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Endocardial Bipolar Voltage Predicts the Need for Additional Ablation Inside the Left Atrial Posterior Wall

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Abstract

Background

Several reports have shown that prognosis of patients with non-paroxysmal atrial fibrillation, who were treated with pulmonary vein isolation with left atrial posterior wall isolation may be superior to those who were treated with pulmonary vein isolation alone. In patients undergoing posterior wall isolation, additional ablation inside the posterior wall is a predictor of posterior wall isolation reconduction in the long term. This study aimed to identify predictors of the need for additional ablation inside the posterior wall.

Methods

In total, 77 patients with non-paroxysmal atrial fibrillation who underwent first-time pulmonary vein isolation with left atrial posterior wall isolation were retrospectively examined. All patients underwent placement of a linear lesion in the left atrial roof and floor. Patients were grouped according to need for additional ablation inside the posterior wall.

Results

First-pass posterior wall isolation was achieved in 32 patients (42%). Three required additional gap ablation and 42 required ablation inside the posterior wall. Complete posterior wall isolation was eventually achieved in all. In the multivariate analysis, maximum voltage (3.68 ± 1.94 mV vs 2.38 ± 1.49 mV; $p=0.02$) and mean voltage (1.94 ± 1.03 vs 1.28 ± 0.91 mV; $p=0.03$) at the roof line were significantly higher in patients with an additional ablation.

Conclusions

High endocardial bipolar voltage at the left atrial roof line was an independent predictor of additional ablation inside the posterior wall. Therefore, we think that when obtaining left atrial posterior wall first-pass isolation, it is necessary to note whether there is a high-voltage region in the

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left atrial roof.

Key Words: Atrial fibrillation; Catheter ablation; Left atrial posterior wall isolation; Left atrial roof line; Left atrial floor line

Introduction

Pulmonary vein isolation (PVI) via catheter ablation is a standard treatment for atrial fibrillation (AF). However, PVI alone is insufficient for many patients with non-paroxysmal AF and an additional procedure may be required. Additional procedures that may improve catheter ablation effectiveness include linear ablation of the left atrial (LA) roof and mitral isthmus[1)], complex fractionated atrial electrogram ablation[2)], low-voltage area ablation[3)], and LA posterior wall isolation (PWI)[4)].

The LA posterior wall is important in initiation and maintenance of AF[5-9)]. PVI with LA PWI may be superior to PVI alone in the treatment of non-paroxysmal AF[10)]. However, achieving PWI via roof and floor linear ablation combined with gap ablation is difficult. Further ablation inside the posterior wall is frequently necessary.

Successful first-pass isolation is associated with treatment durability and lower risk of recurrence[11,12)]. Performing additional ablation inside the posterior wall is a predictor of PWI reconduction in the long term[13)]. Therefore, first-pass blockage across the roof and floor lines and avoiding additional ablation inside the posterior wall are considered important when performing PWI.

Indicators of acute reconduction after PVI include ablation index (AI), which incorporates catheter tip contact force (CF), power, and radiofrequency (RF) time into its calculation; force-time integral (FTI); and LA voltage[14,15)]. This study aimed to identify predictors of the need for additional ablation inside the posterior wall in patients undergoing PWI.

Methods

Study patients

We conducted a retrospective cohort study at Osaka Metropolitan University Hospital that examined patients with non-paroxysmal AF who underwent catheter ablation for the first time between June 2018 and July 2020. Patients who had undergone a previous LA catheter ablation procedure were excluded. Non-paroxysmal AF was defined as continuous AF with episode duration $>$7 days[16)].

Catheter ablation procedure

All patients underwent AI-guided catheter ablation using a three-dimensional navigation system (CARTO 3; Biosense Webster, Irvine, CA, USA). An LA voltage map was created during high right atrial pacing in sinus rhythm. If the patient was in AF, sinus rhythm was restored before mapping via low-energy (10 to 30 J) internal cardioversion achieved with a BeeAT catheter (Japan Lifeline, Tokyo, Japan) placed in the coronary sinus. Bipolar signals, high-pass filtered at 30 Hz and low-pass filtered at 500 Hz, were acquired using a multipolar multispline catheter with 2-mm interelectrode spacing (PENTARAY NAV; Biosense Webster). Ablation was performed using a 3.5-mm tip-irrigated catheter with CF sensor (Navistar Thermocool SmartTouch™ Surround Flow, Biosense Webster). After confirming completion of bilateral PVI, linear lesions were created at the roof and the floor. All lesions were created at a target AI ≧550 for the roof line, ≧450 for the floor line, and ≧400 for the esophageal segments. Inter-lesion distance target was 2 to 4 mm. Each lesion was created using 35

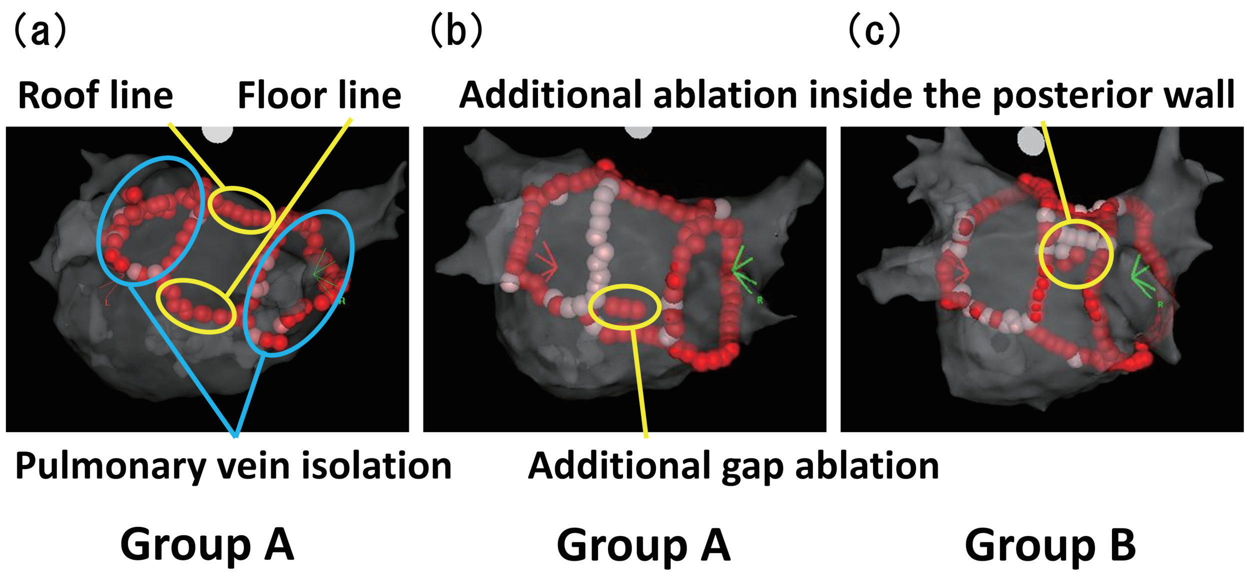

Figure 1. Posterior wall isolation techniques. Group A comprised patients in whom isolation was successfully achieved by (a) a single ablation line on the roof and floor alone or with (b) additional gap ablation. (c) In group B patients, isolation required additional ablation inside the posterior wall.

W at the roof and 30 W at the floor. Parameter settings in the VisiTag module of the CARTO 3 system were catheter stability (3 mm for 3 s) and minimum CF (50% of time >5g). An esophageal temperature monitoring catheter (SensiTherm; St. Jude Medical Inc., Saint Paul, MN, USA) was used. RF energy delivery was immediately stopped if the temperature exceeded 41°C. Completion of PWI was confirmed by the disappearance of atrial sharp potentials within the isolated posterior area and the lack of LA excitation with high output stimulation in the posterior wall. If isolation was not achieved after performing single linear lesions at the roof and floor, additional ablation was performed along the lesions based on further mapping. If isolation was still not achieved, additional ablation inside the posterior wall was performed with reference to the earliest activation until isolation was achieved. The procedure was evaluated using the bipolar voltage at a point closest to the ablation point. If necessary, cavotricuspid isthmus ablation, superior vena cava isolation, and premature atrial contraction/non-pulmonary vein triggers were performed at the operator's discretion.

Data and outcomes

Study patients were divided into two groups according to how the posterior wall was isolated (Fig. 1). In group A, isolation was achieved by a single ablation line or a single line with additional gap ablation; in group B, isolation required additional ablation inside the posterior wall. Clinical, laboratory, and echocardiographic data and patient comorbidities and medications were collected from the medical records. Characteristics of catheter ablation procedures were exported and analyzed offline. For each roof or floor line, number of RF lesions, line length, and RF time were measured. For each RF tag, mean values were calculated for FTI and AI. Mean and minimum values were calculated for RF power, impedance drop, CF, and voltage.

Statistical analysis

Continuous variables are expressed as means with standard deviation and were compared using the Mann-Whitney U test. Categorical variables are expressed as numbers with percentage and were compared using Fisher's exact test. Multivariable predictors of LA posterior wall ablation were examined using logistic regression analysis with adjustment for patient's age. All p-values were two tailed, with $p < 0.05$ indicating statistical significance. All statistical analyses were performed using JMP software version 10.0.0 (SAS Institute, Cary, NC, USA) and R statistical software version 4.0.2 (R Foundation for Statistical Computing).

Ethical statement

Institutional ethics committee approval was obtained. All patients provided informed consent. This study was approved by the Ethical Committee of Osaka City University Graduate School of Medicine (approval number: 4264).

Results

Patient and procedural characteristics

During the study period, 117 patients with non-paroxysmal AF underwent initial RF catheter ablation. PWI was not performed in 18 because of advanced patient age or prolonged procedural time. Ninety-nine patients underwent PVI with additional PWI. Among these, superior vena cava isolation was performed in two patients, premature atrial contraction/non-pulmonary vein trigger ablation in seven, and linear ablation of the anterior left atrium in one. Twenty patients in whom pulmonary vein-left atrium voltage maps were not obtained because of immediate recurrence of AF after cardioversion were excluded. Two patients in whom PWI was discontinued at the operator's discretion were also excluded. Therefore, 77 patients were included for analysis (Fig. 2).

Ablation outcomes

We took on average 2359±734 points for the voltage map of the entire LA, and used the bipolar voltage at the point nearest to the ablation point for our data. PVI was successful in all patients. For PWI, first-pass block across roof and floor lines was observed in 32 patients (42%); two required additional ablation at the roof line and one at the roof and floor line. Therefore, 35 patients

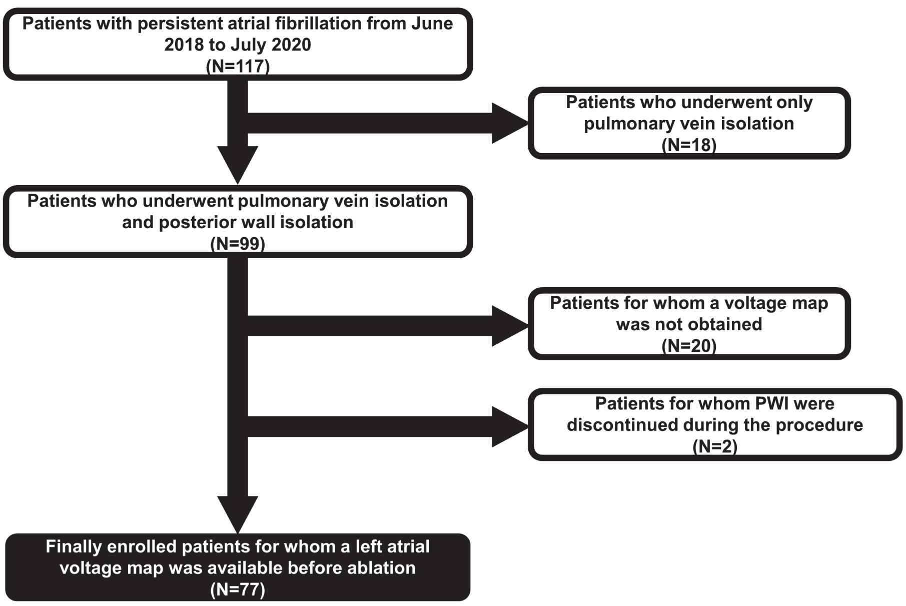

Figure 2. Study flow chart.

Table 1. Patient characteristics

	Total number (n=77)	Group A (n=35)	Group B (n=42)	p-value
Age, years	65.3±10.7	68.2±8.3	62.9±11.8	0.04*
Male, n (%)	57 (74.0)	24 (68.6)	33 (78.6)	0.32
BMI	24.2±3.8	24.0±4.0	24.5±3.7	0.42
Duration of AF (months)	17.9±22.7	18.9±18.9	16.9±25.9	0.59
CHA_2DS_2VASc-score	2.6±1.5	2.7±1.5	2.5±1.6	0.69
Comorbid disease				
Congestive Heart failure, n (%)	27 (35.1)	11 (31.4)	16 (38.1)	0.54
Hypertension, n (%)	54 (70.1)	24 (68.6)	30 (71.4)	0.76
Diabetes mellitus, n (%)	9 (11.7)	5 (14.3)	4 (9.5)	0.52
History of stroke or TIA, n (%)	11 (14.3)	3 (8.6)	8 (19.1)	0.19
Vascular disease, n (%)	10 (13.0)	4 (11.4)	6 (14.3)	0.71
Echocardiographic parameters				
Left atrial diameter (mm)	44.4±6.0	44.6±6.3	44.1±5.8	0.81
Left atrial volume index (mL/m^2)	40.1±13.0	40.6±16.3	39.7±9.5	0.84
Left ventricular EF (%)	50.9±11.4	51.1±10.8	50.8±12.1	1.0
Moderate or severe MR, n (%)	56 (72.7)	25 (71.4)	31 (73.8)	0.82
Moderate or severe TR, n (%)	48 (62.3)	24 (68.6)	24 (57.1)	0.30
Laboratory data				
eGFR (mL/min/1.73 m^2)	70.6±75.9	59.8±16.3	79.6±101.4	0.25
BNP (pg/mL)	140.3±160.8	180.5±220.6	106.8±71.0	0.11
Antiarrhythmic agents, n (%)	10 (13.0)	4 (11.4)	6 (14.3)	0.71

Data are presented as mean±standard deviation or n (%).

BMI, body mass index; AF, atrial fibrillation; TIA, transient ischemic attack; EF, ejection fraction; MR, mitral regurgitation; TR, tricuspid regurgitation; eGFR, estimated glomerular filtration rate; and BNP, brain natriuretic peptide.

comprised group A. Group B, who required additional ablation inside the LA posterior wall, comprised 42 patients. Complete PWI was achieved in all.

