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ORIGINAL ARTICLE

Osteoporosis is highly prevalent in Japanese males with chronic obstructive pulmonary disease and is associated with deteriorated pulmonary function

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Abstract Osteoporosis has recently been recognized as a major comorbidity in chronic obstructive pulmonary disease (COPD). We conducted a cross-sectional study in a cohort of 136 Japanese males with COPD to evaluate the prevalence of vertebral fracture (VF) and to explore its relationship with pulmonary function parameters. VFs were present in 108 (79.4 %); multiple and severe (SQ grade 2 or 3) VFs were found in 77 (56.6 %) and 25 (18.4 %), respectively. Multivariate logistic regression analyses revealed that decrease in forced expiratory volume in one second (FEV1.0)/forced vital capacity (FVC) [odds ratio (OR) 0.963, 95 % confidence interval (CI) 0.929–998, $p = 0.036$] was associated with the presence of VF after adjustment for age and that FVC (OR 0.462, 95 % CI 0.220–0.968, $p = 0.041$) and current smoking (OR 2.992, 95 % CI 1.128–7.940, $p = 0.028$) were associated with VF severity (grade 2–3 vs. 1). We also found that FEV1.0 was the sole independent determinant of the number of VFs by stepwise multivariate linear regression ($p < 0.001$). Bone mineral density (BMD) values were available in 49 subjects. Mean T scores were -2.0 ± 1.2 in femoral neck, -1.4 ± 1.2 in total hip and -1.1 ± 1.4 in lumbar spine. Nineteen patients (38.8 %) had a BMD T score less than -2.5. BMD Z scores of all the sites showed a progressive decrease as GOLD stage of COPD advanced ($p < 0.05$). Our results indicate a high prevalence of osteoporosis in Japanese male COPD patients and a strong inter-relationship between the two diseases, re-emphasizing the urgent need for appropriate intervention to maintain both bone and lung health.

Keywords Chronic obstructive pulmonary disease (COPD) · Osteoporosis · Vertebral fracture · Bone mineral density · COPD assessment test (CAT)

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Introduction

Chronic obstructive pulmonary disease (COPD) is described as a preventable and treatable disease that is characterized by progressive airflow limitation. Although COPD is primarily caused by an abnormal response of the lung tissue to cigarette smoking and other harmful particles or gases, it is often associated with various comorbidities including atherosclerosis, muscle wasting and osteoporosis, contributing to diminished quality of life and increased mortality of the affected subjects [1].

Among such systemic features of COPD, osteoporosis is now recognized as a major comorbidity that needs clinicians' attention and appropriate therapeutic intervention [1, 2]. Indeed, the prevalence of osteoporosis and vertebral fractures in patients with COPD has been reported to be as high as 9–69 % [3] and 24–63 % [2], respectively. Conversely, a recent report indicates that COPD is the most frequent cause of secondary osteoporosis in men, followed by corticosteroid use, hypogonadism and other disorders [4]. Although many observational studies have reported association of COPD with decreased bone mineral density (BMD) and/or vertebral fractures (VFs) [5–14], the etiological and pathophysiological link between COPD and osteoporosis has not been well understood, and whether or not particular pulmonary

function parameters correlate with vertebral fractures (VFs) and bone loss in COPD patients remains controversial. In Japan, only a few studies have investigated osteoporosis in subjects with COPD [15–18].

In the present study, we thus aimed to evaluate the prevalence of vertebral fractures (VFs) and low BMD in Japanese male subjects with COPD. We also explored the association of VFs and BMD with pulmonary function parameters. The results indicate high prevalence of osteoporosis in COPD patients in Japan and illustrate a complex interactive relationship between the two diseases.

Materials and methods

Subjects

This is a cross-sectional study enrolling 136 Japanese males who were diagnosed with COPD and had a lateral spine X-ray examination. Subjects were recruited at either Teikyo University Chiba Medical Center or Yarita Hospital from April 2011 until July 2013. Diagnosis and classification of COPD was made according to the Global Initiative for Chronic Obstructive Lung Disease criteria (GOLD) [19]. We excluded patients with a secondary cause of osteoporosis such as hyperthyroidism, hyperparathyroidism, chronic renal failure (GFR less than 30 mL/min), corticosteroid use for other diseases, type 1 diabetes mellitus and bone metastatic cancer. Height and weight were measured and body mass index (BMI) was calculated. Information on medical history, smoking status and corticosteroid use was obtained from patient interviews and medical records. Smoking exposure was estimated by pack-years, calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person had smoked. The COPD assessment test (CAT) in the Japanese version was used to evaluate impairment of general health status in 30 subjects. The CAT is composed of 8 items of relevant symptoms, viz., cough, phlegm, chest tightness, breathlessness, activity limitation at home, confidence in leaving home (mental), sleep and energy (vigor) [20, 21]. The study protocol was approved by an institutional ethical committee and informed consent was obtained from all the participants.

Pulmonary function test

Pulmonary function tests were performed under stable condition in all patients. Vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume in one second (FEV1.0) were measured by spirometry and the FEV1.0/FVC ratio was determined. Patients with FEV1.0/FVC less than 0.7 were diagnosed as having COPD, and classified into four stages by FEV1.0 expressed as percent of predicted values (FEV1.0 %predicted) according to the GOLD criteria [19]: stage 1 (equal to or more than 80 % of predicted), stage 2 (50–80 % of predicted), stage 3 (30–50 % of predicted) and stage 4 (less than 30 % of predicted).

Assessment of vertebral fractures (VFs)

The number of VFs was evaluated using thoracic and lumbar spine X-rays. Lumbar spine images were unavailable in 50 subjects. Six subjects had only a lumbar spine X-ray examination. The severity of vertebral fractures was morphologically assessed according to the semi-quantitative method of Genant et al. [22], and classified into 3 grades: grade 1 (20–25 % reduction in anterior, middle and/or posterior height and 10–20 % reduction of the projected vertebral area), grade 2 (25–40 % reduction in heights and 20–40 % reduction of the projected vertebral area) and grade 3 (equal to or more than 40 % reduction in heights).

BMD measurement

Bone mineral density was measured at lumbar spine (L1–4), femoral neck and total hip using dual energy X-ray absorptiometry (Discovery W: Hologic Inc., Bedford, MA, USA). BMD was expressed as an absolute value, *T* scores (standard deviations from a young, sex-specific reference mean BMD) and *Z* scores (standard deviations from age- and sex-specific reference mean BMD). For lumbar spine BMD measurement, we excluded vertebrae that were affected by local structural change or artifact. According to the WHO criteria, *T* score less than −2.5, between −2.5 and −1.0, and more than −1.0 was defined as osteoporosis, osteopenia and normal BMD, respectively [23].

