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ORIGINAL ARTICLE

Increased incidence of pre-diabetes mellitus at a department of rheumatology: a retrospective study

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Abstract We aimed to retrospectively review the incidence of pre-diabetes mellitus (preDM), one of the factors in metabolic syndrome screening, in patients with rheumatic diseases. We examined the levels of hemoglobin A1c (HbA1c) in a total of 498 patients with rheumatic diseases between April 2007 and March 2008 at the Department of Rheumatology in Nagasaki University Hospital. Of the 498 patients, 409 (82.1%) had HbA1c levels higher than 5.6% (National Glycohemoglobin Standardization Program; NGSP) and were recommended for health guidance with a focus on metabolic syndrome. Serum HbA1c levels higher than 6.0%, a possible indicator of DM, were seen in 227 patients (45.6%). Serum HbA1c levels higher than 6.5%, which constitute a high risk for DM, were found in 115 patients (23.1%). PreDM increased gradually with age. Our results suggest that the incidence of preDM may be higher in patients with rheumatic diseases than in patients with other diseases and that these patients should receive healthcare guidance to prevent metabolic syndrome.

Keywords Diabetes mellitus · Hemoglobin A1c (HbA1c) · Metabolic syndrome · Rheumatoid arthritis

Introduction

The International Diabetes Federation (IDF) estimated that the number of patients with diabetes mellitus (DM) was 285 million in 2010, and will reach 438 million in 2030 [1]. In Japan, the Westernization of eating habits and lifestyles has been steadily increasing the incidence of metabolic syndrome for some time now. The Ministry of Health, Labor and Welfare reported that approximately 18.4% of Japanese people older than 40 years of age suffered from or were suspected of having DM in 2007 [2]. The same ministry suggested that a level of hemoglobin A1c (HbA1c) (National Glycohemoglobin Standardization Program; NGSP) of 6.0% or greater was a possible indicator of DM, and that a level of HbA1c of 6.5% or greater was a strong indicator of the presence of DM, and thus they carried out a nationwide screening for DM among those with HbA1c levels of 6.5% or higher. The results of this screening showed that 25.6% of individuals in the general population had serum HbA1c levels of 6.0% or greater, and 10.5% had levels of 6.5% or greater.

It has been shown that patients whose HbA1c level is 5.6% or greater develop DM twice more than those with levels lower than 5.6%. Accordingly, healthcare guidance with a focus on metabolic syndrome was given to these patients in Japan, starting in April 2009.

Although it has been suspected that the incidence of DM is high in patients with rheumatic diseases, there have been

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few reports about the relation between pre-diabetes mellitus (preDM) and rheumatic diseases. Therefore, we screened patients whose HbA1c was 5.6% or greater at our university hospital, and attempted to prevent the onset of metabolic syndrome or DM in this population by means of healthcare guidance.

Patients and methods

Patients

In total, 5,008 patients whose HbA1c levels were examined at Nagasaki University Hospital (excluding the Departments of Pediatrics and Endocrinology/Metabolism) between April 2007 and March 2008 were retrospectively enrolled in this study. Among these patients, there were 500 patients with rheumatic diseases who visited the Department of Rheumatology. We studied 498 of these patients (121 men and 377 women; mean age: 57.8 ± 13.7 years; range: 20–85 years) who were at least 20 years of age. The former HbA1c data were employed for this study when there were duplicated data in the same patients. The data of some patients whose doses of prednisolone were unknown or those who stopped receiving regular outpatient treatment were excluded. The characteristics of the patients are summarized in Table 1. The patient cohort included 180 patients with rheumatoid arthritis (RA), 55 patients with systemic lupus erythematosus (SLE), 15 patients with scleroderma, 15 patients with polymyositis/dermatomyositis (PM/DM), 48 patients with Sjogren's syndrome, and 37 patients with vasculitis syndrome. The average level of HbA1c was 5.8 ± 1.1%; 321 patients (64.5%) were taking prednisolone (mean ± SEM: 8.7 ± 7.8 mg/day; range 1–50 mg/day).