Follow-up

During the average follow-up period of 823±300 days, 24 patients (31%) experienced atrial arrhythmia recurrence (10 patients with atrial tachycardia and 14 patient s with AF). There was no significant difference in the recurrence rate between group A and B [12 patients (34.3%) vs 12 patients (28.6%) p=0.59].

Group comparisons

Patient characteristics are summarized in Table 1. Overall, mean age was 65±11 years and 74% of patients were men. Mean CHA_2DS_2 -VASc score was 2.6±1.5. Mean LA dimension and left ventricular ejection fraction were 44.4±6 mm and 50.9%±11.4%, respectively.

Mean age was significantly younger in group B (62.9±11.8 years vs 68.2±11.8 years; p=0.04). Sex, body mass index, CHA_2DS_2-VASc score, brain natriuretic peptide concentration, and echocardiographic measurement parameters did not significantly differ between the groups.

Ablation parameters according to group are shown in Table 2. Maximum voltage (3.68±1.94 mV vs 2.38±1.49 mV; $p<0.01$; Fig. 3) and mean voltage (1.94±1.03 vs 1.28±0.91 mV; $p<0.01$; Fig. 3) at the roof line were significantly higher in group B. At the floor line, although maximum voltage was significantly higher in group B (4.47±2.81 mV vs 3.21±1.89 mV; p=0.02), mean voltage did not

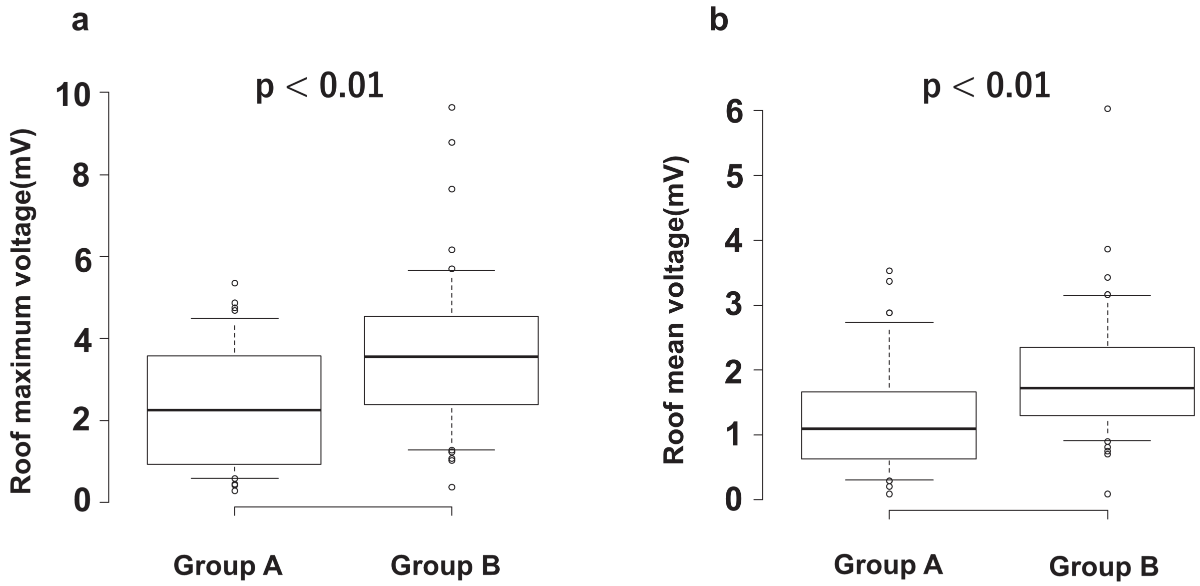

Figure 3. (a) Left atrial roof maximum voltage in groups A and B. (b) Left atrial roof mean voltage in groups A and B.

significantly differ between group B (2.25±1.43 mV) and group A (1.62±0.92 mV). Other indicators, such as power, impedance drop, AI, FTI, CF, length line, and maximum inter-lesion distance, did not significantly differ between groups.

Predictors of additional ablation inside the LA posterior wall

In the multivariate analysis with age adjustment, mean and maximum voltage at the roof line were independent predictors of additional ablation inside the posterior wall (Odds Ratio [95% confidence interval] = 1.97 [1.07-3.61] and 1.52 [1.08-2.13]) (Table 2). Receiver operating characteristic curve analysis showed cutoff values for mean voltage at the roof line 1.29 mV (area under the curve, 0.71; sensitivity, 79%; specificity, 60%) and maximum voltage at the roof line of 3.08 mV (area under the curve, 0.70; sensitivity, 67%; specificity, 69%).

Discussion

The major findings of this study are as follows: (1) Complete first-pass PWI was achieved via blockage across roof and floor lines in 32 patients (42%) and three (4%) required additional gap ablation near the initial roof or floor line. (2) Additional ablation inside the posterior wall was needed to achieve PWI in 42 patients (55%). (3) Additional ablation inside the LA posterior wall achieved complete PWI in all patients. (4) In multivariate analysis, mean and maximum voltage at the roof line were independent predictors of additional ablation inside the posterior wall. To our knowledge, this is the first study to show that endocardial bipolar voltage is a useful predictor of additional ablation inside the posterior wall during PWI.

The effect of adding PWI to PVI when treating non-paroxysmal AF is controversial. The multicenter international randomized Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part Ⅱ (STAR AF Ⅱ) demonstrated that adding complex fractionated atrial electrocardiogram ablation or linear ablation to PVI did not improve outcomes compared to PVI alone in patients with non-paroxysmal AF[17]. However, the linear ablation arm of this trial did not incorporate LA PWI. Pathologic remodeling in the LA posterior wall appears to be involved in AF

Table 2. Comparisons of ablation parameters between the two study groups

Procedural characteristics	Group A (n=35)	Group B (n=42)	p-value	Age adjusted p-value
Roof line				
Number of RF lesions	8.0±2.9	8.0±2.3	0.76	0.63
Min. power (W)	31.4±3.9	31.4±3.7	0.92	0.58
Mean power (W)	32.6±3.4	32.4±3.5	0.82	0.61
Min. impedance drop (Ω)	4.3±2.5	4.0±2.4	0.82	0.51
Mean impedance drop (Ω)	8.8±2.4	8.0±2.3	0.13	0.12
Min. contact force (g)	9.3±5.3	9.1±3.7	0.92	0.74
Mean contact force (g)	22.8±6.0	21.9±4.0	0.54	0.33
Mean force-time integral	500.3±97.7	504.5±98.6	0.84	0.51
Mean ablation index	501.4±57.3	501.4±59.0	0.93	0.42
Mean voltage (mV)	1.28±0.91	1.94±1.03	0.002*	0.03*
Max. voltage (mV)	2.38±1.49	3.68±1.94	0.003*	0.02*
Line length (mm)	21.2±8.8	21.0±5.8	0.65	0.78
Max. interlesion distance (mm)	5.1±1.1	5.3±1.0	0.25	0.35
Total RF time (s)	251.8±143.5	268.8±146.0	0.71	0.60
Floor line				
Number of RF lesions	7.9±2.2	9.0±3.4	0.16	0.08
Min. power (W)	28.1±2.5	28.8±2.4	0.25	0.07
Mean power (W)	30.4±2.4	30.6±2.9	0.59	0.53
Min. impedance drop (Ω)	4.0±2.2	4.3±2.6	0.72	0.60
Mean impedance drop (Ω)	8.8±2.1	9.0±2.1	0.72	0.84
Min. contact force (g)	7.1±4.3	7.3±4.2	0.87	0.54
Mean contact force (g)	20.7±4.4	20.6±3.9	0.87	0.91
Mean force-time integral	338.3±62.4	345.3±47.7	0.38	0.40
Mean ablation index	421.4±19.0	426.5±21.1	0.26	0.05
Mean voltage (mV)	1.62±0.92	2.25±1.43	0.09	0.19
Max. voltage (mV)	3.21±1.89	4.47±2.81	0.02*	0.16
Line length (mm)	23.6±6.6	26.9±9.2	0.17	0.10
Max. interlesion distance (mm)	5.5±0.8	5.4±1.0	0.42	0.48
Total RF time (s)	283.5±174.3	289.6±150.5	0.62	0.67

Data are presented as mean±standard deviation unless otherwise indicated.
RF, radiofrequency; Min, minimum; and Max, maximum.

pathogenesis and more aggressive treatment of this region correlates with improved ablation outcomes[18]. Thiyagarajah et al reported that PWI can be achieved in most patients undergoing AF ablation; the risk of complications is low and the 12-month rate of freedom from atrial arrhythmia is acceptable[19]. Another study reported that PWI in addition to PVI plus linear lesions was efficient and caused no deterioration in LA pump function in patients with non-paroxysmal AF[10].

However, PWI durability is not high[20]. Tamura et al reported that ablation inside the posterior wall is a predictor of PWI reconduction and aiming to complete line ablation without ablating the inside of the posterior wall may lead to improved durability[13]. Therefore, our study aimed to identify predictors of additional ablation inside the posterior wall.

Among the various parameters examined, maximum and mean LA roof voltage were the independent predictor. We hypothesize that high LA roof voltage indicates a thick roof wall, which causes difficulty with completing the roof block line; therefore, these patients require additional ablation inside the posterior wall. Although there are only few reports investigating the relationships between wall thickness and LA voltage, there have been reports showing that the thicker LA walls have higher LA voltages[14)].

Other reasons may also explain why completing the roof block line is challenging. Pambrun et al reported that the atrial myocardium between the superior pulmonary veins is thicker and consistently contains adipose tissue separating the septopulmonary bundle from the septoatrial bundle. They also suggested that myocardial thickness and fat interposition may explain difficulties in creating a transmural lesion during roof line ablation[21)]. Yokokawa et al reported that a left sinus node artery may act as an epicardial heat sink, preventing adequate heating of the LA roof during linear ablation[22)]. These studies demonstrate that epicardial conduction across the roof line is related to difficulties with linear ablation of the LA roof and achieving a completely transmural lesion is important for roof line ablation. In addition to the report that it is difficult to create a roof line due to the various factors mentioned above, there is also a report that the durability of the roof line was lower than that of the floor line, which indicates our hypothesis[13)]. In our study, additional ablation inside the posterior wall was necessary to complete PWI in patients with high roof voltage; therefore, avoiding high-voltage areas when creating a roof line might increase the PWI success rate. Furthermore, it has been reported that additional ablation inside the posterior wall is associated with poor durability of treatment[13)]. Therefore, in patients with high roof voltage, durability might be improved by increasing stability of the ablation catheter, setting a higher AI, or shortening the inter-lesion distance. Other than procedural parameters, patients in group B were significantly younger than those in group A. It has been reported that patients who have low voltage areas, defined as bipolar voltage of ≦0.5 mV in LA, was significantly older than patients who did not have low voltage areas[23)]. Therefore, the significant difference in age between the groups may affect the interpretation of the present results. In the present multivariate analysis with age adjustment, we found that mean and maximum voltage at the roof line were independent predictors of additional resection within the posterior wall.

This study had several limitations. First, the AI criteria (≧550 in the roof line and ≧400 in the floor line) and inter-lesion distance (2-4 mm) were selected arbitrarily based on our experience to minimize risks of complications and dislocation, which could have affected data interpretation. Future studies should investigate these variables in patients undergoing PWI. Second, we did not have LA wall thickness data from imaging studies, as our study was retrospective in design. However, previous studies have shown a direct and positive correlation between LA wall thickness and LA voltage. Third, we were unable to prove that incomplete roof block was a direct cause of the need for additional ablation inside the posterior wall. Fourth, bipolar voltage does not simply reflect myocardium wall thickness. It can also reflect various factors such as conduction direction; depending on the conduction direction, it may be possible that we have underestimated the voltage.

In conclusion, when performing PWI, high endocardial bipolar voltage at the LA roof line is an independent predictor of additional ablation inside the posterior wall. Therefore, we believe that when obtaining left atrial posterior wall first-pass isolation, it is necessary to note whether there is a high-voltage region in the left atrial roof.

Acknowledgements

All authors have no COI to declare regarding the present study.

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Relationship between Work Life Balance and Temperament among Japanese Workers

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Abstract

Background

Work life balance is an important issue for working people. To understand the impact of work and family, both positive and negative influences should be considered. Although the relationship between individual differences and work life balance has been studied, no study has examined the relationship between temperament and work life balance. Therefore, this study aimed to clarify the relationship between temperament and work-family spillover.

Methods

This web-based, cross-sectional study was conducted among 839 eligible Japanese workers. We used the Japanese version of the Survey Work-Home Interaction -NijmeGen to measure the four aspects of work-family spillover (positive/negative, work to family/family to work). Furthermore, the full version of the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego-auto questionnaire version was used to evaluate the five temperaments. Hierarchical multiple linear regression analysis was used.

Results

Cyclothymic, irritable, and anxious temperaments indicated significantly higher scores of work to family negative spillover. Cyclothymic and irritable temperaments also indicated significantly higher scores and depressive temperament indicated a significantly lower score of family to work negative spillover. Hyperthymic temperament indicated a significantly higher score, and irritable temperament indicated a significantly lower score of work to family and family to work positive spillover.

Conclusions

To promote better work life balance, it is important to recognize workers' temperament for themselves and workplace.

Key Words: Work life balance; Temperament; Work family spillover; Self-care; SWING

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Introduction

Recently, changes in the industrial structure and diversification of work styles have made it difficult to clearly distinguish between working and non-working time. Therefore, work life balance (WLB) has become an important issue[1]. Workers are expected to spend time both at work and in family matters, such as housework, nursing and childcare. Because both are equally important, it is crucial to strike a balance between work and family. Concepts related to WLB and the impact of work and family life have been studied extensively. Work-family conflict (WFC) arises when the demands of work and family roles cannot be reconciled[2]. WFC has been shown to be related with various health issues, such as higher burnout[3], depression, poor physical health and heavy alcohol use[4]. In contrast, work-family enrichment (WFE), a concept with a positive view on the relationship, implies that experiences in one role enrich and strengthen the other[5]. WFE has shown to be related with positive health effects, such as lower depression[6] and burnout and higher life satisfaction[3].

It is necessary to consider the negative and positive aspects of spillover, as well as its direction (family to work, work to family) to understand their impact[7]. Negative spillover between work and family has been considered as a chronic stressor, and may cause a physiological stress response[8]. Previous studies showed that it was associated with poor physical and mental health, self-reported musculoskeletal pains[9], possibility of obesity[10], depression symptoms[11] and anxiety and emotional strain[6]. Positive spillover from work to family and family to work were associated with better physical and mental health and fewer chronic diseases and better mental health and well-being, respectively[10].