Statistical analysis

All statistical analyses were performed using SPSS Version 21(IBM Inc., Tokyo, Japan). To compare continuous variables, analysis of variance (ANOVA) with post-hoc Tukey HSD test or Student's *t* test were performed as appropriate. Discrete variables were presented as percentages and compared with Pearson's Chi-squared test. Multivariate logistic regression analyses were performed to identify the determinants of the presence and the severity of fractures (grade 2 or 3 compared with grade 1). Spearman's correlation tests were used to examine correlates of the number of vertebral fractures or FEV1.0, and multivariate linear regression analyses were performed to

identify independent determinants. A p value less than 0.05 was considered significant.

Results

Patient characteristics

Characteristics of the 136 study subjects are shown in Table 1. There was no significant difference in age among GOLD stages, whereas height and BMI were significantly lower in stage 4. As expected, all the parameters of respiratory function decreased as the stages advanced, and more patients in advanced stages were receiving home oxygen therapy and had been exposed to corticosteroids. The proportion of current smokers was the lowest in GOLD 3, but there was no significant difference in pack-years smoked. Of the 136 patients, only 4 had been treated for osteoporosis with alendronate alone or in combination with alfacalcidol. A diagnosis of osteoporosis had never been made in any of the other subjects. As for non-traumatic, non-vertebral fractures, the medical record and patient interview revealed a history of one hip, one forearm and seven rib fractures.

Vertebral fracture (VF)

The overall prevalence of VFs was 79.4 % (108/136), and two or more VFs were observed in 77 subjects (56.6 %) (Table 1). More than half of the VFs occurred at Th7, Th8, Th11, Th12 and L1. Severe fractures with SQ Grade 2 or 3 were present in 25 (18.4 %) subjects. Neither VF prevalence nor the average per person-number of VFs was statistically different among GOLD stages. Grade 2 or 3 VFs tended to increase as GOLD stage advanced, without statistical significance.

Compared with subjects without VFs, those with VFs were slightly older and shorter in height (Table 2). Among pulmonary parameters, only FEV1.0/FVC was significantly lower in the fracture group. Multivariate logistic regression analysis revealed that FEV1.0/FVC was the only independent determinant of the presence of VFs after adjustment for age (Table 3). The contribution of FEV1.0/FVC, however, became insignificant after further adjustment for height. The results remained basically unchanged after an adjustment for FVC and FEV1.0.

As for the severity of VFs, the subject group with grade 2 or 3 VFs had a shorter stature and lower FVC, and included more current smokers, compared with the group

Table 1 Patient characteristics

	Total	GOLD 1	GOLD 2	GOLD 3	GOLD 4
Number of subjects (%)	136 (100)	23 (17)	46 (34)	44 (32)	23 (17)
Age (years)	71.6 ± 8.9	68.0 ± 10.3	71.8 ± 7.9	73.3 ± 7.9	71.8 ± 10.6
Height (cm)	162.6 ± 5.8	165.6 ± 7.6	162.9 ± 5.4	161.5 ± 4.6*	160.9 ± 5.7*
BMI (kg/m^2)	21.5 ± 3.2	22.3 ± 2.8	22.2 ± 3.1	21.5 ± 3.3	19.4 ± 3.1*·**·***
Pack-years smoked	60.4 ± 37.8	67.5 ± 58.4	57.5 ± 33.1	63.4 ± 31.1	52.6 ± 31.3
Current smoking (%)	33.8	56.5	32.6	22.7*	34.8
VC %predicted	81.3 ± 21.7	109.5 ± 16.6	87.9 ± 14.6*	71.7 ± 14.7*·**	58.6 ± 10.6*·**·***
FVC (L)	2.61 ± 0.95	3.68 ± 0.72	2.80 ± 0.55*	2.25 ± 0.98*·**	1.88 ± 0.68*·**
FEV1.0 (L)	1.40 ± 0.69	2.43 ± 0.51	1.61 ± 0.35*	0.97 ± 0.33*·**	0.75 ± 0.42*·**
FEV1.0/FVC (%)	52.2 ± 12.7	66.1 ± 4.0	57.9 ± 8.6*	45.4 ± 10.7*·**	39.7 ± 8.5*·**
FEV1.0 %predicted	55.8 ± 25.8	96.7 ± 18.0	66.3 ± 9.2*	39.4 ± 5.3*·**	25.2 ± 5.6*·**·***
Inhaled corticosteroid use (%)	40.4	26.1	26.1	56.8*·**	47.8**
Oral and/or intravenous corticosteroid use[a] (%)	17.0	8.7	8.7	27.3**	21.7
Home oxygen therapy (%)	22.2	4.3	13.0	25.0*	52.1*·**·***
Vertebral fracture (VF) (%)	79.4	65.2	84.8	77.3	87.0
Multiple VFs (%)	55.1	52.2	52.2	56.8	60.9
Number of VFs per person	2.1 ± 1.9	1.8 ± 1.8	1.8 ± 1.3	2.2 ± 2.2	2.7 ± 2.0
Grade 2 or 3 VF (%)	18.4	13.0	21.7	13.6	26.1

Values of the continuous variables are expressed as mean ± SD

ANOVA with post-hoc Tukey HSD test was performed for continuous variables, and chi-squared test was used for discrete variables

BMI body mass index, *VC* vital capacity, *FVC* forced vital capacity, *FEV1.0* forced expiratory volume in one second, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *Grade* SQ grade according to Genant [6]

[a] Defined as current oral corticosteroid use or past oral and/or intravenous corticosteroid use

*, **, *** Significantly different from GOLD 1, 2 and 3, respectively ($p < 0.05$)

Table 2 Clinical characteristics and pulmonary function in subjects with and without vertebral fracture

	Non-fracture group ($n = 28$)	Fracture group ($n = 108$)	p value
Age (years)	68.3 ± 9.9	72.5 ± 8.5	**0.023***
Height (cm)	165.3 ± 6.4	161.9 ± 5.4	**0.005***
BMI (kg/m^2)	22.1 ± 3.5	21.4 ± 3.2	0.312
Pack-years smoked	59.7 ± 28.5	59.7 ± 28.5	0.938
Current smoking (%)	39.3	32.4	0.493
VC %predicted	85.0 ± 27.2	80.4 ± 20.1	0.314
FVC (L)	2.75 ± 1.09	2.58 ± 0.92	0.415
FEV1.0 (L)	1.62 ± 0.85	1.34 ± 0.63	0.115
FEV1.0/FVC (%)	57.3 ± 12.6	50.8 ± 12.4	**0.016***
FEV1.0 %predicted	59.8 ± 27.7	54.8 ± 25.3	0.358
Inhaled corticosteroid use (%)	32.1	42.6	0.315
Oral and/or intravenous corticosteroid use[a] (%)	14.3	17.6	0.677
Home oxygen therapy (%)	14.3	24.1	0.266

Values of the continuous variables are expressed as mean ± SD

Student's t test was performed for continuous variables, and Chi-squared test was performed for discrete variables to compare fracture group with non-fracture group

BMI body mass index, *VC* vital capacity, *FVC* forced vital capacity, *FEV1.0* forced expiratory volume in one second

[a] Defined as current oral corticosteroid use or past oral and/or intravenous corticosteroid use

* $p < 0.05$ (shown in bold)

with grade 1 VFs. No other parameters were significantly different between the two groups (data not shown). Multivariate logistic regression with these parameters as covariables indicated that FVC and current smoking were independently associated with severe VFs (Table 4).

