal BP variations may be involved in the factor of room temperature. The research group in Taiwan included 13280 patients and 10894 researchers, and various factors were analyzed [16]. As a result, joint influence of SBP, fasting glucose and HbA1c could predict the incidence of CVD, stroke and death associated with 16-35% elevated risk. Furthermore, combined influence of SBD, DBP, fasting glucose and HbA1c were involved in all-cause mortality and CVD mortality associated with 29-81% elevated risks.

Seasonal changes in some risk factors for CVD were studied. They included BP, HbA1c, HDL, T-Cho, BMI and smoking habits as CVD risks [17]. The study included 411 cases for analysis with calculators of UKPDS-CHD 1.33%, UKPDS-Stroke 0.84%, ASCVD 2.21%. Concerning seasonal variations, systolic BP was mainly responsible for the changed risk for UKPDS-Stroke and ASCVD scores. Seasonal changes in diabetes mellitus (DM) and coronary artery disease (CHD) have been reported, which may be related to vasopressin (VP) concentration [18]. VP is known to show seasonal variation, and then these relationships were studied. The surrogate marker of VP would be copeptin, which were collected for 5 population cohorts (n=25 thousand). As a result, copeptin values showed 5.81 pmol/L (M/F = 7.18/4.44), and exhibited seasonal changes with peak in winter and nadir in late summer. The adjusted variation in median was 0.62 pmol/L (M/F=0.98/0.46). From analyses of these data, seasonal variation may increase risk of 4% of DM incidence and 2% of CAD incidence.

Concerning our current study, the subjects were rather elderly T2D patients, who were provided vildagliptin and metformin (EquMet) for years. This combination can be applied for safer situation for older age and decreased renal function [19,20]. HbA1c variation showed similar tendency during 2015-2021. The crucial problem of COVID-19 started from Dec 2019. However, HbA1c variation seems to receive unremarkable influence. From a latest report, HbA1c changes were followed up during COVID-19 pandemic [21]. As a result, usual seasonal changes were also found with higher in winter-spring and lower in summer-autumn during COVID-19 pandemic period. However, mean HbA1c values were slightly higher compared to previous 2 years. The data were 7.53% vs 7.34%/7.39%, associated with larger difference during winter. Future observation would be required to judge longer period influence of COVID-19 pandemic.

Some limitations may be present in this study. Seasonal HbA1c variation would be influenced by several factors such as temperature, blood pressure and CVD, as well as COVID-19 problems. Multi-focal further evaluation will be required for this matter. In conclusion, this article described seasonal HbA1c variations associated with influences of possible several biomarkers. It is expected that this report will contribute some diabetic practice and research.

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Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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