Recently, as a factor affecting WLB, the relationship between individual differences and WLB has been studied. As antecedents of WFC, personality traits, such as negative affect and neuroticism, were found to have strong predictive validity than many work and non-work stressors and support factors[12]. A meta-analysis examined the relationship between the Five-Factor Model of Personality (FFM) and negative and positive forms of work and non-work spillover and found that each personality variable was related to both directions of spillover for all personality variables and forms. Furthermore, extraversion, agreeableness, and conscientiousness were negatively related to and neuroticism was positively related to work to family negative spillover. Meanwhile, extraversion, agreeableness, conscientiousness and openness to experience were positively related to work to family positive spillover[13]. Personality is influenced by the environment and develops during the maturation process[14], while temperaments are stable across one's lifespan[15]. Temperament is believed to be the biological basis for personality development[14]. Hagop Akiskal developed the concept of five emotional temperaments by adding anxiety type to the four basic states proposed by Kraepeli[16]. The five temperaments are depressive, irritable, anxious, hyperthymic, and cyclothymic. Temperament involves an inherent bias in how a person views and acts and causes the person to be more prone to certain behaviors[17]. Therefore, we considered that temperament impacted workers' WLB. However, limited research on the relationship between temperament, as an individual factor, and WLB has been conducted. This study clarified the relationship between temperament and work-family spillover.

Methods

An online, cross-sectional survey was conducted in Japan through an research company, Macromill, Inc. Japan, on 16-17 December 2020[18]. The inclusion criteria were: lived in Japan, were employed, and aged between 20-65. The objective was to recruit approximately 1000 Japanese workers from various employment types from the approximately 10 million people registered with Macromill, Inc. Participants were informed their voluntary participation. An informed consent form was completed by all participants and were assured that the researcher would not have access to personal information (e.g., name, telephone number, address of house) from Macromill, Inc. All participants received Macromill Points. Macromill Point is an original point service of Macromill, Inc. and the participants can exchange these points for prizes or cash.

We gathered a total of 1070 workers and excluded participants with at least one missing entry. The final analytic sample included 839 eligible participants. This study was conducted in accordance with the Declaration of Helsinki and its future amendments. The study design was approved by the Ethical Committee of Osaka City University (Authorization Number 4245). All data were stored only in our database, and the participants' employers or institutions did not have access to the data or knew who had participated.

The Survey Work-Home Interaction-NijmeGen (SWING) was developed in 2005 and measured work-home interaction[7]. The reliability and validity of the Japanese version have been confirmed[19]. We used the Japanese version of the SWING (SWING-J) to measure four aspects of work-family spillover: (1) work to family negative spillover (WFNS): eight items, (2) family to work negative spillover (FWNS): four items, (3) work to family positive spillover (WFPS): five items, and (4) family to work positive spillover (FWPS): five items. The responses were rated on a 4-point Likert scale, which ranged from 0 (never) to 3 (always). The scores for each item were totalled, and a higher score indicated greater spillover. The Cronbach's α's for the present sample were 0.874, 0.805, 0.756 and 0.740 for WFNS, FWNS, WFPS, and FWPS, respectively.

Temperaments were assessed by the full version of the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego-auto questionnaire version (TEMPS-A) developed by Akiskal et al[20]. The reliability and validity of the Japanese version have been confirmed[21]. The TEMPS-A was a yes-no self-reporting questionnaire that assessed temperaments. The instrument consisted 110 items and was divided into five types of temperaments: depressive, cyclothymic, hyperthymic, irritable, and anxious. Higher scores suggested a greater magnitude of the temperament. A stability of the temperaments by the TEMPS-A has already been shown, regardless of the temperament type, gender, or age[15].

We collected their demographic information, which included age, gender, marital status, family income, number of children who lived together, and number of people who required care who lived together. Participants also reported information on work-related variables: position classification, type of employment, work pattern and frequency of working from home.

We conducted Spearman's correlation analysis of the TEMPS-A and SWING-J scores. To examine the independent influence of temperament on work-life balance, we performed a hierarchical multiple linear regression using the TEMPS-A and SWING-J scores, while adjusting for the effects of demographic variables and work-related variables. Statistical significance was set at $p < 0.05$. We used the SPSS version 28.0 software (SPSS Inc., Chicago, IL) for statistical analyses.

Results

Table 1 shows the subjects' characteristics and the TEMPS-A and SWING-J scores. The mean age was 46.5±10.5 years. The participants consisted of 638 (76.0%) males and 201 (24.0%) females. Of

Table 1. Participants' characteristics. Total (N=839)

	Range	Mean (SD)	n (%)
Age (years)		46.5 (10.5)	
20-29			59 (7.0)
30-39			163 (19.4)
40-49			264 (31.5)
50-59			255 (30.4)
≧60			98 (11.7)
Gender			
Male			638 (76.0)
Female			201 (24.0)
Marital status			
Unmarried			292 (34.8)
Married			547 (65.2)
Family income (million yen)			
<4			184 (21.9)
≧4			655 (78.1)
Children living together			
No			439 (52.3)
Yes			400 (47.7)
People requiring care living together			
No			800 (95.4)
Yes			39 (4.6)
Position classification			
Non-manager			465 (55.4)
Manager			374 (44.6)
Type of employment			
Regular			689 (82.1)
Temporary			150 (17.9)
Work pattern			
Daytime			705 (84.0)
Shift			134 (16.0)
Working at home			
No			608 (72.5)
Yes			231 (27.5)
Temperaments			
Depressive	0-20	9.0 (4.1)	
Cyclothymic	0-21	6.8 (5.0)	
Hyperthymic	0-20	6.7 (4.4)	
Irritable	0-21	5.8 (4.3)	
Anxious	0-26	7.5 (6.2)	
Spillover			
WFNS	0-24	6.4 (4.8)	
FWNS	0-12	2.3 (2.4)	
WFPS	0-15	5.7 (3.1)	
FWPS	0-15	6.1 (3.1)	

SD, standard deviation; WFNS, work to family negative spillover; FWNS, family to work negative spillover; WFPS, work to family positive spillover; and FWPS, family to work positive spillover.

Table 2. Correlation between the temperaments and spillovers

	WFNS	FWNS	WFPS	FWPS
Depressive	0.289**	0.270**	−0.022	−0.024
Cyclothymic	0.430**	0.461**	0.080*	0.079*
Hyperthymic	0.204**	0.146**	0.343**	0.381**
Irritable	0.396**	0.450**	−0.043	−0.012
Anxious	0.384**	0.408**	−0.034	−0.039

** p<0.01, *p<0.05.

WFNS, work to family negative spillover; FWNS, family to work negative spillover; WFPS, work to family positive spillover; and FWPS, family to work positive spillover.

Table 3. The temperament effects for WFNS, FWNS, WFPS, and FWPS

	WFNS		FWNS		WFPS		FWPS	
	Step 1 β	Step 2 β	Step 1 β	Step 2 β	Step 1 β	Step 2 β	Step 1 β	Step 2 β
Age (years)	−0.183***	−0.109**	−0.171***	−0.087*	0.031	0.011	0.053	0.034
Gender	−0.023	−0.044	−0.081*	−0.067	0.114**	0.072	0.100*	0.062
Marital status	0.007	−0.005	−0.019	−0.038	0.097*	0.081	0.107*	0.088*
Family income (million yen)	0.009	0.02	−0.023	−0.012	−0.022	−0.057	0.006	−0.033
Presence of children living together	0.145**	0.12**	0.126**	0.104**	0.081	0.05	0.088*	0.054
Living with a person who required care	0.006	−0.017	0.068*	0.046	0.067	0.059	0.022	0.013
Position classification	0.059	0.061	−0.003	0.001	0.078	0.048	0.057	0.025
Type of employment	−0.039	−0.069*	−0.001	−0.034	0.031	0.036	0.024	0.027
Work pattern	0.063	0.052	0.051	0.042	0.004	−0.008	0.025	0.011
Working at home	0.038	0.04	0.027	0.032	0.049	0.038	0.004	−0.007
Depressive		0.01		−0.085*		−0.031		−0.01
Cyclothymic		0.195***		0.286***		−0.01		−0.007
Hyperthymic		0.032		−0.033		0.371***		0.393***
Irritable		0.105*		0.269***		−0.148**		−0.111*
Anxious		0.155**		0.045		0.046		0.005
R	0.257a	0.485b	0.225a	0.517b	0.206a	0.398b	0.197a	0.413b
R2	0.066	0.235	0.051	0.268	0.042	0.158	0.039	0.171
R2 Change score	0.066	0.169	0.051	0.217	0.042	0.116	0.039	0.132
F	5.839***	16.868***	4.424***	20.044***	3.667***	10.305***	3.34***	11.289***
Adjusted R2	0.55	0.221	0.039	0.254	0.031	0.143	0.027	0.156

* p<0.05, ** p<0.01, *** p<0.001.

WFNS, work to family negative spillover; FWNS, family to work negative spillover; WFPS, work to family positive spillover; and FWPS, family to work positive spillover.

these, 292 (34.8%) were unmarried and 547 (65.2%) were married. The number of participants with family incomes over 4 million yen was 655 (78.1%). Furthermore, 400 (47.7%) participants lived with children and 39 (4.6%) lived with people who required nursing care. The participants consisted of 465 non-managers (55.4%) and 374 (44.6%) managers, 689 (82.1%) regular and 150 (17.9%) temporary workers, and 705 (84.0%) daytime and 134 (16.0%) shift workers. Of these, 608 (72.5%) did not work at home or telecommute at all.

Spearman's correlations between the temperaments and work-home interaction according to the SWING-J is shown in Table 2. The results were interpreted based on Guilford's rule of thumb. Depressive, irritable and anxious temperaments scores were positively correlated with WFNS and FWNS. Cyclothymic and hyperthymic temperaments scores were positively correlated with WFNS, FWNS, WFPS, and FWPS.

Table 3 shows the results of the hierarchical multiple linear regression analysis of the TEMPS-A and SWING-J scores. Step 1 shows that age and the presence of children living together had significant associations with WFNS scores. Step 2 shows that the temperament variables explained the additional 16.9% of the variance ($F=16.87$, $p<0.001$). Cyclothymic, irritable and anxious temperaments indicated significantly high scores of WFNS. Step 1 shows that age, gender, the presence of children living together and living with a person who required care had significant associations with FWNS scores. Step 2 shows that the temperament variables explained the additional 21.7% of the variance ($F=20.04$, $p<0.001$). Cyclothymic and irritable temperaments indicated significantly higher scores and depressive temperament indicated a significant lower score of FWNS. Step 1 shows that gender and marital status had significant associations with WFPS scores. Step 2 shows that the temperament variables explained the additional 11.6% of the variance ($F=10.31$, $p<0.001$). Hyperthymic temperament indicated a significantly higher score, and irritable temperament indicated a significant lower score of WFPS. Step 1 shows that gender, marital status and the presence of children living together had significant associations with FWPS scores. Step 2 shows that the temperament variables explained the additional 13.2% of the variance ($F=11.29$, $p<0.001$). Hyperthymic temperament indicated a significantly higher score, and irritable temperament indicated a significantly lower scores of FWPS.

Discussion

We investigated the effects of temperament on work-family interaction after adjusting for sociodemographic and work-related factors. We used the TEMPS-A and SWING-J to evaluate the temperaments and consider the balance for both work and family life, respectively. The association between spillover and temperaments was discussed.

Temperaments and negative spillovers

Higher scores of cyclothymic and irritable temperaments were associated with higher WFNS and FWNS. Cyclothymic temperament was characterized by being unstable in mood, energy, socialization, and self-esteem and unevenly gifted and dilettante, whereas perceptive, compassionate, and romantic[20]. Cyclothymic temperament was associated with agitation following a stressful event[23] and risk of depressive symptoms[24]. Irritable temperament was the darkest, characterized by being sceptical and critical (considered intellectual virtues), and individuals tended to be moody, complaining, jealous, angry and violent[20]. Previous study regarding the relationship between occupational stress and temperaments found that this temperament was associated with role and interpersonal conflict[25]. Furthermore, irritable temperament was noted to be vulnerable to occupational stress[25]. In addition, work stress was cited as an antecedent of WFNS[8]. Workers with irritable temperament may be more likely to experience conflicts in various aspects. A previous study showed that cyclothymic and irritable temperaments were positively related to negative affect, risky behavior and restlessness, and negatively related to positive affect and preference for being with someone. Furthermore, individuals with high cyclothymic and irritable temperament were more likely to perceive situations as stressful and experience higher levels of negative emotions toward stressful environments[22]. Workers with these temperaments are easily irritated and stressed both at home and work, and may not be able to relieve their feelings, which may interfere with both sides. Therefore, workers with these temperaments may be more likely to experience high WFNS and FWNS. These could be associated with the higher WFNS and FWNS results in this study. Higher score of anxious temperament was associated with higher WFNS in this study. Anxious temperament was characterized by worry, vigilance and tension for external dangers[20]. It was associated with the risk of depressive symptoms[24] and role and interpersonal conflict[25], noted to be vulnerable to occupational stress[25]. Workers may be more likely to experience conflicts in various aspects and therefore workers with anxious temperament may be more likely to experience higher WFNS. In this study, although workers with anxious temperament were prone their family life being interrupted by work demand even when they were not at work, there was no indication that their work life was more likely to be affected by family demands. Family-related stressors such as family distress and family support have been identified as antecedents of FWNS[26]. Anxious temperaments are vulnerable to occupational stress[25], but may not be vulnerable to family-related stress, therefore workers with anxious temperament may not be associated with higher WFNS. Higher score of depressive temperament was associated with lower FWNS. Depressive temperament was characterized by a tendency to be tied to daily life, self-blaming, shy, unassertive, sensitive to criticism, but self-denying, willing to work for someone else rather than be the boss[20]. Even if they have some problems at home or with friends, they may tend to over-adapt and behave in the workplace.

Temperaments and positive spillovers

Higher score of irritable temperament was associated with lower WFPS and FWPS. It was associated with spillover in all four directions, with higher and lower levels for negative and positive spillover, respectively. Workers with irritable temperament may find it difficult to use developed work skills and roles at home and vice versa.