As shown in Table 5, age and pulmonary function parameters correlated with the number of VFs. Multivariate linear regression analysis revealed that FEV1.0 ($\beta = -0.279$, $p = 0.001$) was the sole independent determinant of the number of VFs after stepwise variable selection excluding age, body mass index, height, FEV1.0/FVC, inhaled corticosteroid use, current oral or past oral and/or intravenous corticosteroid use, current smoking, pack-years smoked and home oxygen therapy. FVC was significant when included instead of FEV1.0, but significance disappeared when included simultaneously with FEV1.0 (data not shown), suggesting that FEV1.0 was the predominant determinant of the number of VFs. Conversely, among correlates of FEV1.0 (Table 6), the number of VFs was an independent determinant of FEV1.0 in addition to height and home oxygen therapy, as shown in Table 7.

Bone mineral density

The number (%) of subjects whose BMD was available at each GOLD stage was 15 (30.6 %), 19 (38.8 %), 11 (22.4 %) and 4 (8.2 %), respectively, with the sum being 49 subjects. Mean T scores were −2.0 ± 1.2 in femoral neck, −1.4 ± 1.2 in total hip and −1.1 ± 1.4 in lumbar spine. In this subpopulation, BMI was significantly lower in stage 4, and all the pulmonary parameters were worse in advanced stages (data not shown), as observed in the whole cohort. Compared to the whole cohort of 136 subjects, these 49 subjects tended to be at earlier GOLD stage with a significantly higher mean value of FEV1.0 %predicted (66 vs. 56 %, $p = 0.02$). There was no difference in any other parameter. According to the WHO criteria, 19 (38.8 %) had osteoporosis, 21 (42.9 %) had osteopenia, and 9 (18.4 %) had normal BMD. According to the 2012 Japanese diagnostic criteria for osteoporosis [24], 41 subjects (83.7 %) were diagnosed as having osteoporosis. The higher value with the Japanese criteria is due to an extremely high prevalence of VFs in our subjects. Only five subjects were diagnosed with osteoporosis by BMD without fragility fractures.

We then examined whether or not GOLD stages were associated with BMD. As shown in Fig. 1, BMD Z scores at all sites measured showed a progressive decrease as GOLD stage became advanced, with values in GOLD 3 or

Table 3 Determinants of prevalent vertebral fractures

	Model 1			Model 2		
	OR	95 % CI	p value	OR	95 % CI	p value
Age	1.051	1.000–1.104	0.051	1.026	0.968–1.087	0.386
FEV1.0/FVC	0.963	0.929–0.998	**0.036***	0.966	0.902–0.984	0.063
Height	–	–	–	0.931	0.852–1.017	0.112

Multivariate logistic regression analysis with forced entry of the listed parameters was performed according to presence or absence of VFs ($n = 136$)

FVC forced vital capacity, *FEV1.0* forced expiratory volume in one second, *OR* odds ratio, *CI* confidence interval

* $p < 0.05$ (shown in bold)

Table 4 Independent determinants of the severity of vertebral fractures

	OR	95 % CI	*p* value
Height	0.959	0.868–1.059	0.406
FVC	0.462	0.220–0.968	**0.041***
Current smoking	2.992	1.128–7.940	**0.028***

Multivariate logistic regression analysis was performed according to the presence of grade 2 or 3 vertebral fractures ($n = 25$) compared with grade 1 vertebral fractures ($n = 83$). The analysis was done by forced entry of the three variables showing a significant association with grade 2 or 3 fractures in univariate analysis

FVC forced vital capacity, *OR* odds ratio, *CI* confidence interval

* $p < 0.05$ (shown in bold)

Table 5 Correlates of the number of vertebral fractures

	ρ	*p* value
Age	0.194	**0.024***
Height	−0.138	0.109
BMI	0.039	0.649
FVC	−0.184	**0.032***
FEV1.0	−0.258	**0.002***
FEV1.0/FVC	−0.248	**0.004***
FEV1.0 %predicted	−0.145	0.093
Pack-years smoked	−0.038	0.667

Spearman's correlations were performed between FEV1.0 and each variable

BMI body mass index, *FVC* forced vital capacity, *FEV1.0* forced expiratory volume in one second

ρ Spearman rank correlation coefficient

* $p < 0.05$ (shown in bold)

Table 6 Correlates of FEV1.0

	ρ	*p* value
Age	−0.360	**<0.001***
Height	0.312	**<0.001***
BMI	0.235	**0.006***
Pack-years smoked	−0.022	0.801
Number of vertebral fractures	−0.252	**0.003***
Grade of fracture	−0.169	0.050

Spearman's correlations were performed between FEV1.0 and each variable

BMI body mass index, *FVC* forced vital capacity, *FEV1.0* forced expiratory volume in one second, *Grade* SQ grade according to Genant [6]

ρ Spearman rank correlation coefficient

* $p < 0.05$ (shown in bold)

4 subjects being significantly lower than those in GOLD 1. Femoral neck BMD was significantly correlated negatively with age, and positively with height, BMI and pulmonary function parameters (data not shown). In multivariate linear regression analysis, FEV1.0 and BMI were significant predictors of femoral neck BMD after stepwise variable selection excluding height, FEV1.0/FVC, home oxygen therapy, current smoking, inhaled corticosteroid use, current oral and past oral and/or intravenous corticosteroid use (data not shown). However, the significance of the association between femoral neck BMD and FEV1.0 disappeared after adjustment for age ($p = 0.074$). Lumbar BMD gave no significant results, probably reflecting imprecision of the measurement caused by VFs.