Data analysis

Using data from the archives of the Clinical Laboratory Department of Nagasaki University Hospital, we retrospectively analyzed findings in patients in whom HbA1c was measured at the Department of Rheumatology. We entered the types of disease and the details of treatments into an electronic chart system. Ethical approval was obtained from the institutional review board (IRB) of Nagasaki University. We divided the patients into 4 groups based on their levels of HbA1c: group a, HbA1c <5.6%; group b, HbA1c ≥5.6% (preDM); group c, HbA1c ≥6.0%; and group d, HbA1c ≥6.5%. The patients who had already been treated for DM were included in the HbA1c ≥6.5% group.

Influence of age and steroid therapy on preDM

We calculated the number of preDM patients who were indicated for healthcare guidance with a focus on metabolic syndrome, and divided these patients into age groups by decade of life. We also calculated the number of preDM patients who had received steroid therapy. In addition, we examined the relationship between the serum HbA1c levels and the doses of prednisolone they received.

Statistical analysis

Data were analyzed using chi-square for independence test. A probability value of less than 0.05 denoted the presence

Table 1 Baseline characteristics of patients with rheumatic diseases

	Rheumatic diseases		Total	
Patients (*n*)	498		5,008	
Age (years)	57.8 ± 13.7		62.0 ± 15.7s old	
Male: female (*n*)	121: 377		2,672: 2,336	
Prednisolone (*n* (%))	321(64.5%) (8.7 ± 7.8 mg/day; range 1–50 mg/day)		ND	
HbA1c	5.8 ± 1.1% (range 3.4–15.1%)		5.6 ± 0.9% (range 3.2–15.1%)	
Classification (*n*) (including patients with more than one condition)	Rheumatoid arthritis	180	Cardiac diseases	729
	Systemic lupus erythematosus	55	Gastrointestinal diseases	571
	Scleroderma	15	Neurological diseases	317
	Dermatomyositis/polymyositis	15	Dermatological diseases	295
	Sjogren's syndrome	48	Respiratory diseases	290
	Vasculitis syndrome	37	Renal diseases	224
	Others	148	Others	2,582

HbA1c hemoglobin A1c, *ND* not determined

of a statistically significant difference. Pearson's correlation coefficient test was used to correlate the HbA1c level and dose of prednisolone.

Results

Classification of patients with rheumatic diseases according to serum HbA1c level

We first classified the patients into those with DM and those with preDM, based on the serum HbA1c levels (Table 2). Serum HbA1c levels were 6.5% or greater in 115 patients (23.1%). The number of patients with serum HbA1c levels between 6.0 and 6.4% was 112 (22.5%). The number of patients with serum HbA1c levels between 5.6 and 5.9% was 182 (36.5%). Taken together, these results indicate that the serum HbA1c levels in 409 patients (preDM including DM, 82.1%) were 5.6% or greater. The number of patients whose HbA1c levels were 5.6% or greater was significantly higher than that of total patients in all HbA1c ranges.

Table 2 Classification of rheumatic diseases according to serum HbA1c levels

HbA1c	Rheumatic diseases 498 cases *n* (%)	Total 5,008 cases *n* (%)	*p* value
≥6.5%	115 (23.1%)	946 (18.9%)	<0.05
6.0–6.4%	112 (22.5%)	984 (19.6%)	<0.01
5.6–5.9%	182 (36.5%)	1503 (30.0%)	<0.01
<5.6%	90 (18.1%)	1575 (31.4%)	<0.01

Relationship between HbA1c and age

In our study, the HbA1c levels of 409 patients were 5.6% or greater (Fig. 1). We classified these patients according to their age by decade. There were 113/123 individuals (91.9%) in their 60s, which was the largest age group. The population ratios of those with HbA1c levels of 5.6% or greater increased until the 60s, and did not change substantially thereafter. The ratios of RA patients were significantly higher than those of the total patients in the range over the 30s ($p < 0.05$).