In contrast, higher score of hyperthymic temperament was not associated with negative spillover. However, it was associated with higher WFPS and FWPS. It is associated with many positive traits, such as cheerfulness, fun-loving, outgoing, joking, optimistic, self-confident, full of ideas, eloquent, active, no fatigue despite short sleep and leadership preference. However, it is also associated with a low likelihood of admitting to being single-minded, risk-taking and meddlesome[20]. This was generally consistent with previous studies in which extraversion and experiential openness were particularly strong predictors of positive spillover[13]. Hyperthymic temperament has been shown to be protective against mental disorders and occupational stress[10,25,27]. In previous study, cyclothymic, depressive, irritable and anxious temperaments showed significant correlations between cognitive complaints and depressive symptoms, while hyperthymic temperament did not[28]. Hyperthymic temperament is positively correlated with happiness and elation, and individuals have a positive outlook on daily life[22]. Workers may use their experiences and demands at work or home more effectively in another situation using their ideas.

The strengths and limitations are discussed. This was the first study on the relationship between temperament and work to family spillover using two measures with reliability and validity. Our findings help workers understand the effect of temperaments on work-family positive or negative spillover, which could lead to a better WLB. However, this study has some limitations. First, we could not determine the causal relationship between temperaments and work-family spillover due to the cross-sectional design. However, considering the stability of temperament, we believe they affected spillovers. Second, we did not explore the interaction effects between positive and negative spillover and work to family and family to work spillover. Future studies should consider these effects. Third, this study was a small, short-term, web-based survey conducted in Japan. Hence, sample bias may have influence the result and replicability cannot be confirmed. Furthermore, differences in the number of children and people who required care, and their ages were not examined. Furthermore, the survey was conducted during the COVID-19 pandemic, and it was possible that the participants' working conditions and family life were different from normal conditions. Future longitudinal studies with a larger sample and detailed questionnaire should be conducted.

Our study suggested that a hyperthymic temperament was more likely, while irritable and cyclothymic temperaments were less likely, to achieve better WLB for Japanese workers due to higher positive spillover. Our findings may help workers better manage their work and family life by understanding their own temperament and recognizing their susceptibility to negative and positive influences. A previous study showed that increased time in moderate leisure-time physical activity buffered the association between increased negative spillover and poorer health[29]. Moreover yoga and massage therapy have been demonstrated to reduce occupational stress in previous studies with healthcare workers[30] and stretching programs promoted health in desk workers[31]. Encouraging workers to have short exercise routines may benefit their health and job performance[32]. It may be desirable for workers with large negative spillover to have exercise habit and engage in moderate exercise to maintain their health, do yoga, get massage therapy, stretch during breaks and walk on the way to work. It may also be important for workers, especially with irritable and cyclothymic temperaments, to promote help-seeking behavior at the workplace and adjust workload if they have any family problems, and seek help for their family life when the workload is heavy or stressful. Recognition of workers' temperaments by supervisors, co-workers and family might lead to great support both at work and home.

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The Comorbidity of Autism Spectrum Disorder Slows Body Mass Index Gain in Adult-onset Avoidant/Restrictive Food Intake Disorder

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Abstract

Background

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition, expanded the criteria for avoidant/restrictive food intake disorder (ARFID) to apply to adults as well as children. Therefore, previous studies of ARFID focused on childhood-onset, and none examined the clinical features and prognosis of adult-onset only. Comorbidity of autism spectrum disorder (ASD) and ARFID is common in children, but the prevalence of such comorbidity in adult-onset ARFID is unclear. This study examined the characteristics of adult-onset ARFID with ASD comorbidity and its weight course during treatment.

Methods

This study was a retrospective chart review of 34 patients with ARFID with onset after the age of 18. The participants were divided into two groups according to ASD comorbidity, and their clinical characteristics and body mass index (BMI) gain over one year from treatment initiation were compared.

Results

ASD comorbidity was present in 44.1% of the sample. ASD characteristics were associated with onset and background psychopathology. The group with comorbidity exhibited significantly higher values than the group without comorbidity for ineffectiveness ($p=0.030$) and interoceptive awareness ($p=0.040$) on the Eating Disorder Inventory. Further, ASD comorbidity had a significantly negative impact on BMI gain during treatment ($p=0.014$). The slopes were 0.11 and 0.19 for the group with and without comorbidity, respectively.

Conclusions

Approximately half of the adult-onset ARFID group had ASD comorbidity, which was a factor in poor prognosis. When treating adult-onset ARFID, therapists should consider the possibility of

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comorbidity and diagnose appropriately, as special interventions may be needed based on ASD characteristics.

Key Words: Avoidant/restrictive food intake disorder; Autism spectrum disorder; Adult-onset; Prognosis; Outpatient

Introduction

Avoidant/restrictive food intake disorder (ARFID) is similar to anorexia nervosa (AN), characterized by poor food intake, significant weight loss, and social dysfunction. However, ARFID differs from AN in that the former does not have a core eating disorder pathology, such as a drive for thinness, fear of gaining weight/becoming fat, or body image disturbances. Although ARFID usually occurs in infancy or early childhood[1], adult onset has been observed in clinical situations[2]. Adults with ARFID were diagnosed with eating disorder not otherwise specified, a residual diagnostic criterion, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-Ⅳ)[3]. Revisions to the DSM-5[1] expanded the diagnostic criteria for "infantile or early childhood feeding disorder" in the DSM-Ⅳ to apply to any age group; thus, adult ARFID, which was previously considered eating disorder not otherwise specified, came into focus. Studies of children with feeding disorders have reported ARFID prevalence ranging from 1.5%-64%[4-10]. A survey of patients aged 15-40 years with eating disorders, including adult cases, reported that ARFID accounted for 9.2% of the clinical sample[11]. Previous studies have not focused on whether the onset of ARFID occurs in adulthood, even if it is diagnosed in adulthood. To the best of our knowledge, there are no existing reports of ARFID that were limited to adult onset (AO); most reports on its clinical features and prognosis focused on childhood-onset cases[5,6,12,13].

Childhood-onset ARFID was reported to be comorbid with autism spectrum disorder (ASD) in 3%-13% of cases[7,14]. ASD is a neurodevelopmental condition associated with restricted, repetitive, or stereotypical behaviors or interests, as well as impairments in social communication and social reciprocity[1]. In a prognostic study of all eating disorders, the presence of autistic traits was found to be a negative predictor of treatment outcomes for eating disorders[15,16]. Furthermore, Bourne et al stated that ASD comorbidity with childhood-onset ARFID is a significant health risk[17]. However, no studies have evaluated whether ASD comorbid with AO-ARFID leads to a poorer prognosis.

As weight regain is an essential goal of treatment, it is of great significance to examine the factors that influence weight change when considering prognosis. In this study, we examined the characteristics of eating behavior and psychopathology, clinical background, and treatment-induced changes in the body mass index (BMI) of AO-ARFID patients, to assess the effect of ASD comorbidity on the course of treatment.

Methods

Participants

A retrospective chart review was conducted of a cohort of patients with eating disorders who made their first visit to the outpatient clinic specializing in eating disorders at the Department of Neuropsychiatry, Osaka Metropolitan University Hospital (former Osaka City University Hospital) between January 1, 2014, and December 31, 2021. After the initial visit, a comprehensive clinical management process was conducted, based on supportive psychotherapy, one of the standard treatments for eating disorders, that encourages patients to self-manage their eating behavior problems through empathy for the patient while monitoring the patients' physical condition. Patients with ARFID who met the DSM-5 criteria and were 18 years old and older at onset age of ARFID were included in the study. Patients were excluded who discontinued after the first visit or continued seeing their doctor but did not track their weight during the treatment process.

Study variables at entry and during treatment

At the initial visit, a psychiatrist with extensive clinical experience in eating disorders performed a pre-treatment evaluation of the patients. Information from the patients and their family members was also collected at the time of this visit, including medical history related to eating behavior and developmental characteristics in childhood, factors related to the development of eating disorders, current eating behavior, presence of a drive for thinness and a fear of gaining weight or becoming fat, attitudes toward weight and body shape, and the presence of comorbid psychiatric or physical illnesses. We measured height and weight and calculated BMI at the time of the first visit. The age of onset and duration of illness were assessed based on the individual's medical history. Age of onset was defined as the age at which eating behavior abnormalities started, along with weight loss. Patients' weight was recorded for up to one year from the first visit, or less if the treatment was terminated due to improvement of underweight status or improvement of life obstacles. The frequency of visits and weight measurements varied among patients; thus, monthly measurements were used for this study.

Diagnosis

At the initial visit, the psychiatrist made a tentative diagnosis of ARFID and ASD according to the DSM-5 diagnostic criteria, based on the information collected from the patients and their families. Several psychiatrists reviewed the subsequent progress of the patients and made a final diagnosis. In the DSM-5[1)], ARFID is characterized by significant weight loss, significant nutritional deficiency, dependence on enteral feeding or oral nutritional supplements, and marked interference with psychosocial functioning (Criterion A). However, this diagnosis is applied only if the disturbance is not caused by food unavailability or cultural practices (Criterion B), the patient has no body image disorder (Criterion C), or the condition cannot be explained by medical or psychiatric illness (Criterion D).

Procedure

We classified AO-ARFID patients using the three subtypes of ARFID based on eating behavior characteristics proposed by Norris et al[18)], who classified ARFID into three subtypes: (1) ARFID-aversive subtype (aversion to the physical changes associated with food ingestion, such as vomiting, abdominal pain, choking), (2) ARFID-limited intake subtype (overall lack of interest in eating food), and (3) ARFID-limited variety subtype (avoidance due to sensory sensitivities, such as picky eating or preoccupation with food texture)[18)]. We classified patients with multiple subtypes into one of the three subtypes by identifying the predominant factor at ARFID onset[18)].

We administered the Eating Disorder Inventory (EDI)[19)] during the initial consultation to identify psychopathological features. The EDI is a widely used multidimensional inventory consisting of 64 items that comprise eight subscales, three of which measure eating disorder pathology (drive for thinness, bulimia, and body dissatisfaction), and five that measure psychopathology commonly associated with, but not unique to, eating disorders (ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness and maturity fears). Participants selected whether each item applied to them as "always", "usually", "often", "sometimes", "rarely", or "never". These six responses were coded into four categories between 0 and 3, with the most symptomatic response receiving a score of 3, the second highest a score of 2, the next highest a score of 1, and the remaining receiving a score of 0. The scores for all items on each scale were summed to obtain a total score. The validity and reliability of the Japanese version of the scale has been documented previously[20].

Statistical analyses

Clinical and psychopathological variables were compared in the AO-ARFID group, classified by ASD comorbidities. Continuous variables were subjected to the Shapiro-Wilk normality test and Mann-Whitney *U* test and reported as median and first-third quartiles. Categorical variables were subjected to the chi-squared test or Fisher's exact test and reported as frequencies and proportions.

Weight gain in patients with eating disorder does not occur at a constant pace during treatment. Therefore, an analysis of BMI change associated with AO-ARFID treatment was conducted using a linear mixed model assuming a random intercept because of its flexibility in accommodating different numbers of BMI measurements among participants and its ability to capture overall trends rather than temporal points. The independent variable was BMI, which was measured at one-month intervals from the start of treatment. The model was set up with a random intercept among participants. Duration from the start of treatment was used as a covariate (Duration). To examine the impact of ASD comorbidity (ASD) on duration after treatment initiation, the model included the interaction between duration and ASD comorbidity (Duration×ASD). The categorical variable of ASD comorbidity was dummy coded (ASD=0, without ASD comorbidity; ASD=1, with ASD comorbidity). A p value of less than 0.05 was considered statistically significant.

Most analyses were conducted using IBM SPSS Statistics for Mac, ver.26 (SPSS Japan, Tokyo, Japan). The linear mixed model analysis was conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 4.1.2 (The R Foundation for Statistical Computing)[21].

Ethical statement

This study was reviewed and approved by the Osaka City Graduate School Ethics Committee (2020-106).

Results

During the study period, 927 patients made their first visit to the outpatient clinic specializing in eating disorders, of whom, 72 (7.8%) were ARFID and 44 were AO-ARFID patients (including two male). Of the 44 patients, 10 did not meet the inclusion criteria and were excluded; thus, 34 patients (32 female and 2 male) comprised the final sample for this study. There were 15 and 19 patients respectively in the groups with and without ASD comorbidity, of whom 6 and 5 patients, respectively, terminated treatment in less than a year.

Table 1 shows the clinical characteristics and background of AO-ARFID participants with and without ASD comorbidities. Fifteen (44.1%) patients had ASD comorbidity. There were no significant differences between the groups with and without ASD comorbidity in term of sex, age at first visit, age of onset, duration of illness, BMI at first visit, height at first visit, body weight at first visit, hospitalization within one year of first visit, or number of visits. Participants with ASD comorbidity had a higher percentage of continuous subthreshold ED pathology from childhood than participants without ASD comorbidity (53.3% vs 15.8%, p=0.030). Detailed interviews with the former patients revealed symptoms such as picky eating, lack of interest in food and small appetite. However, these symptoms did not interfere with daily life and did not meet DSM-5 diagnostic criteria for ARFID in

Table 1. Comparison of clinical characteristics and background between ARFID patients with and without ASD comorbidity

	Total (n=34)	With ASD (n=15)	Without ASD (n=19)		
Clinical characteristics	Number (%)	Number (%)/ Median (IQR)	Number (%)/ Median (IQR)	p value	
Sex (female)	32 (94.1)	14 (93.3)	18 (94.7)	1.000	a
Age at first visit (years)	30.7 (21.6-44.1)	27.3 (20.3-41.1)	35.7 (22.8-52.3)	0.160	b
Age of onset (years)	24.6 (19.7-40.2)	23.6 (18.3-30.6)	27.9 (20.0-48.8)	0.099	b
Duration of illness (years)	1.2 (0.58-4.4)	1.2 (0.58-10.5)	1.3 (0.42-4.3)	0.876	b
BMI (kg/m^2)	14.1 (13.1-15.3)	14.8 (13.7-17.7)	13.7 (12.9-15.2)	0.052	b
Height (cm)	160.0 (155.0-163.0)	160.0 (155.0-161.0)	160.0 (156.0-163.0)	0.372	b
Body weight (kg)	36.0 (33.0-42.0)	36.0 (33.0-42.0)	35.0 (32.0-40.0)	0.256	b
Clinical background					
Hospitalization within 1 year after initial visit [1]	11 (32.4)	3 (20.0)	8 (42.1)	0.271	a
Number of consultations (times)	-	13 (5.5-17)	14 (10.5-19)	0.639	b
Continued subthreshold ED pathology from childhood [2]	11 (32.4)	8 (53.3)	3 (15.8)	0.030*	a
History of physical illness	14 (41.2)	3 (20.0)	11 (57.9)	0.026*	c
Somatic symptoms	18 (53.0)	5 (33.3)	13 (68.4)	0.042*	c
Predominant ARFID subtype					
1) ARFID-aversive	22 (64.7)	9 (60)	13 (68.4)	0.724	a
2) ARFID-limited intake	7 (20.6)	5 (33.3)	2 (10.5)	0.199	a
3) ARFID-limited variety	1 (2.9)	1 (6.7)	0 (0)	0.441	a
N/A	4 (11.8)	0 (0)	4 (21.1)	0.113	a

Continuous variables are reported as median and IQR and compared by Mann-Whitney *U* test. Categorical variables are reported as number (percentage) and compared by χ^2 test or Fisher's exact test. a: Fisher's exact test, b: Mann-Whitney *U* test, c: χ^2 test. 1: No patient was hospitalized more than once during the study period. 2: Patients with abnormal eating behavior not diagnostic of an eating disorder since childhood. ARFID, avoidant/restrictive food intake disorder; ASD, autism spectrum disorder; BMI, body mass index; ED, eating disorder; and IQR, interquartile range. *$p<0.05$.

childhood. Members of the group without ASD comorbidity were more likely to have a history of physical illness (20.0% vs 57.9%, p=0.026), such as gastrointestinal disease, and current somatic symptoms (33.3% vs 68.4%, p=0.042).