Table 7 Multivariate linear regression analysis for predictors of FEV1.0

	β	*p* value
Height	0.391	**<0.0001***
Home oxygen therapy	−0.250	**0.001***
Number of vertebral fractures	−0.225	**0.003***

Adjusted $R^2 = 0.294$

After stepwise variable selection, age, BMI, pack-years smoked, current smoking, inhaled corticosteroid use, current oral or past oral and/or intravenous corticosteroid use, and SQ grade of vertebral fractures were excluded

β standardized β coefficient

* *p* value <0.05 (shown in bold)

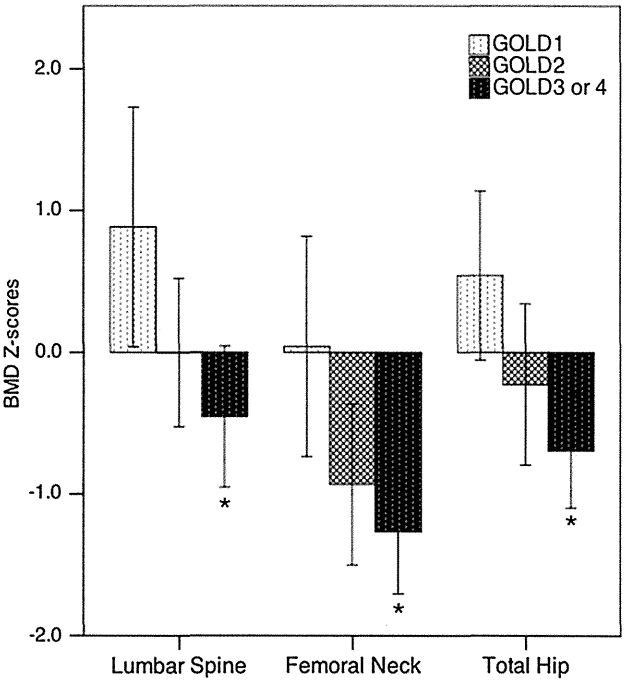

Fig. 1 BMD *Z* scores at lumbar spine, femoral neck and total hip in each GOLD stage. BMD at three sites was measured in 49 subjects, and *Z* scores in each GOLD stage were compared. *Error bars* indicate standard deviations. ANOVA with a post-hoc analysis by Tukey's HSD test was used to determine statistical significance. *$p < 0.05$ compared with GOLD 1

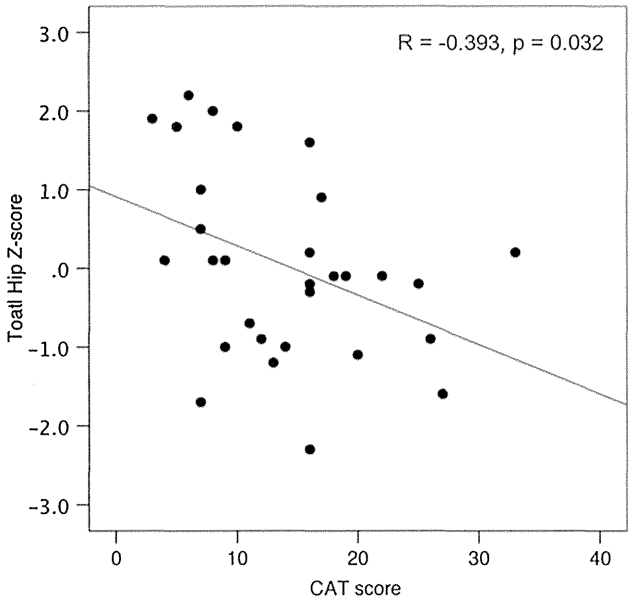

Fig. 2 Negative correlation between total hip BMD *Z* scores and COPD assessment test (CAT) scores. Total hip BMD *Z* scores were two-dimensionally plotted against CAT scores in 30 subjects. Pearson's correlation coefficient (*R*) and *p* value are shown

Interestingly, CAT scores also showed a weak but significant negative correlation with total hip and femoral neck BMD *Z* scores (Fig. 2 and data not shown), illustrating a potential impact of general health status on BMD in COPD patients. No other anthropometric, bone or pulmonary parameter showed a significant correlation with CAT scores.

Discussion

In this cross-sectional study, we demonstrated an extremely high prevalence of VF (79.4 %) in Japanese men with COPD. The prevalence of osteoporosis in subjects whose BMD was available was 38.8 % according to the WHO criteria, and was much higher (83.7 %) according to the Japanese diagnostic criteria for osteoporosis [24]. The substantial difference observed here is due to the fact that the WHO criteria depend solely on BMD and do not take prevalent fractures into account. We found that, besides age, FEV1.0/FVC was the sole predictor of the presence of VF in COPD, and that lower FVC was associated with the presence of grade 2 or 3 VF. Moreover, FEV1.0 was significantly negatively associated with the number of VFs. Conversely, the number of VFs was among the independent predictors of FEV1.0, together with height and use of home oxygen therapy, and BMD was associated with CAT scores reflecting health status impairment in COPD. We believe that our findings indicate a strong inter-relationship between COPD and osteoporosis.

The prevalence of vertebral fracture in COPD

The prevalence of VF (79.4 %) observed in this study is markedly higher than in previous studies (24–63 %) [2, 7, 10–12, 14]. Compared with previous studies, subjects in this study were leaner and slightly older, with the average BMI and age being 21.5 and 71.6 years, respectively. Furthermore, a high proportion of patients were receiving home oxygen therapy, especially in GOLD 3 or 4. These differences could account for the high prevalence of VF in the present study. Ethnic differences may also be involved, although the true incidence of COPD-associated osteoporosis in Japan is currently unknown.

Decreased BMD in COPD

The present study confirmed that COPD is associated with decreased BMD. The *Z* score of BMD at any site showed a progressive decrease as GOLD stage became advanced. FEV1.0 was associated with femoral neck BMD, but BMI and age, well-established risk factors of bone loss, seemed to contribute more strongly to femoral neck BMD. Previous studies reported that BMD in COPD patients was lower than in healthy subjects [13, 25, 26], and that progression of GOLD stage was associated with lower BMD [8, 13]. There are, however, some conflicting reports showing negative results in terms of dependency on GOLD stages [7] and association with pulmonary function parameters [27]. In our study, BMI was significantly lower in advanced GOLD stages, whereas no pulmonary function parameter remained to be an independent predictor of BMD after adjustment for BMI and other confounders. These results suggest that weight loss is a major contributor to BMD decrease in advanced COPD. It is also notable that BMD was not correlated with the number or severity of VFs with or without adjustment for age and BMI (data not shown), implying that not only BMD decline but also deterioration of bone quality may be involved in COPD-associated fractures [17]. The discrepancy between lumbar spine BMD and VF prevalence should, however, be interpreted with caution due to possible over-estimation of lumbar spine BMD. At least 34 fractures of lumbar vertebrae were observed in 49 subjects whose BMD was measured. Indeed, if we took the lowest *T* score among L1–4 instead of the mean, the average lumbar spine BMD *T* score decreased from −1.1 to −2.6, suggesting fracture or deformation-related over-estimation (data not shown). In addition, the sample number may have been insufficient to detect the contribution of BMD to VF. Thus, the issue of bone quality remains an open question.