Relationship between HbA1c and steroid therapy

Of the 498 patients examined in this study, 320 patients received steroid therapy, and 178 patients did not. We compared the average HbA1c level and the number of patients whose HbA1c was 5.6% or greater between the patients taking and those not taking steroid therapy (Table 3). Among the 320 patients with steroid therapy, the

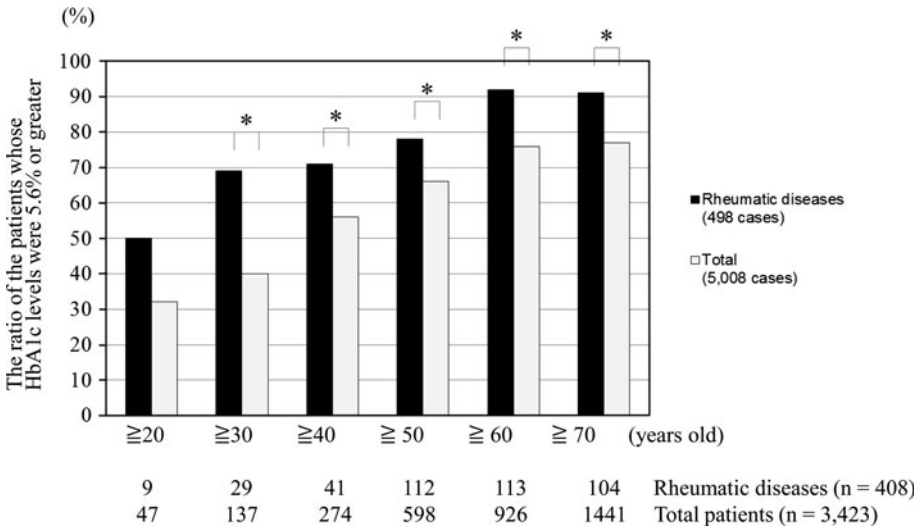

Fig. 1 The pre-diabetes mellitus (preDM) population in each age group. We divided the patients according to age by decade and compared the prevalences, in each decade, of patients whose hemoglobin A1c (*HbA1c*) level was 5.6% or greater, which is considered a high risk factor for potential DM. *Black bars* indicate the patients with rheumatic diseases. *Gray bars* indicate the total patient population. The numbers of patients whose HbA1c values were 5.6% or greater in each age group are also indicated. *$p < 0.05$

Table 3 Relationship between HbA1c and steroid therapy

	HbA1c (%) (mean ± SD)	Percentiles		χ^2 for independence test
		HbA1c < 5.2%	HbA1c ≥ 5.2%	*p* value
Prednisolone (+) $n = 320$	5.74 + 0.94	18.1% ($n = 58$)	81.9% ($n = 262$)	$p = 0.954$
Prednisolone (−) $n = 178$	5.79 ± 1.25	18.0% ($n = 32$)	82.0% ($n = 146$)	

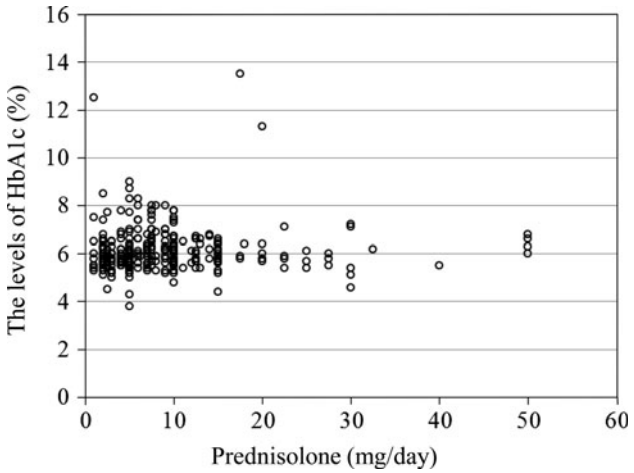

Fig. 2 The relationship between HbA1c levels and doses of steroid. Of the total number of 498 subjects examined in this study, 320 patients received steroid therapy. We examined the relationship between steroid therapy and serum HbA1c levels in these 320 patients. The *horizontal axis* indicates the doses of corticosteroids taken daily (mg/day, converted to the prednisolone dose) and the *vertical axis* indicates the serum HbA1c levels (%)

level of HbA1c was 5.6% or greater in 262 patients (81.9%). Among the 178 patients without steroid therapy, the level of HbA1c was 5.6% or greater in 146 patients (82.0%). There was no significant difference in the average HbA1c level or in the number of patients whose HbA1c was 5.6% or greater between the patients with and without steroid therapy ($p = 0.954$).

We also examined the relationship between steroid therapy and the serum HbA1c level (Fig. 2). However, there was no significant correlation between these parameters.