We also categorized the 34 patients with AO-ARFID into three subtypes[18]. The "aversive subtype" accounted for 22 (64.7%) patients, the "limited intake subtype" for 7 (20.6%), and the "limited variety subtype" for 1 (2.9%). Five (14.7%) patients had multiple subtypes. Four (11.8%) patients had no subtypes, all of whom were in group without ASD comorbidity. There were no significant differences in the proportions of the three subtypes between the groups with and without ASD comorbidity.

Table 2 shows the differences in core eating disorder pathology and psychopathology related to eating disorders according to the EDI between the AO-ARFID groups with and without ASD comorbidity. The group with ASD comorbidity had significantly higher scores than the group without comorbidity for ineffectiveness (p=0.030) and interoceptive awareness (p=0.040). Although not significantly different, the group with ASD comorbidity tended to have higher levels of perfectionism than the group without ASD comorbidity (p=0.053). There were no significant differences between

Table 2. Comparison of EDI between ARFID groups with and without ASD comorbidity at baseline

	With ASD (n=15)	Without ASD (n=19)	
	Median (IQR)	Median (IQR)	p value
Drive for thinness	1.0 (0.0-2.0)	1.0 (0.0-2.5)	0.794
Bulimia	0.0 (0.0-2.0)	0.0 (0)	0.165
Body dissatisfaction	10.5 (6.3-15.0)	10.0 (9.0-13.0)	0.984
Ineffectiveness	11.0 (7.0-18.0)	6.0 (4.0-10.0)	0.030*
Perfectionism	3.0 (2.0-7.0)	1.0 (0-3.5)	0.053
Interpersonal distrust	7.0 (3.0-9.0)	4.0 (1.0-9.0)	0.202
Interoceptive awareness	5.0 (3.0-8.0)	2.0 (0-3.5)	0.040*
Maturity fears	5.0 (3.0-13.0)	4.5 (3.0-8.75)	0.545

Continuous variables are reported as median and IQR and compared by Mann-Whitney *U* test. EDI, Eating Disorder Inventory; ARFID, avoidant/restrictive food intake disorder; ASD, autism spectrum disorder; and IQR, interquartile range. $^{*}p<0.05$.

Table 3. Results from linear mixed models in ARFID

					Random effects	
	Fixed effects				Participant	Item
Parameters	Estimate	SE	*t*	p value	SD	SD
Intercept	14.5	0.47	30.9	<0.001**	2.0	-
Duration	0.19	0.021	9.1	<0.001**	-	-
ASD	0.61	0.71	0.86	0.39	-	-
Duration×ASD	−0.078	0.032	−2.5	0.014*	-	-

The independent variable was BMI, measured at one-month intervals from the start of treatment. The model was set up with a random intercept among participants. The covariates were Duration, ASD, and Duration×ASD. The "Duration" term represented the passage of time (months) from the start of treatment. The "ASD" term represented the presence of ASD comorbidity (ASD=0, without ASD comorbidity; ASD=1, with ASD comorbidity). The "Duration×ASD" term represented the interaction term between "Duration" and "ASD". ARFID, avoidant/restrictive food intake disorder; ASD, autism spectrum disorder; and BMI, body mass index. $^{*}p<0.05$, $^{**}p<0.01$.

the two groups in drive for thinness, bulimia, body dissatisfaction, interpersonal distrust, and maturity fears.

Table 3 shows the results of a linear mixed model analysis that compared treatment outcomes between the groups with and without ASD comorbidity in terms of the impact of duration and the presence of ASD comorbidity at baseline, with BMI change as the outcome. There was a main effect of duration (Estimate=0.19, SE=0.021, t=9.1, $p<0.001$), no main effect of presence of ASD (Estimate =0.61, SE=0.71, t=0.86, p=0.39), and a significant interaction between duration and presence of ASD (Estimate=−0.078, SE=0.032, t=−2.5, p=0.014). Although not presented in the table, subgroup analysis of the groups with and without ASD comorbidity revealed that the slope of BMI change per month was 0.11 for the group with ASD comorbidity and 0.19 for the group without ASD comorbidity.

Discussion

In this study, the prevalence, clinical characteristics, and impact of ASD comorbidity on BMI gain during the one-year treatment period were examined in participants with AO-ARFID. The results showed that AO-ARFID was associated with a high incidence of ASD comorbidity. ASD comorbidity was associated with severe psychopathology and a slower BMI gain during the course of treatment.

First, the current study found that the BMI gain in the AO-ARFID group was slowed significantly by ASD comorbidity. No differences were found in background factors that might have influenced BMI between the groups with and without ASD comorbidity. In previous studies of the prognosis of eating disorders, autistic traits were considered a predictor of negative outcomes of treatments for eating disorders[15,16]. A 30-year follow-up study reported that AN with ASD comorbidity was associated with prolonged core symptoms such as anorexia and a deterioration in other psychiatric symptoms and socioeconomic status[22]. No studies to date have focused on the prognosis of AO-ARFID with ASD comorbidity; however, the current study suggests that ASD traits and ASD-specific psychopathology may play a role in treatment responsiveness in AO-ARFID as well as in other eating disorders.

Second, AO-ARFID patients with ASD comorbidity had more severe psychopathology than those without ASD comorbidity. The EDI showed that the group with comorbid ASD exhibited significantly worse effectiveness and interoceptive awareness compared to the group without comorbid ASD. "Ineffectiveness" denotes feelings of general inadequacy, insecurity, worthlessness, and not being in control of one's life[19]. In the AO-ARFID group with ASD comorbidity, severe ineffectiveness may make it difficult to have a positive outlook or expectation of treatment and may also cause resistance to weight gain. "Interoceptive awareness" reflects one's lack of confidence in recognizing and accurately identifying the emotions and sensations of hunger or satiety[19]. The group with ASD comorbidity was more confused about their sense of physical symptoms and feelings, which may have made it more difficult for them to be proactive in treatment. Although not significantly different, the group with ASD comorbidity tended to have higher levels of perfectionism than the group without comorbidity. "Perfectionism" indicates excessive personal expectations of superior achievement. The group with ASD comorbidity may have been prone to conflicts between perfectionistic achievement standards and their own abilities. This is an important treatment-related factor that represent the background psychology of eating disorders.

Third, the clinical background of AO-ARFID differed between the groups with and without ASD comorbidity. In the group with ASD comorbidity, subthreshold eating disorder-related pathology (e.g., picky eating, lack of interest in food, and small appetite) was more common in early childhood and persisted into adulthood. Subthreshold eating disorder pathology may have evolved into eating behavior problems seen in ARFID due to the increased stress load arising from the demands of social functioning in adulthood[23,24]. In contrast, the group without ASD comorbidity was significantly more likely to have a history of physical illness, such as gastrointestinal disease and current somatic symptoms. This was consistent with previous reports[25,26]. The three subtypes did not differ significantly in frequency between the AO-ARFID groups with and without ASD comorbidity. The most common "aversive subtype" was found in the group with ASD comorbidity with nine patients (60.0%), whereas "limited variety subtype" accounted for only one patient (6.7%). In contrast, a previous report suggested that "limited variety subtype" is the most common in childhood-onset ARFID with ASD comorbidity[17]. These differences in symptoms were consistent with the finding that food avoidance or restriction based on sensory aspects improve in adulthood to a level that does not interfere with daily life[27]. In addition, the group without ASD comorbidity contained atypical cases that did not fit into any of the three subtypes[18]. Thus, it is possible that some AO-ARFID patients without ASD may be difficult to classify in terms of the three principal features of ARFID that are used for childhood-onset cases, and that a separate classification for adults may be necessary. The clinical characteristics of AO-ARFID did not differ significantly between the groups, but most of the patients were female in this study. This result was similar to a Japanese report on ARFID after adolescence[2]. In contrast, reports of childhood-onset ARFID indicate that 30% of patients were male[4,5,28]. This discrepancy suggests that male may be less likely to develop ARFID in adulthood. This is in agreement with the higher incidence of female in any type of eating disorders. However, we cannot rule out the possibility of adult male refraining from seeking medical attention. It has been suggested that the stigma that eating disorders are female diseases and prejudice against mental illnesses may be holding male back from seeing a doctor[29,30]. Further research on age-specific sex ratios of ARFID is warranted to clarify this hypothesis.

Finally, this study showed that 44.1% of patients with AO-ARFID had ASD comorbidity. The comorbidity prevalence in AO-ARFID may be higher than in previous reports of childhood-onset ARFID (comorbidity 3%-13%)[7,14]. Patients with ASD often display picky eating and prefer their own routine (what, when, and how they consume), which is reported to correlate with poor attention switching[28]. These “food obsessions” have been reported to have serious effects on physical and mental health[31]. In childhood, eating behavior problems may be considered only a symptom of ASD, and thus ARFID may remain underdiagnosed. Psychological intervention tailored to the ARFID subtype in children is the treatment for ARFID (e.g., reduction of postprandial discomfort symptoms for the “aversive subtype”, education and training in disinterest for the “limited intake subtype”, and reduction of anxiety about sensory avoidance for the “limited variety subtype”). In children, ARFID with ASD comorbidity is treated with consideration of ASD characteristics. Therapists need to not only provide tailored treatment to ARFID subtypes, but also guidance to overcome social difficulties (which also affect ARFID symptoms) related to the patient’s autism spectrum characteristics, such as limited, repetitive, and stereotyped behaviors and interests, and impaired social communication and interpersonal interactions. In adults, specific treatment has not yet been defined. Nevertheless, the same treatment strategy may be effective for AO-ARFID with ASD comorbidity as for children. Further research on the treatment of adult ARFID (as well as on special handling of cases with ASD comorbidity) is expected.

In conclusion, approximately half of the participants with AO-ARFID in this study had ASD comorbidity, and the comorbidity prevalence was higher than that in previous reports of childhood-onset ARFID. ASD comorbidity was found to slow BMI gain during the course of treatment. The psychopathology of AO-ARFID with ASD comorbidity was more severe than that of the group without ASD comorbidity, which may worsen the prognosis of the former group. Therapists should be mindful of the possibility of ASD comorbidity and make an appropriate diagnosis. Interventions that consider the characteristics of ASD may have therapeutic effects for patients with AO-ARFID. This study is the first to focus on the impact of ASD on AO-ARFID, and may provide insight into effective treatment strategies in the future. In addition, some patients in the group without ASD comorbidity did not fit the childhood-onset ARFID classification system and may have a different pathophysiology from that of childhood cases. Therefore, further studies are needed in this regard.

Limitations

The present study had several limitations. First, this was a single-center study and may not be generalizable to the entire AO-ARFID population. Second, the sample size was small. Although low prevalence of AO-ARFID comorbid with ASD limits the sample size, we hope that the characteristics and course of AO-ARFID will become clearer as the number of cases increases in the future. Finally, although the present study followed weight progress over a one-year period, further long-term observation of weight change is necessary for accurate prognostic evaluation.

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Effectiveness of Financial Incentives for a Pedometer-based Walking Promotion Program

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Abstract

Background

Physical inactivity significantly contributes to poor health and disease onset. Physical inactivity is also associated with severe economic burdens. Japan's Ministry of Health, Labour and Welfare cite the provision of various health promotion incentives aimed at health-indifferent groups, which comprise individuals less interested in health promotion. This study investigates the relationship between medical costs and a pedometer-based walking program that provides monetary incentives based on daily step counts.

Methods

The study sample included 11560 citizens aged 40-75 years, who lived in Takaishi City and were enrolled in the National Health Insurance between October 2016 and March 2018.

Results

The ordinal logistic regression analysis results showed that participation in a walking promotion program with a health-promoting financial incentive was correlated with a reduction in healthcare costs over one year in a sample of Takaishi City residents. The difference in the yearly medical cost between the walking and control groups was 21261324 yen/year. The reductions were more than the total monetary incentives paid under the program, which totaled 7462000 yen/year.

Conclusions

It was suggested that a walking promotion program with incentives implemented on a municipal scale has the effect of reducing medical expenses. As program context differs widely from region to region and country to country, future investigations are required to select appropriate incentive schemes for programs offered in other regions and countries.

Key Words: Health care cost; Health-promotion incentive; Japan; Pedometer-based walking program; Physical inactivity

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Introduction

Physical inactivity is a significant contributor to poor health and disease development. According to the World Health Organization (WHO), inactivity is the fourth leading risk factor for death and a significant risk factor for mortality. Eliminating physical inactivity is expected to relieve other diseases such as hypertension, dyslipidemia, and obesity[1). Physical inactivity is also associated with severe economic burdens. Physical inactivity generates USD 53.8 billion internationally, most of which is paid by the public sector[2).

To reduce physical inactivity, it is especially important to approach and encourage the health-insensitive population to become more interested in health. Financial incentive programs have been reported as an effective means to encourage involvement in physical activity, and Japan's Ministry of Health, Labour and Welfare (MHLW) has identified the provision of various health promotion incentives as an effective way to reach the health-insensitive population. Previous studies indicate the effectiveness of a health-promoting financial incentive (HPFI)[3). Giles et al reviewed the literature on the effectiveness of financial incentive interventions in promoting healthy behavior changes among non-clinical adults living in high-income countries and revealed that compared with usual care or no intervention, interventions with financial incentives are more effective in promoting healthy behavioral changes[4). Pedometers, which are used to assess physical activity, are also considered effective in promoting activities of daily living in a wide range of age groups; however, most of the reported studies have been conducted among hospitalized patients, while few have been conducted among non-clinical adult populations[5-7). Although it is important to investigate the effects of preventive medicine policies on lowering healthcare costs for the aging population in later stages of life, current research on the effects of municipal-level programs that distribute pedometers to citizens (including healthy people), evaluate their activity levels, and provide incentives based on the distance walked is scant. Furthermore, research on the effectiveness of such programs at the municipal level is also limited. Therefore, this study used real data from a city where a pedometer-based walking program was implemented to investigate the relationship between a walking program with financial incentives based on the number of steps taken per day and real data on medical costs.