Association between vertebral fracture and pulmonary function

Vertebral fracture and COPD stage

We found that FEV1.0/FVC and age, but not GOLD stage, were associated with the presence of VF. Some previous studies indicated increased prevalence of VF [11, 17] and vertebral deformities [9] with advanced GOLD stage, while others found no significant correlation between COPD stages or pulmonary function and the presence of VF [7, 14, 28]. The lack of such association in the current study may be due the fact that the subjects were relatively older, showing extremely high fracture prevalence. It seems plausible that VF occurs in early stages of COPD, in part independently of BMD decrease.

Vertebral fracture and FEV1.0/FVC

It is of note that among pulmonary function parameters lower FEV1.0/FVC was the only independent predictor of VF in our study. In both COPD and healthy subjects, an association between FEV1.0/FVC and VF has never been reported. Previous studies focused on GOLD stage defined by FEV1.0 %predicted or absolute value of FEV1.0 and paid little attention to FEV1.0/FVC. Although FEV1.0/FVC is decreased by definition in COPD, progression of COPD is accompanied by decrease in FVC, resulting in a further decline in the absolute amount of FEV1.0 but relatively preserved FEV1.0/FVC. Thus, FEV1.0 %predicted is considered to reflect clinical progression of COPD more precisely than FEV1.0/FVC, and is used for staging. The exact pathological process of the disease progression is, however, incompletely understood. COPD involves both small airway obstruction and parenchymal destruction, and recent reports have suggested that narrowing and loss of terminal bronchioles precedes emphysematous destruction [29]. In addition, a subset of subjects with COPD is known to exhibit concomitant bronchial inflammation of larger airways and fibrotic changes [30–32]. The former would further increase airway resistance while the latter would preferentially cause FVC loss with minimal changes in FEV1.0/FVC. Such variations in spatial and temporal patterns of disease progression will determine the course of changes in respiratory mechanics and may also distinctively affect bone metabolism. The role of FEV1.0/FVC in COPD-associated osteoporosis requires further investigation.

Fracture severity and pulmonary function

In our study, lower FEV1.0 was significantly associated with multiple fractures. Conversely, the number of VFs and home oxygen therapy use were independent predictors of FEV1.0. Moreover, lower FVC was associated with the presence of grade 2 or 3 VF. These findings indicate a close relationship between impaired pulmonary function and progression of osteoporosis. One obvious explanation for this relationship would be the possibility that multiple and/or severe fractures result in thoracic deformity and fragility, ultimately disturbing pulmonary function. However, few reports have demonstrated this seemingly simple concept [33], and in these studies pulmonary diseases were excluded. Low thoracic muscle mass and/or strength could also disturb respiratory function in fragile elderly subjects with severe fractures. Thus, the direct impact of VF on respiratory function still remains an open question. Less clear is the etiological significance of decreased FEV1.0 and FVC in osteoporosis progression. One prospective study [34] reported that patients who developed osteoporosis during the 3-year follow-up showed a significant decrease in FEV1.0 whereas those who did not become osteoporotic showed no significant changes in FEV1.0. Another recent report in Japan has demonstrated that COPD patients with a history of acute exacerbations exhibited more progressive BMD decrease than those without exacerbation [16]. Further studies will be necessary to establish a causal link between COPD and osteoporosis progression.

General health status and osteoporosis in COPD

Staging of the disease does not necessarily reflect general performance and daily activities of COPD patients. In fact, it has been reported that osteoporosis was associated with higher MRC (Medical Research Council) dyspnea scores [35], although there are also conflicting reports demonstrating that MRC dyspnea scores of patients who developed osteoporosis did not change significantly during a 3-year follow-up period [34]. Recently, CAT scores have come to be used globally instead of the MRC dyspnea scale as a tool for assessment of the health status impairment of COPD. We found that CAT scores negatively correlated with total hip BMD Z scores after adjustment for BMI. Severe pulmonary symptoms of COPD would restrict physical activity, which may account for reduced BMD in weight-bearing bones. As far as we know, this is the first report demonstrating an association of CAT scores with bone loss.

Study limitations

The current study has several limitations. First, due to the cross-sectional study design and the small sample size, we were unable to determine the actual fracture incidence. We need large-scale prospective studies to examine the

incidence of vertebral fracture. Second, non-COPD controls were not enrolled. Third, spine X-ray for fracture survey as well as BMD measurement was incomplete. The number of VFs may therefore have been underestimated. Finally, although we defined COPD by the standard spirometric test, it was not based on post-bronchodilator examination, raising a concern that a small minority of subjects diagnosed as having COPD may have had asthma.

Conclusion

In conclusion, our study demonstrated an extremely high prevalence of VF in Japanese males with COPD. Distinct pulmonary function parameters were found to be associated with the presence, severity and number of VFs, and BMD decline, suggesting a complex bidirectional interaction between COPD and osteoporosis. Despite the high prevalence of VF and strong inter-relationship between COPD and osteoporosis, only a few patients were treated for osteoporosis in our study, as well as in previous studies in other countries [5, 7]. Thus, emphasis should be put on the urgent need for an appropriate and timely intervention for COPD-associated osteoporosis, which would protect against fractures and might also improve the prognosis of pulmonary function in patients with COPD. Large-scale longitudinal studies will be necessary to define the exact condition and timing of treatment initiation for osteoporosis in COPD subjects, and such knowledge of COPD-associated osteoporosis should be widely publicized to raise the awareness of physicians treating COPD.

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Conflict of interest All authors have no conflicts of interest.

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Mini Review

Type B Insulin Resistance Syndrome as an H. *Pylori*-Associated Autoimmune Disease

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Abstract

Type B insulin resistance syndrome (IRS) is characterised by production of autoantibodies against the insulin receptor (IR). These autoantibodies block insulin binding to the IR, resulting in severe insulin resistance. Some patients with this syndrome paradoxically exhibit episodic hypoglycaemia. Relatively burdensome therapies, including immunosuppression and plasmapheresis, are reportedly effective in some patients, but there are as yet no established therapeutic strategies for type B IRS. We experienced two cases with type B IRS who also had immune thrombocytopenic purpura (ITP). In one case, eradication of Helicobacter pylori (HP), aimed at treating ITP, cured type B IRS. In the other case, anti-IR and anti-platelet antibodies were detected only during pregnancy, and after delivery, these autoantibodies and hypoglycemic symptoms disappeared. These two cases suggest that elimination of immune-disturbing triggers can lead to a complete cure of type B IRS. In this review, we discuss the pathogenesis of type B IRS focusing particularly on the possible involvement of HP infection and the therapeutic potential of HP eradication for the treatment of this refractory syndrome. We recommend that physicians examine type B IRS patients for HP infection and eradicate this microorganism if present, since HP eradication can easily be performed with few adverse effects.