Discussion

Some studies have reported a significant association between RA and DM [3] [4]. Dessein et al. [5] reported that the prevalence of type 2 diabetes in patients with RA was 10% (8/79), which was not significantly different from that in patients with osteoarthritis (3%; 1/37). Simard and Mittleman reported that there was no statistically significant association between the prevalence of RA and that of DM in subjects aged >60 years [6]. It should be noted that these studies employed very small numbers of subjects with RA and DM, and thus they may have lacked sufficient power to pick up a moderate association between these two conditions. We examined serum HbA1c levels in a total of 498 patients with rheumatic diseases, including 180 RA patients. We found a significantly higher prevalence of DM and of preDM in patients with rheumatic diseases compared to the prevalence in the total cohort of patients of the university hospital. This is the first report concerning the incidence of preDM in patients with rheumatic diseases.

In the present study, in the patients with rheumatic disease the percentage of the population with an HbA1c level of more than 5.6% was more than 50% for every examined decade of age. In particular, the prevalence of preDM in the patients with rheumatic disease was significantly higher than that in the total cohort of patients aged over 30s. We considered that these patients (i.e., those with rheumatic disease and preDM) were the indication for health guidance to prevent metabolic syndrome, even when they were under 40 years old. Why was the incidence of preDM and DM so high in the patients with rheumatic disease? Increased levels of systemic inflammation might predispose individuals to the development of insulin resistance [7]. Gonzalez-Gay et al. [8] reported that tumor necrosis factor (TNF)-alpha blockade resulted in a reduction of serum insulin levels and improvement of insulin resistance in RA patients. In a future study, we would also like to consider the relationship between glucose tolerance and inflammation markers such as C-reactive protein. In addition, decreased activities of daily living (ADL) in RA patients might also contribute to the high serum HbA1c levels.

It is known that corticosteroids increase blood glucose concentrations [9]. Corticosteroids probably act by interfering with the intracellular mechanisms of glucose metabolism or insulin resistance [10]. Insulin concentrations are increased with the administration of corticosteroids, but the increase is generally not sufficient to maintain normoglycemia [11]. However, there are not many reports about the prevalence of corticosteroid-induced DM. Conn and Poynard [12] performed a meta-analysis of reviews of the adverse effects of steroid therapy and reported that the odds ratio for developing DM among patients undergoing steroid therapy was 1.7 (95% confidence interval [CI] 1.12–2.16, $p = 0.02$). Panthakalam et al. [13] reported that nine (8.8%) of 102 patients with established RA developed DM during corticosteroid treatment that lasted for a median duration of 24 months. However, their study enrolled primarily elderly subjects. Elderly people easily develop glucose intolerance, as shown in Fig. 1. Corticosteroids might have a greater influence on the development of DM in elderly people. Blackburn et al. [14] demonstrated that the risk of DM in oral corticosteroid users increased consistently in a time-dependent manner. Therefore, our findings of the lack of a significant correlation between HbA1c and corticosteroid use may have been due to the fact that we did not fix the period after starting the administration of corticosteroids.

We compared the prevalence of patients whose HbA1c was 5.6% or greater among patients with RA, SLE, and Sjogren's syndrome (data not shown). The prevalence of patients with an HbA1c level of 5.6% or greater was 82.2% in patients with RA, 80.2% in those with SLE, and 77.4%

in those with Sjogren's syndrome, but we did not find any significant difference among these diseases.

Some limitations of this study should be discussed. First, this study was performed as a retrospective study. We did not screen all patients at the department of rheumatology, and thus the prevalence of patients whose HbA1c was 5.6% or greater was likely higher than it would have been in the department overall. Second, the subjects whose HbA1c levels were 5.6% or greater included patients undergoing treatment for DM. Despite these limitations, our results do support the idea that the incidence of preDM may be higher in patients with rheumatic diseases than in patients with other diseases. Monitoring how many cases of preDM shift to DM will be useful information for risk assessment.

Conclusion

Rheumatologists should be aware of a higher prevalence of preDM in patients with rheumatic diseases. In the long term, hyperglycemia may increase cardiovascular risk [15] and the risk of metabolic syndrome. We expect that the elucidation of a correlation between rheumatic diseases and preDM will contribute to a better prognosis for patients with rheumatic diseases.

Conflict of interest None.

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