Methods

This study used data from a program implemented in Takaishi City, Osaka Prefecture, from October 2016 to March 2018, which provided incentives for the number of daily steps taken, as measured using a pedometer. This program was designed by the government to promote longevity by encouraging people to start and continue exercising. The incentive based on the number of steps taken was designed to provide the program to health-conscious individuals who voluntarily began exercising as well as to those who were indifferent to health promotion or who did not exercise regularly.

The city's program was widely publicized, with information being distributed to all residential homes, the city's website, and posters placed throughout the city. The city, which is located in an industrial area of Osaka, has a population of 56000, of which 27% are above 65 years. Takaishi City residents who wished to participate in the walking program were required to register at the city office, where they received a pedometer (Activity Meter with FeliCa AM-150; Tanita Corp., Tokyo, Japan). The participants could also use the pedometer application on their smartphones. The content of the research was made public on the city's bulletin board and website. Participants who agreed to participate in the study at the time of registration were included. Participants could refuse participation by informing the contact person in charge of accepting refusals for information use.

Participants brought their pedometers to special machines installed at community centers, post offices, and stores in the city, and registered their daily number of steps monthly. Depending on the number of steps taken on that day, up to 6000 points (one-point equaled 1 yen) were awarded over the course of a year, which could then be exchanged for money certificates. The study participants were National Health Insurance (NHI) enrollees aged between 40 and 75 years, who resided in Takaishi City between October 2016 and March 2018. As there is no private health insurance in Japan, all the residents are required to join one of the two public health insurance schemes[7,8]. This study used a claims dataset from one of these schemes, the NHI, which covers the self-employed (e.g., farmers and fishermen), retirees, and their dependents, and the remaining 25% of the population. This dataset included the following information: ID number, a month for which each hospital/clinic was assigned a national diagnosis code by inpatient or outpatient, the type of claims, that is, medical claims or direct primary care claims (medical bills), number of days per month, national diagnosis codes (corresponding to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems), and medical bills (medical expenses). The data were extracted and prepared for analysis in accordance with the rules for the use of personal information. In addition to these data, basic resident register data maintained by the city were analyzed to obtain background information on participants (date of birth, sex, whether or not they had moved, and date of death) and program step count data to collect step counts. Considering the time lag between exposure (program participation) and the effect of medical cost reduction, we defined the month in which the number of steps was registered as the baseline month, treated the following day, and the days after as the month in which program participation was effective, and conducted the analysis. The participants were treated as the walking group throughout the analysis period if they had participated in the program at least once even if no steps were registered after the month in which the participants had registered for the program. This research plan was approved by the ethics committee of our university [blinded for anonymous review].

Analyses

This study aimed to evaluate the effect of program participation on medical costs. In establishing control and walking groups, it was necessary to pay attention to factors other than program participation that might affect medical costs for both groups. The walking program, which was the subject of this study, was not designed for research purposes but was designed by the city to promote exercise among its residents. In other words, the data obtained were not prepared for research. Moreover, only the minimum necessary items were collected; therefore, there were no data on factors that might affect healthcare costs (medical history, smoking history, and body mass index), which have been reported and generally collected in previous studies on the effect of exercise on health care costs. Therefore, to adjust as much as possible for background on non-walking medical costs in the walking and control groups, we used medical cost data for the past six months, excluding the baseline month, and to estimate the potential medical costs that could be needed in that month, we defined that value as the baseline medical cost. Additionally, the year and month were also matched to adjust for time biases, such as seasonal variations in medical costs (point-in-time matching). We defined non-participants as those who had never registered any steps and matched them one-on-one with program participants on age, sex, year, and baseline medical expenses (categorized in 5000 yen increments). Repeated data were used in this study.

The analysis was initially conducted using a mixed-effects model. However, the analysis was problematic because the residuals did not meet normality; therefore, an ordinal logistic regression analysis was conducted on medical costs during the first every 12 months of participation, with the dependent variable being monthly medical costs and the independent variables being program participation, sex, age, time since participation, and baseline medical costs (Mean monthly medical expenses in the past 6 months from period0). A two-sided 5% significance level of R version 4.0.1 (https://www.r-project.org/foundation/) was used to conduct the analysis.

Results

Table 1 summarizes the descriptive statistical analyses. During the observation period, there were 11560 citizens aged 40-75 years who resided in Takaishi City and had registered with the NHI. Of these, 18.3%, or 2119 persons, had registered their steps. Of the sample, which had a median age of 64.0 years, 55% were women, with a median cost per month of 7144.2 yen.

Data with duplicate IDs, unknown dates of birth, and so on were excluded and only appropriate data were used to select one control subject with the same background factors for each participant. As a result of the matching, there were 1945 people in both the walking group and the control group. Table 2 lists the number of participants used in the analysis. The walking and control groups showed insignificant demographic differences. Regarding medical expenses, the results were lower for both groups compared to Table 1. This would predict that the walking program would enroll more people between the ages of 40 and 75 with relatively low healthcare costs.

Figure 2 shows the step registration rates of the program participants. The results showed that 86.4% of the participants registered their steps for more than 80% of the days during the registration period. Figure 3 and Table 3 show the results of the ordinal logistic analysis. It was estimated that the odds of an increase in medical expenses in the walking group would be lower than in the control group throughout the entire period, and a significant difference was observed especially in the period from 2 to 11, which indicated that participating in an HPFI program was associated with a reduction in healthcare costs over 12 months.

The yearly medical costs for each group were as shown in Table 4. The total medical costs per year was 31402791 yen in walking group and 52664115 yen for control group. Based on these results, the project medical cost reduction was estimated to be approximately 21261324 yen/year, which was higher than the average of 7462000 yen/year of total financial incentives paid by Takaishi City to the walking program participants.

Table 1. Characteristics of the study sample

Takaishi citizens aged 40-75 with NHI		11560
Age, years old (median [IQR])		64.00 [51.00, 69.00]
Sex, % (freq)	Women	55.1 (6375)
	Men	44.9 (5185)
Baseline cost, yen/month (median [IQR])		7144.17 [0.0, 21699.17]
Project participants, % (freq)	No	83.4 (9637)
	Yes	16.6 (1923)

NHI, National Health Insurance; and IQR, Interquartile Range.

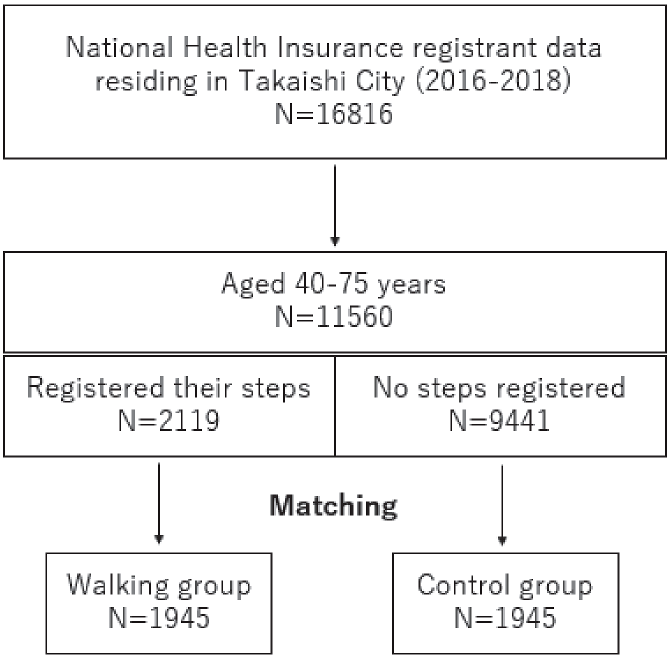

Figure 1. Process of study selection.

Table 2. Demographic data for the walking group and matched control group

		Walking	Control	Overall	p*
N		1945	1945	3890	
Sex, % (freq)	Women	69.1 (1344)	69.1 (1344)	69.1 (2688)	1
	Men	30.9 (601)	30.9 (601)	30.9 (1202)	
Age (years old), (median [IQR])		65 [53.00, 70.00]	65 [53.00, 70.00]	65 [53.00, 70.00]	0.908
Age categories (years old), % (freq)	40-44	9.4 (183)	9.4 (183)	9.4 (366)	1
	45-49	9.7 (189)	9.7 (189)	9.7 (378)	
	50-55	8.4 (163)	8.4 (163)	8.4 (326)	
	55-59	8.6 (167)	8.6 (167)	8.6 (334)	
	60-64	12.5 (243)	12.5 (243)	12.5 (486)	
	65-69	25.9 (504)	25.9 (504)	25.9 (1008)	
	70-75	25.5 (496)	25.5 (496)	25.5 (992)	
Baseline Cost (yen/month) (median [IQR])		1008 [0.00, 9521.00]	1149 [0.00, 9327.00]	1079.5 [0.00, 9418.50]	0.62
Cost categories (yen/month), % (freq)	0-4999	59.0 (1147)	59.0 (1147)	59.0 (2294)	1
	5000-9999	7.9 (153)	7.9 (153)	7.9 (306)	
	10000-14999	7.3 (142)	7.3 (142)	7.3 (284)	
	15000-19999	6.0 (116)	6.0 (116)	6.0 (232)	
	20000-24999	4.2 (82)	4.2 (82)	4.2 (164)	
	25000-29999	3.4 (66)	3.4 (66)	3.4 (132)	
	30000-	12.3 (239)	12.3 (239)	12.3 (478)	

*Comparison between the walking and control groups. [Sex, Age categories, Cost categories: Chi-square test without continuity correction. Age, Baseline cost: Mann-Whiteny U test].

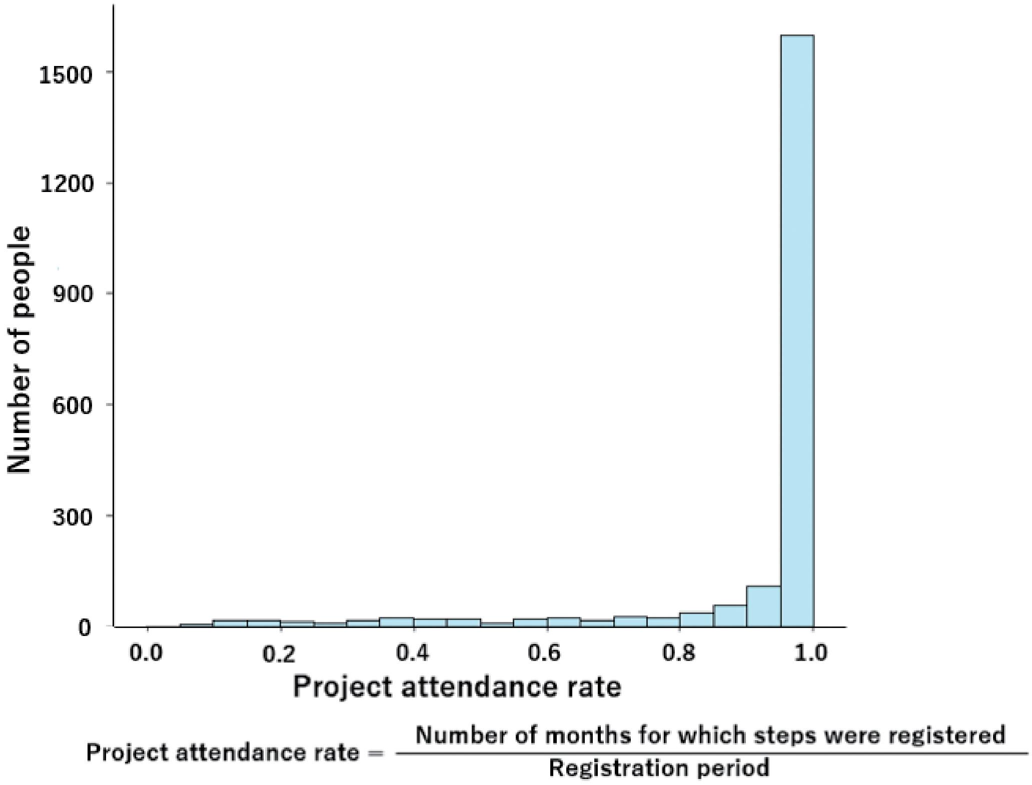

Figure 2. Step registration rates of the program participants.

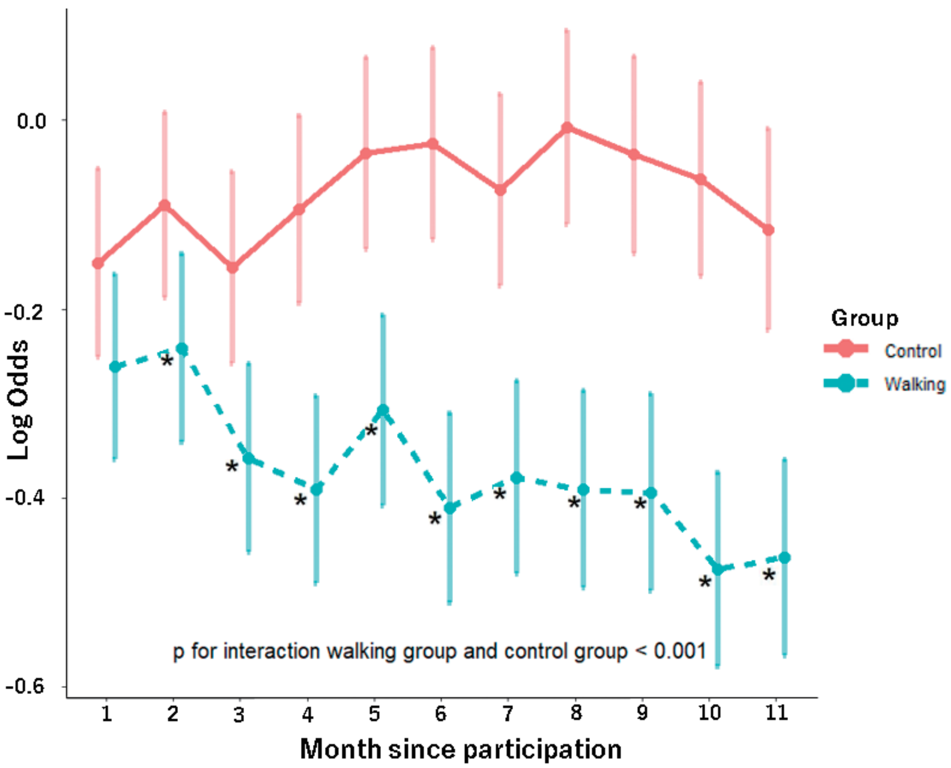

Figure 3. Ordinal logistic analysis plot of the relationship between project participation and health care costs. An ordinal logistic analysis was performed for each month's medical expenses for the walking and control groups, and a * was noted for months when the p value was less than 0.05.