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ABBREVIATIONS

IRS: Insulin Resistance Syndrome; **HP**: Helicobacter Pylori; **ITP**: Immune Thrombocytopenic Purpura

INTRODUCTION

Type B insulin resistance syndrome (IRS), a rare cause of severe insulin resistance, is characterised by production of autoantibodies against the insulin receptor (IR) [1], and is classified into an autoimmune disease. This syndrome is frequently associated with other autoimmune diseases [2]. Although type B IRS induces severe hyperglycaemia, some patients with this syndrome exhibit episodic hypoglycaemia, considerably impairing quality of life. There are as yet no established therapeutic strategies for this syndrome.

We recently experienced a case of type B IRS who also had immune thrombocytopenic purpura (ITP). These two disorders had developed simultaneously. Surprisingly, in this case, eradication of Helicobacter pylori (HP) cured not only ITP but also type B IRS [3], suggesting involvement of HP in the pathogenesis of type B IRS. Consistent with this, HP reportedly affects host immunity [4] and is related to the development of several autoimmune diseases. We recently reported another case of type B IRS with ITP. In this case, anti-IR and anti-platelet antibodies were detected only during pregnancy, followed by the disappearance of these autoantibodies and symptoms after delivery [5]. These two cases suggest that elimination of the triggers which may disturb immune system can stop the production of autoantibodies, thereby leading to complete recovery from type B IRS.

Herein, we discuss the pathogenesis of type B IRS focusing particularly on possible involvement of HP infection, and also the therapeutic potential of HP eradication for type B IRS. The aim of this review is to provide insights for developing a novel therapeutic approach for type B IRS, a refractory syndrome with severe insulin resistance.

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SIDE HEADINGS/SUBHEADINGS

Type B insulin resistance syndrome

Type B IRS was first reported in 1976, as an autoimmune disorder characterised by severe insulin resistance and marked hyperinsulinaemia caused by acquired production of antibodies against the IR [1]. On the other hand, type A IRS, which features severe insulin resistance from birth, is caused by mutations in the IR gene. Type B IRS is a rare cause of severe insulin resistance and, to date, there are about 100 case reports. IR antibodies mediate the development of insulin resistance by several proposed mechanisms; 1) Inhibition of insulin-binding to the IR by antibodies [1], 2) IR number reduction via internalization of the receptor elicited by binding of antibodies [6], 3) Inhibition of intracellular IR signaling by antibody-mediated sustained association of the IR with insulin receptor substrates [7]. Although type B IRS usually induces hyperglycaemia via the mechanisms described above, some patients with this syndrome experience hypoglycemic attacks [8]. Although the precise mechanisms underlying occasional hypoglycemia remain uncertain, one possible explanation is the presence of both inhibitory and stimulatory types of IR-antibodies [9]. Autoantibodies associated with type B IRS are generally polyclonal [1,10], and IR-antibodies with various characteristic may exist simultaneously, leading to the appearance of various symptoms. Alternatively, dissociation of inhibitory IR-antibodies from the IR by unknown mechanisms might suddenly induce potent insulin signaling due to hyperinsulinaemia.

Type B IRS and HP infection

Type B IRS is frequently associated with other autoimmune diseases. One third of type B IRS patients meet the diagnostic criteria for systemic lupus erythematosus (SLE) or Sjögren syndrome. In addition, cases with other concomitant autoimmune diseases, including ITP, have also been reported [3,11-22] (Table 1). We recently experienced a case with both type B IRS and ITP [3]. The patient had initially presented with hypoglycemic symptoms, and hyperglycemia later became evident. Interestingly, even during the hyperglycemic period, sudden hypoglycemic attacks occurred irregularly. Platelet numbers were markedly decreased. It was recognized in retrospective that the onsets of hyperglycemia and thrombocytopenia were almost simultaneous. This patient had both anti-IR and anti-platelet antibodies at very high titers and was shown to be chronically infected with Helicobacter pylori (HP). In this case, aimed at treating ITP, HP eradication therapy, with amoxicillin, lansoprazole and clarithoromycin, was administered, because HP eradication is already a well-established ITP therapy [23]. HP was fully eradicated by this therapy, resulting in reduced anti-platelet antibodies and increased platelet number to the normal level. Surprisingly, HP eradication ameliorated not only ITP but also type B IRS. Anti-IR antibodies became undetectable, resulting in lowering of the HbA1c level to normal without diabetes treatment. Furthermore, the hypoglycemic attacks completely disappeared [3]. At present, five years after HP eradication, no recurrence has been observed, indicating complete cure of type B IRS by HP eradication.

Table 1: Reported series of type B IRS-associated autoimmune diseases.

Associated autoimmune disease	Author	Year	References
Rheumatoid Arthritis	Kramer et al.	1998	11
Hashimoto Disease	Hirano et al.	1997	12
	Fereau et al.	2007	13
Systemic Sclerosis	Weinstein et al.	1980	
	Jannette et al.	1982	16
	Bloise et al.	1989	
Mixed Connective Tissue Disease	kramer et al.	1998	11
	Semple et al.	2007	17
	Malek et al.	2010	18
Graves Disease	Tran et al.	2009	19
Primary Biliary Cirrhosis	Selinger et al.	1987	20
	Arioglu et al.	2002	21
Immune Thrombocytopenic Purpura	Selinger et al.	1987	20
	Imai et al.	2009	3
Autom immune Hepatitis	Fereau et al.	2007	13
Immune Complex Glomerulonephritis	Sims et al.	1987	22

The first report showing the effectiveness of HP eradication against ITP was published in 1998 by an Italian group [24]. Thereafter, similar results were reported by several groups mostly from Japan and Italy, establishing HP eradication as a novel therapeutic approach for ITP. A recently published meta-analysis revealed HP eradication to be effective in more than 50% of HP-positive ITP patients [23]. Since HP eradication is a less-invasive approach than immune-suppression and splenectomy, commonly employed ITP therapies, HP eradication has now become a first-line therapy for HP-positive ITP patients.

In the case with type B IRS associated with ITP, HP eradication simultaneously cured both ITP and type B IRS [3]. Since spontaneous remission of type B IRS was reported [8], the possibility that type B IRS was remitted independently of HP eradication cannot be excluded. However, in addition to the simultaneous developments of type B IRS and ITP, these two disease states improved at exactly the same time after HP eradication. This clinical course strongly suggests HP involvement in the development of type B IRS and that HP eradication was responsible for its elimination.