Table 3. The result of the correlation between participation in the walking project or not and monthly medical expenses over 12 months, performing ordinal logistic regression analysis for each month from the start of walking as Period 0 to Period 11 after 12 months.

Period	Odds Ratio (95% CI)	p
1	0.90 (0.79-1.01)	0.08
2	0.86 (0.76-0.97)	0.02
3	0.82 (0.72-0.93)	<0.01
4	0.74 (0.66-0.84)	<0.01
5	0.76 (0.67-0.87)	<0.01
6	0.68 (0.60-0.77)	<0.01
7	0.73 (0.65-0.84)	<0.01
8	0.68 (0.60-0.78)	<0.01
9	0.70 (0.61-0.80)	<0.01
10	0.66 (0.58-0.76)	<0.01
11	0.71 (0.62-0.81)	<0.01

Period; The period since the subject registered for the walking project, with the month of registration being 0. The method of analysis was ordinal logistic regression analysis, with medical costs as the objective variable and explanatory variables as participating in the walking project or not, sex, age, and baseline medical cost.

Table 4. Total medical costs per person in the walking group and control group during the 12-month follow-up period

		Walking	Control
N		1945	1945
Cost (yen/year)	median[IQR]	1074 [0,18878]	6172 [0,20423]

IQR, Interquartile Range.

Discussion

The ordinal logistic regression analysis results showed that participating in a walking promotion program with an HPFI correlated with a reduction in healthcare costs. There was a difference of 21261324 yen/year in the medical cost between the walking and control groups.

A total of 2848 participants enrolled in the walking program, of which 1945 participants were between the ages of 40 and 75 years whose data were used for the study. This was projected to further reduce health care costs. Up to 6000 yen/year per person was reimbursed based on the number of daily steps. The average annual incentive amount paid by the city to the participants was 7462000 yen/year, which is lower than the projected medical cost reduction. This result indicates that a municipal policy that provides incentives of up to 6000 yen/year, based on the number of daily steps recorded on a pedometer, reduces medical costs to a greater extent than the amount of incentive paid by the city.

According to WHO, regular physical activity is essential for a healthy world. Therefore, in 2018, it published the Global Action Plan on Physical Activity to reduce physical inactivity by 15% by 2030[9]. Previous studies indicate that HPFI may effectively promote exercise[10-15]. Finkelstein et al[11] examined the effects of HPFI in a two-arm, single-blind, randomized controlled trial in which financial incentives were given according to the number of aerobic exercise minutes recorded weekly on a pedometer over four weeks. The results showed that the incentivized group exercised 1.7 times more per week than the control group. Therefore, the researchers concluded that associating moderate financial incentives with aerobic exercise minutes could be an effective as well as a cost-effective approach to increasing physical activity. That report had the advantage of using a randomized comparison design, but with a small sample size of only 51 participants. In contrast, the current study was conducted on a municipal level and included 1945 walkers, which were more than those in the previous studies.

Most previous studies that used pedometers to collect information were conducted face-to-face or by manual input, limiting the sample size from which information can be collected. Moreover, most studies were conducted on relatively small populations. Takaishi City operated the program using a system that utilized information and communication technology. In this study, the use of activity meters equipped with Felica simplified the collection of step counts, making it possible to research on a municipal scale. Using this automated system, participants could bring their pedometers to upload sites (registration terminals) located throughout the city and register their step counts, making it possible for a small number of staff members to manage a large number of participants.

Previous literature includes reports on other instances of HPFI. The possibility of decreasing intervention effects over time after the intervention period has been reported in meta-regressions involving various health promotion interventions, emphasizing the importance of continuing to exercise after the intervention period ends[11,13,16-18]. It has also been reported that the effect of a single incentive, such as points awarded for a health checkup, as well as behavioral change, is unlikely to be sustain[19]. This HPFI-based walking promotion program was implemented for two years and six months, from April 2016 to March 2019. Citizens were given incentives based on the number of steps they took daily but were not penalized for not registering their steps. Therefore, participants were expected to inevitably register their steps less frequently as their interest in the program waned; however, in the end, 86.4% of the participants registered their steps on more than 80% of the days during the year, indicating a very high participation rate. The results also suggest that the HPFI is effective in maintaining high retention rates for relatively long-term interventions. The total participation period depended on the registration start date; hence, the analyses were limited to only 12 months from the registration start date.

This study has certain limitations. As the participants voluntarily chose to participate in the intervention, the results may not apply to the general population. Additionally, although we gave as much consideration as possible to the analysis methods, we cannot rule out the possibility that the lack of data during matching may have resulted in an inadequate adjustment for confounding factors. We could not prove a causal relationship between the number of steps taken and the reduction in medical costs owing to the lack of data on the number of steps taken by those who did not participate in the program. Although HPFI has been shown to be an effective approach for promoting exercise among the health-insensitive population, this study did not collect information on the extent to which the walking group included the health-insensitive population. However, this study was not able to collect information on the extent to which the walking group included people who were indifferent to their health. It has not been possible to determine whether the reduction in medical costs in this program was due to the participation of the health-insensitive and disease-prevention groups, but it is hoped that future studies will shed more light on the effects of the HPFI.

This study's results suggest that a walking promotion program with an HPFI could help reduce healthcare costs. For incentive programs to be effective, the rewards must be appealing to the participants. If the rewards are too small, the program will not work. Conversely, the larger the rewards, the higher the program expenses paid as rewards to the participants. This program's incentives were based on the HPFI guidelines from the MHLW as well as incentives granted by similar policies implemented in Japan. With program context differing widely from region to region and country to country, there is a need for future investigations to inform the selection of appropriate incentive schemes for programs offered in other regions and countries.

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Clinical Significance of the AID Classification in Diabetic Foot Ulcers: Awareness of Arteriopathy, Bacterial Infection, and Foot Deformity

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Abstract

Background

This single-center retrospective study aimed to investigate the impact of our novel AID classification, based on arteriopathy, bacterial infection, and foot deformity, on wound healing in patients with diabetic foot ulcers (DFUs).

Methods

This study included 115 consecutive patients with 129 limbs who were hospitalized for DFU management. The presence of arteriopathy, bacterial infection, and foot deformity was scored as one point each, and wound severity was graded as 1-3. The wound healing rates at 12 months were evaluated. Comprehensive treatment including revascularization, debridement, or offloading was implemented based on the AID concept.

Results

Arteriopathy was observed in 49.6% of patients with DFUs. A total of 82.8% of patients with arteriopathy had DFUs complicated by both bacterial infection and foot deformity; however, 10.9% were complicated by either one. Approximately 14% of patients underwent major amputations. The Kaplan-Meier wound healing curves were significantly ($p=0.002$) different among patients with AID scores of 1, 2, and 3; however, the wound healing rates at 12 months were 89%, 90%, and 88%, respectively.

Conclusions

Diabetic arteriopathy is commonly complicated by bacterial infections of of DFUs and foot deformities. The AID classification effectively stratified the wound healing speed. Furthermore, AID concept-based comprehensive treatment achieved a wound healing rate of approximately 90%.

Key Words: Peripheral artery disease; Diabetes; Wound healing

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Introduction

Diabetes mellitus (DM) is increasing in burden globally, particularly in Asia[1]. DM poses a significant challenge in clinical practice because it changes the nature of peripheral artery disease (PAD) and increases the susceptibility to bacterial infections and foot deformities[2]. Diabetic foot ulcers (DFUs) are an amalgamation of arteriopathy, bacterial infection, and foot deformity[3]. Therefore, a multidisciplinary approach, encompassing vascular and wound management, is indispensable for the treatment of diabetic PAD and DFU.

To date, traditional classification systems have been used in the study of PAD and DFUs, such as Fontaine[4], Rutherford[5], Meggitt-Wagner[6], SINBAD[7], University of Texas[8], Kobe[9], and WIfI[10]. However, the Fontaine and Rutherford systems focus only on the severity of ischemia, while the Meggitt-Wagner, SINBAD, University of Texas, Kobe, and WIfI systems lack a perspective on foot deformities. There is an increasing opportunity to treat patients with DFU in vascular practice. Thus, a simple, easy-to-use, and clinically relevant classification system for DFUs is urgently needed. Given the individual significance of arteriopathy, bacterial infection, and foot deformity in wound management, we recently proposed the Arteriopathy, bacterial Infection and foot Deformity (AID) classification, which has a maximum possible score of 3 points[2]. We aimed to assess the impact of the AID classification on wound healing at 12 months in patients with DFUs.

Methods

This single-center retrospective study included 115 consecutive patients (129 limbs) who were hospitalized for DFU treatment between January 2015 and December 2016. The study protocol was approved by the Medical Ethical Committee of our hospital (No: TGE01275-004; August 9, 2019) and was conducted in accordance with the Declaration of Helsinki. DFU was defined as foot ulcers in patients with DM. Diabetes mellitus was diagnosed based on the American Diabetes Association criteria or the use of antidiabetic agents or insulin[11]. Blood glucose and subsequent fasting blood sugar levels were evaluated at admission. Hyperglycemia was controlled with insulin or an oral hypoglycemic agent, at the discretion of the managing endocrinologist. Wound healing was defined as the complete epithelialization of the wound.

AID classification and scoring

The AID classification comprises three elements: arteriopathy, bacterial infection, and foot deformity. Each component was scored as 0 or 1, and the wound severity was graded with an AID score of 0 (none of the components) to 3 (all components). Representative cases of AID 1, 2, and 3 are shown in Figure 1.

Arteriopathy scoring: To assess the severity of arteriopathy-induced microcirculation disorder, the foot's skin perfusion pressure (SPP) (SensiLase™ PAD3000, Vasamed Inc., Minnesota, USA) was measured. Multiple measurements were obtained for the dorsal and plantar aspects of the affected foot. The lowest values were selected. According to Castronuovo et al[12], an SPP of ≧40 mm Hg at the proximal wound margin is associated with ≧90% likelihood of wound healing in critically ischemic limbs. Thus, arteriopathy was defined as SPP ≧40 mm Hg, scoring 1 point.

Bacterial infection scoring: According to the guidelines of the Infectious Disease Society of America (IDSA)[13] and the International Working Group on the Diabetic Foot (IWGDF)[14], bacterial infection of the wound was defined as the presence of two or more clinical signs (local swelling or induration, erythema >0.5 cm^2 around the wound, local tenderness or pain, increased warmth, and purulent

Figure 1. Representative cases with AID scores of 1, 2, and 3. The simple AID classification can aid in dividing a broad spectrum of diabetic foot ulcers (DFUs) in clinical practice.

discharge) and no other cause for the inflammatory response of the skin (e.g., trauma, gout, acute Charcot's neuro-osteoarthropathy, fracture, thrombosis, or venous stasis). The presence of bacterial infection was scored 1 point.

Foot deformity scoring: According to the guidelines of IWGDF[15], foot deformity was defined as alterations or deviations from the normal shape or size of the foot, such as hammer, mallet, or claw toes, hallux valgus, prominent metatarsal heads, pes cavus, pes planus, pes equinus, or consequences of Charcot's neuro-osteoarthropathy, trauma, amputations, other foot surgery, and other causes. The presence of foot deformities was scored 1 point.

Comprehensive treatment

A comprehensive treatment was considered based on the AID concept. Medical treatment, including antiplatelet therapy or clinically driven antibiotics, and wound care were essential. The need for invasive treatment was determined by a team consisting of a cardiologist, vascular surgeon, and plastic surgeon based on the risks and benefits of the procedure. Endovascular or open revascularization was considered for arteriopathy. Debridement of the infected wound and offloading (knee-high or ankle-high offloading devices, fitting footwear, or surgical offloading interventions) for the foot deformity were implemented based on the principles of good standard care and at an experienced plastic surgeon's discretion[16].

Statistical analysis

Continuous data of the three groups were compared using one-way analysis of variance (ANOVA) followed by Bonferroni's post-hoc test. Categorical data of the three groups were compared using the chi-square or Fisher's exact tests, as appropriate. Patients with different AID scores in the left and right feet were analyzed using the AID score of the first limb. Wound healing, amputation-free survival, and overall survival rates were calculated using Kaplan-Meier analysis and compared using the log-rank test. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS (version 21; IBM Corp., Armonk, NY, USA).

Results

The patient characteristics are shown in Table 1. All patients scored one or higher on the AID scale. The prevalence of coronary artery disease and hemodialysis differed significantly among the three groups ($p=0.003$). In particular, their prevalence was significantly higher in those with AID 3 than in those with AID 1 and 2.

The foot characteristics are shown in Table 2A. Arteriopathy was observed in 49.6% of DFUs,

Table 1. Patient Characteristics

Variable	Overall, n=115	AID score 1, n=19	AID score 2, n=49	AID score 3, n=47	p value
Age, yrs	65.9±12.5	68.5±14.8	62.6±13.0	68.3±10.3	0.05
Male, n (%)	82 (71.3)	12 (63.2)	32 (65.3)	38 (80.9)	0.168
Hypertension, n (%)	83 (72.2)	15 (78.9)	33 (67.3)	35 (74.5)	0.57
Diabetes mellitus, n (%)	115 (100)	19 (100)	49 (100)	47 (100)	
Random blood glucose (mg/dL)	194±91	173±76	213±100	183±85	0.145
HbA1c (%)	7.4±2.0	7.0±1.5	7.9±2.4	6.9±1.5	0.029
Insulin use, n (%)	56 (48.7)	9 (47.4)	26 (53.1)	21 (44.7)	0.708
Dyslipidemia, n (%)	27 (23.5)	7 (36.8)	8 (16.3)	12 (25.5)	0.183
Smoking history, n (%)	62 (53.9)	10 (52.6)	30 (61.2)	22 (46.8)	0.364
Coronary artery disease, n (%)	34 (29.6)	4 (21.1)	8 (16.3)	22 (46.8)*	0.003
Cerebrovascular disease, n (%)	17 (14.8)	3 (15.8)	4 (8.2)	10 (21.3)	0.193
Hemodiaylsis, n (%)	42 (36.5)	2 (10.5)	15 (30.6)	25 (53.2)	0.003

*$p<0.05$ for AID 2 vs 3.

bacterial infection in 87.6%, and foot deformities in 86.8%. A history of a minor amputation was observed in 15.5% (20/129 limbs) of the limbs overall and in 17.9% (20/112 limbs) of the limbs with a foot deformity. Furthermore, AID 3 and AID 2 accounted for 82.8% and 10.9% of patients with arteriopathy, respectively (Fig. 2). There were significant differences in the wound location ($p=0.003$), ankle-brachial index ($p<0.001$), and SPP ($p<0.001$) among the three groups. There was no significant

Table 2A. Foot characteristics

Variable	Overall, n=129	AID score 1, n=22	AID score 2, n=54	AID score 3, n=53	p value
Right, n (%)	74 (57.4)	14 (63.6)	32 (59.3)	28 (52.8)	0.644
Wound location toe/body/heel/crural/extensive, n (%)	57(44)/38 (30)/ 12 (9)/9 (7)/ 13 (10)	5 (23)/7 (32) /0 (0)/6 (27)/ 4 (18)	27 (50)/15 (28)/ 5 (9)/2 (4)/ 5 (9)*	25 (47)/16 (30) /7 (13)/1 (2)/ 4 (8) †	0.003
Arteriopathy, n (%)	64 (49.6)	4 (18.2)	7 (13.0)	53 (100) † ‡	<0.001
Bacterial infection, n (%)	113 (87.6)	9 (40.9)	51 (94.4)*	53 (100) †	<0.001
Foot deformity, n (%)	112 (86.8)	9 (40.9)	50 (92.6)*	53 (100) †	<0.001
Ankle brachial index	0.85±0.23	0.97±0.22	0.96±0.21	0.74±0.20 † ‡	<0.001
Dorsal skin perfusion pressure, mm Hg	44±23	59±29	60±17	29±13 † ‡	<0.001
Plantar skin perfusion pressure, mm Hg	43±24	65±39	54±17	31±15 † ‡	<0.001

*$p<0.05$ for AID 1 vs 2, †$p<0.05$ for AID 1 vs 3, ‡$p<0.05$ for AID 2 vs 3.

Table 2B. Breakdown of comprehensive treatment

Variable	Overall	AID score 1	AID score 2	AID score 3	p value
Revascularization for arteriopathy, n (%)	45 (70.3)	1 (25)	4 (57.1)	40 (75.5)	0.075
Debridement for bacterial infection, n (%)	113 (100)	9 (100)	47 (92.2)	53 (100)	0.08
Offloading for foot deformity, n (%)	101 (90.2)	9 (100)	47 (94)	45 (84.9)	0.177

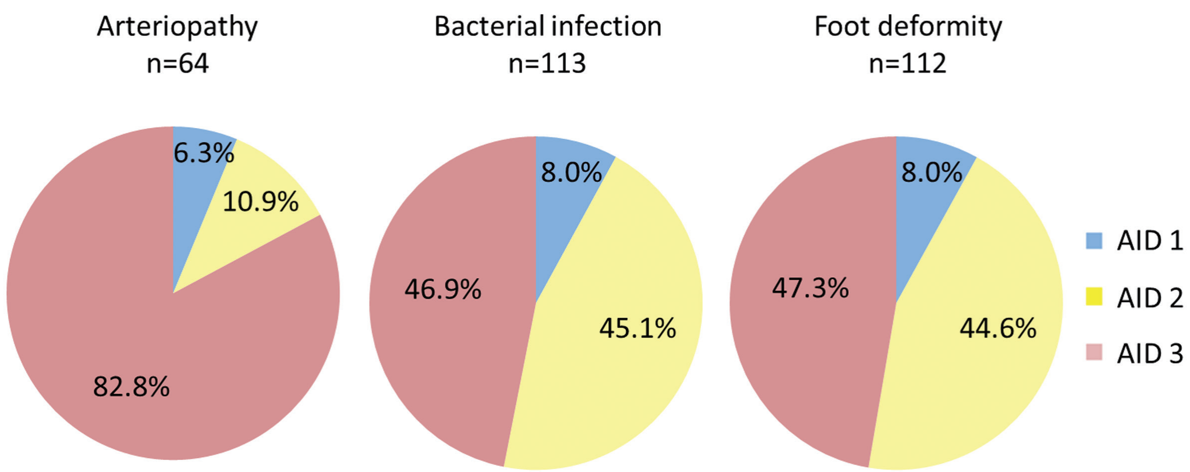
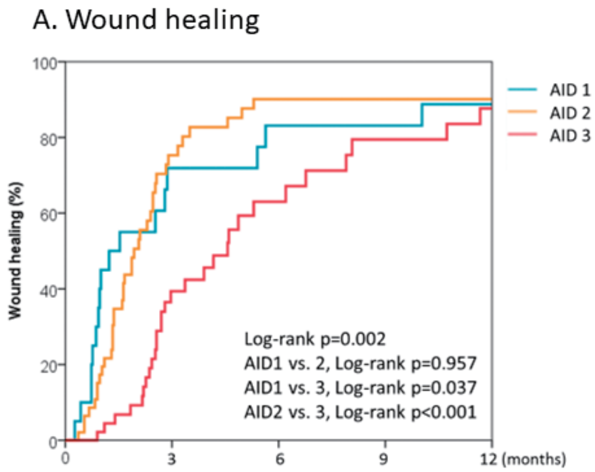
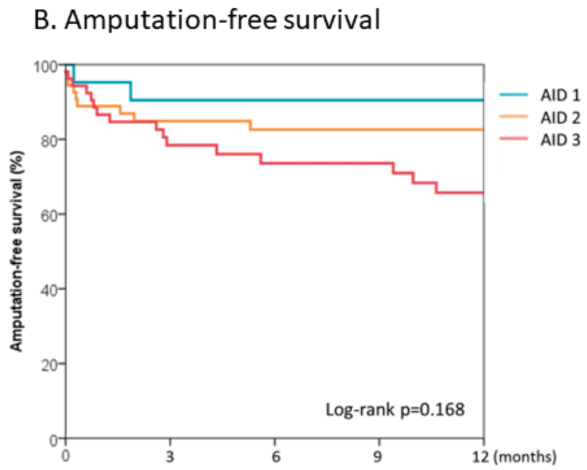


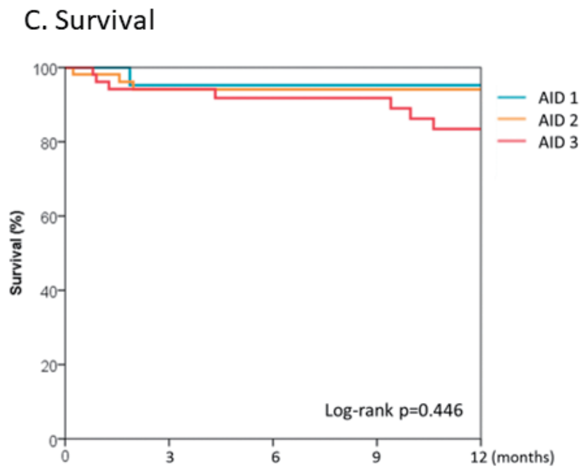
Figure 2. AID scores in arteriopathy, bacterial infection and foot deformity.



	Months	1	3	6	9	12
AID 1	Number at risk	11	5	3	3	2
	Percentage	45%	72%	83%	83%	89%
AID 2	Number at risk	38	10	3	3	2
	Percentage	17%	75%	90%	90%	90%
AID 3	Number at risk	44	21	9	5	3
	Percentage	2%	39%	63%	79%	88%



	Months	1	3	6	9	12
AID 1	Number at risk	20	18	16	16	16
	Percentage	95%	91%	91%	91%	91%
AID 2	Number at risk	46	42	35	33	32
	Percentage	89%	85%	83%	83%	83%
AID 3	Number at risk	45	37	30	28	25
	Percentage	87%	78%	74%	74%	66%



	Months	1	3	6	9	12
AID 1	Number at risk	21	18	16	16	16
	Percentage	95%	95%	95%	95%	95%
AID 2	Number at risk	50	46	40	38	37
	Percentage	98%	94%	94%	94%	94%
AID 3	Number at risk	50	43	35	33	30
	Percentage	96%	94%	92%	92%	83%

Figure 3. Kaplan-Meier estimates of A) wound healing, B) amputation-free survival, and C) overall survival.

difference in the intensity of revascularization ($p=0.075$), debridement ($p=0.08$), or offloading ($p=0.177$) among the three groups (Table 2B). Even in the AID 3 group, revascularization was performed in 75.5% of patients with arteriopathy, debridement in 100% of patients with infected wounds, and offloading in 84.9% of patients with foot deformities.

Seventeen patients (14.8%) died and 18 limbs (14%) were amputated during the study period. According to Kaplan-Meier analysis, wound healing was significantly ($p=0.002$) different among the AID scores of 1, 2, and 3 (Fig. 3A). Patients with AID 3 exhibited the most delayed wound healing ($p=0.037$ for AID 1 vs 3, $p<0.001$ for AID 2 vs 3). With AID-based comprehensive management, wound healing rates of those with AID scores of 1, 2, and 3 at 12 months were 89%, 90%, and 88%, respectively. The amputation-free survival rate of AID 3 was 66% at 12 months, which was the lowest among the three groups, without being statistically significant (Fig. 3B). The overall survival stratified by the AID score was analyzed using the Kaplan-Meier method. The overall survival rate was 83% at 12 months, which was the lowest for AID 3, without being statistically significant (Fig. 3C).

Discussion

The main findings of this study were as follows: 1) arteriopathy was observed in 49% of DFUs; 2) 10.9% of arteriopathy cases were complicated by bacteria-infected wounds or foot deformities, and 82.8% of arteriopathy cases were complicated by both; 3) the intensity of revascularization for arteriopathy, debridement for infected wounds, and offloading for foot deformities was comparable among the AID score groups; and 4) Kaplan-Meier estimates stratified by AID scores demonstrated that those with AID scores of 3 exhibited the most delayed wound healing, but the wound healing rates at 12 months was comparable (89% in AID 1, 90% in AID 2, and 88% in AID 3) .

Considerable attention should be paid to arteriopathy, even in patients with DFUs. Traditional classifications for the assessment of wound severity, such as Fontaine[4)] and Rutherford[5)], are based only on arteriopathy. However, multiple disorders including arteriopathy, bacterial infection, neuropathy, foot deformity, and decubitus are associated with DFUs. To date, Meggitt-Wagner[6)], SINBAD[7)], University of Texas[8)], Kobe[9)], and WIfI[10)] are available for wound assessment, given the importance of several factors in DFUs. The Meggitt-Wagner classification is based on the depth and area of the wound. The University of Texas and WIFI classifications are based on the depth or area of the wound, arteriopathy, and bacterial infection. The Kobe classification focuses on neuropathy, bacterial infection, and arteriopathy. The SINBAD classification is based on neuropathy, wound location, depth or area of the wound, arteriopathy, and bacterial infection. However, these classifications are not frequently utilized in clinical practice because of their complexity. Furthermore, these classifications underappreciate foot deformity, which is affected by neuropathy and a history of amputation[17)]. Thus, a simple, easy-to-use, and clinically relevant classification of DFUs is urgently needed in vascular medicine practice. Here, we propose the AID classification based on arteriopathy, bacterial infection, and foot deformity.

In the present study, approximately half of the patients with AID 3 had coronary artery disease and end-stage renal disease requiring hemodialysis. This suggests that those who scored 3 on the AID classification were the most challenging subset of patients in clinical practice. Arteriopathy-induced microcirculation disorder was observed in 49.6% of patients with DFUs. Furthermore, AID 3 and AID 2 accounted for 82.8% and 10.9% of patients with arteriopathy, respectively. These findings suggest that approximately half of the patients with DFUs were affected by diabetic arteriopathy, and >90% coexist with bacterial infections and/or foot deformities. There was no significant difference in the intensity of revascularization for arteriopathy, debridement for bacterial-infected wounds, or offloading for foot deformity among patient with AID scores of 1, 2, and 3 (Table 2B). These findings suggest that the AID concept-guided comprehensive treatment should be practiced in any severity of DFUs.

Studies that have investigated the relationship between wound classification and wound healing are limited. Alexandrescu et al reported a significantly lower incidence of wound healing at 12 months using the Wagner grading; the incidence was 67% for grade 3-4 wounds, and 89% for grade 1-2 wounds[18]. Weaver et al reported that WIfI stage 3/4 wounds had a lower incidence of healing at 12 months than WIfI stage 1/2 wounds (57.2% vs 77.3%) did[19]. According to a study by Ince et al, which used the SINBAD classification, a score of ≧3 was associated with an increase in healing time[7]. In the present study, Kaplan-Meier estimates demonstrated different wound healing speeds among those with AID scores of 1, 2, and 3. Patients with AID 3 exhibited the most delayed wound healing. However, with an AID-based multidisciplinary treatment approach (revascularization in 76%, debridement in 100%, and offloading in 85%), the wound healing rate at 12 months among the three groups was comparable (88%, 89%, and 90%, in those with AID 3, AID 1, and AID 2, respectively). These findings suggest that the AID score can predict wound healing speed and that an AID-based comprehensive treatment could facilitate wound healing in approximately 90% of the most challenging DFUs. Focusing on each component of the AID classification facilitates treatment planning in clinical practice. Arteriopathy requires revascularization, bacterial infection requires debridement, and foot deformity requires offloading. AID concept-guided comprehensive treatment can ensure optimal treatment, which may result in similar wound healing rates for AID 1 and AID 2, and similar amputation-free survival rates for AID 2 and AID 3 at 12 months follow-up.

Our study had several limitations. First, it was retrospective observational study, which may be affected by confounding factors. Second, a relatively small number of patients were enrolled in this study. Third, the indications, timing, and intensity of revascularization, debridement, and offloading might have been heterogeneous. Finally, the AID classification does not consider the DFU complexity, such as the size, depth, or location of wounds, which might be associated with wound healing. The AID classification is intended to expeditiously appreciate the importance of the three essential components in the management of contemporary DFUs. Larger prospective studies are needed to confirm and externally validate the clinical significance of AID classification.

In conclusion, our study showed that diabetic arteriopathy is commonly complicated by both infected wounds (bacterial) and foot deformities in the context of DFUs. The AID classification was clinically relevant for wound healing stratification. Furthermore, AID concept-guided comprehensive treatment could facilitate wound healing in approximately 90% of all patients with DFUs at 12 months.

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