The case of type B IRS associated with both ITP and primary biliary cirrhosis was previously reported [20]. In this case, main feature of type B IRS was hypoglycaemia.Treatment with prednisolone improved autoimmune features such as thrombocytopenia, liver dysfunction and hypoglycemia. Since that case was reported prior to demonstration of the effectiveness of HP eradication for ITP, HP infection was not examined and eradication therapy was not performed.

HP infection and autoimmune diseases

How is HP infection involved in the development of type B IRS? As mentioned above, HP infection is known to be involved in the pathogenesis of ITP. Additionally, a relationship between HP infection and MALT (mucosa-associated lymphoid tissue) lymphoma is widely accepted [25]. HP reportedly affects the functions of several host immune cells such as macrophages, mast cells, antigen presenting cells and T-cells [4]. These findings allow us to hypothesise that HP infection modulates the host immunity system by multiple mechanisms.

In this regard, a number of previous reports have shown that HP eradication ameliorated other autoimmune diseases besides

ITP [26-32] (Table 2). For instance, HP eradication reduced both blood inflammatory markers and improved symptoms in patients with rheumatoid arthritis [26]. In addition, when HP eradication therapy was administered to a patient with antiphospholipid antibodies syndrome, the autoantibodies diminished, thereby ameliorating symptoms in this patient [27]. Taken together with the case of type B IRS cured by HP eradication [3], these observations suggest the immune system to be disturbed by HP, which is likely to be involved in the common pathogenesis of these autoimmune diseases. HP eradication is speculated to effectively promote recovery from HP-associated autoimmune diseases.

Many elderly Japanese people contracted HP infection early in life, because, in the 1950s, the hygienic environment of Japan was not adequate [33]. In fact, the HP prevalence rate is much higher in elderly than in young people in Japan [34]. Therefore, it is very unlikely that a new HP infection occurred in the old (84 y.o.) patient we experienced [3] at the onset of type B IRS and ITP. Chronic infection with HP would presumably have been present for many years before the development of type B IRS and ITP. Therefore, another trigger, i.e. a so-called second hit, must be necessary for simultaneous development of these two autoimmune diseases. This speculation may be also applicable to the induction mechanism of other HP-associated autoimmune diseases.

What then is the second hit triggering the development of autoimmune diseases induced by HP? As for ITP, there are several hypotheses regarding disease induction by HP [35]. First, antibodies against HP components, such as CagA, cross-react with platelet antigens [36]. Second, Lewis (Le) antigens, which are expressed by HP, are absorbed to platelets and serve as targets for anti-Le antibodies [37]. Third, HP antibodies activate platelets by binding to them via the FcγRIIA or through an interaction between the HP-bound von Will brand factor to platelet glycoprotein 1B, and this activation promotes platelet clearance [38]. Finally, HP infection alters the expression pattern of monocyte Fcγ receptors, thereby enhancing the phagocyte capacity of monocytes [39]. However, these platelet-specific hypotheses cannot explain why autoimmune diseases develop acutely in chronically HP infected individuals or why HP infection induces several other autoimmune diseases besides ITP.

HP interacts with the host gastric epithelial cells via several adhesion molecules and does not typically invade the gastric mucosa. Thus, gastric epithelium disruption might allow HP to invade gastric tissues, leading to HP antigen-presentation [40]. In addition, monoclonal anti-HP antibodies reportedly cross-react with several human tissues, such as the duodenal epithelium, salivary glands and renal tubular cells [41]. Therefore, a trigger, such as gastric epithelium inflammation, which disrupts the gastric epithelium, might be the second hit which promotes the development of autoimmune diseases (Figure 1). However, considering that HP infection is associated with a number of autoimmune diseases, including type B IRS, and that these diseases often co-exist, molecular mimicry of HP antigens to those of human tissues is unlikely to be the main mechanism.

What then is the mechanism whereby multiple autoimmune diseases, e.g. ITP and type B IRS [3], develop simultaneously and can be cured together by HP eradication? One possible answer to this question is that, urease, produced by HP, activates B-1 cells, a subpopulation of B lymphocytes, leading to the production of autoreactive antibodies [42]. In addition, HP infection is reportedly associated with helper T-cell polarization [43]. This helper T-cell polarization may disrupt the host's immune tolerance, leading to simultaneous development of multiple autoantibody-induced diseases. These mechanisms may contribute in complex ways to acute and simultaneous development of diseases induced by multiple autoantibodies (Figure 1), although further investigations are required to elucidate the precise mechanism.

Type B IRS and pregnancy

We recently reported another case of type B IRS with ITP. The patient was a 32-year-old woman with an unremarkable past medical history. Severe hypoglycemic attacks accompanied by sudden loss of consciousness had started to occur during gestational week 9. After hospitalization, intrauterine fetal death became apparent and hypoglycemic attacks remitted. Two years later, hypoglycemia recurred during gestational week 8 of her

Table 2: Reported series showing improvement of autoimmune diseases with HP eradication.

Autoimmune disease	Therapeutic outcomes of HP Eradication	Author	Year	References
Rheumatoid Arthritis	•Improvement of clinical presentation such as arthralgia, swollen joint and morning stiffness •Lowering of laboratory pararmeters including ESR and CRP	Zentilin et al.	2002	26
Antiphospholipid Antibodies Syndrome	•Improvement of symptoms such as Raynaud's phenomenon, migraines •Disappearance of antiphospholipid antibodies	Cicconi et al.	2001	27
Autoimmune thyroid diseases	•Significant reduction of thyroid autoantibodies	Bertalot et al.	2004	28
Behçet Disease	•Improvement of clinical presentation such as oral and genital ulcer and arthralgia	Apan et al.	2007	29
Schönlein-Henoch Purpura	•Disappearance of cutaneous lesions •Improvement of proteinuria	Machet et al.	1997	30
Idiopathic Chronic Urticaria	•Disappearance of cutaneous symptoms	Di Campli et al. Wustlich et al	1998 1999	31 32

second pregnancy. Thrombocytopenia also appeared during this pregnancy. Clinical examination on admission revealed anti-IR antibodies and anti-platelet antibodies in this patient. *In vitro* study revealed that her anti-IR antibodies stimulated tyrosine phosphorylation of the IR, presumably resulting in hypoglycemia. Fortunately, a healthy baby was delivered by Caesarian section at gestational week 39, despite frequent hypoglycemic attacks and thrombocytopenia. It was noteworthy that, after delivery, anti-IR and anti-platelet antibodies disappeared along with complete resolution of both hypoglycemia and thrombocytopenia. In this case, hypoglycemia occurred only during two her pregnancies and the anti-IR antibodies disappeared after delivery, suggesting a significant causal relationship between pregnancy and the development of type B IRS [5]. Taken together with the aforementioned HP-eradication case, the course of these patients suggests a common mechanism to underlie the production of anti-IR and anti-platelet antibodies. Pregnancy is often accompanied by alterations of systemic immune function such as helper T-cell polarization [44]. Therefore, certain immune system-altering conditions, such as HP infection and pregnancy, can trigger the development of type B IRS. More importantly, these cases strongly suggest that type B IRS, a refractory syndrome, can be cured by elimination of immune-disturbing triggers.

HP eradication for type B IRS

There is no established therapy for type B IRS. Since type B IRS is regarded as an autoimmune disease, immunosuppressive drugs such as prednisolone [9,16,20,22,45,46], cyclophosphamide [16,18,22,46-48], cyclosporine [11,48] and azathioprine [21] have been used for treatment. In some cases, these immunosuppressive drug combinations were reported to be effective (Table 3). Additionally, type B IRS was successfully treated with immunoglobulin [19], plasmapheresis [45, 48, 49], IGF-1[50] or rituximab, an antibody against B-cell surface antigen CD-20 [18] (Table 3). However, cases not responding to these therapies have also been reported [21, 50]. Due to the rarity of type B IRS cases,

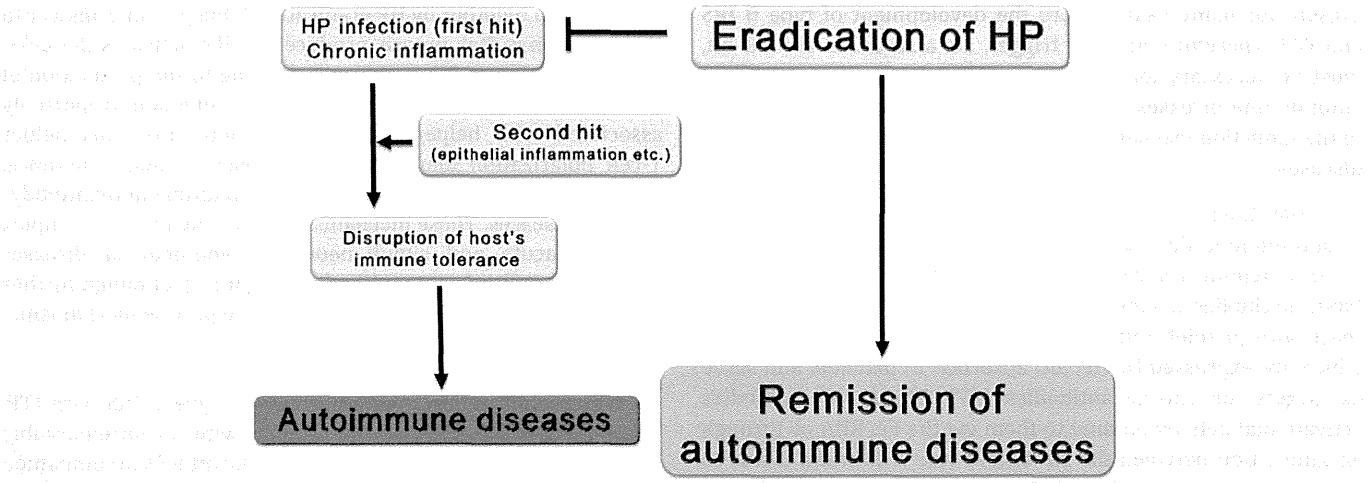

Figure 1 Hypothetical mechanism of autoimmune disease remission with HP eradication.

Table 3: Reported therapeutic approaches for type B IRS.

Therapeutic approach	Therapeutic outcome	Author	Year	References
Predonisolone	Remission	Taylor et al. Selinger et al.	1982 1987	9 20
Cyclophosphamide Predonisolone	Remission	Kawanishi et al. Simset al. Bloise et al.	1977 1987 1989	46 22 16
Cyclophosphamide and Mycophenolate mofetil	Remission	Gel et al.	2003	47
Plasmapheresis	Remission	Muggeo et al.	1979	49
Plasmapheresis and Predonisolone	Remission	Page et al.	2007	45
Plasmapheresis, Cyclophosphamide and Cyclosporin	Remission	Eriksson et al.	1998	48
Cyclosporin	Remission	Krerner et al	1998	11
IGF-1	(Plasmapheresis, cyclophosphamide and cyclosporin Yamamoto et al. combined therapy was not effective)	Yamamota et al.	2000	50
Azathioprine	Remission	Arioglu et al.	2002	21
Rituximab, Cyclophosphamide and Pulse steroids	Remission (All seven treated patients achieved remission)	Malek et al.	2010	18
Immunoglobulin	Remission	Tran et al.	2009	19
Eradication of Helicobacter Pylori	Remission	Imai et al.	2009	3

it is difficult to conduct cohort studies to examine the effectiveness of these therapies.

The case with type B IRS cured by HP eradication [3] suggests this to be a promising therapeutic strategy for type B IRS. As mentioned above, an established therapy for type B IRS is lacking. HP eradication is a relatively benign therapy with fewer adverse effects compared with previously reported therapeutic approaches such as immunosuppressive therapies. In addition, HP eradication can easily be performed with no need for specialised equipment, and unlike immunosuppressive therapy, the required treatment period is very short, only one week. In fact, administrations of immune suppressors for several months to years were required to maintain remission in previously reported cases [9,45,48]. In addition, the remission durations of 7 type B IRS patients receiving intensive combination immune suppressive therapy ranged from 2 to 16 months [18], while the case with type B IRS associated with ITP [3] has maintained remission status for more than five years since HP eradication. Therefore, if the effectiveness of HP eradication for type B IRS is confirmed, this therapeutic strategy may be of major benefit to patients with this syndrome. We recommend that physicians worldwide screen type B IRS patients for HP infection and attempt eradication therapy in those who are HP-positive.

DISCUSSION AND CONCLUSION

In this review, we have shown the therapeutic potential of HP eradication for type B IRS. However, at present, HP infection rates in type B IRS patients are unclear and whether chronic HP infection is a common feature of type B IRS remains an open question. Therefore, future studies are necessary to examine HP infection rates in type B IRS patients. In addition, the effectiveness of HP eradication in HP-positive type B IRS patients should be examined in cohort studies. However, the rarity of type B IRS makes it difficult to perform clinical surveillance. Therefore, we hope that this review will inspire physicians worldwide to examine HP infection in type B IRS patients and attempt eradication therapy in HP-positive type B IRS patients. Accumulation of these data would clarify the significance of HP infection in the pathogenesis of type B IRS and allow HP eradication to be established as a curative therapy for this disease.

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