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당뇨병전기 성인의 신체운동과 류마티스 발생률

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Physical Activity and Prevalence of Rheumatoid Arthritis in Korean Adults with Prediabetes in the 2009-2013 National Health Cohort Study

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ABSTRACT

Background: Rheumatoid arthritis is highly prevalent in overweight patients with type 2 diabetes mellitus and can be reduced by physical activity via altered proinflammatory parameters. However, the association between the frequency of physical activity and the prevalence of rheumatoid arthritis in prediabetic patients remains unclear and was evaluated in this study. **Methods:** Utilizing the Korean National Health Insurance Sharing Service database, 58,391 adults, who met the research criteria and underwent a general medical check-up between 2009 and 2013, were selected for this study. To analyze the data, a logistic regression with a proc survey logistic procedure was used. **Results:** The study revealed that the cumulative rheumatoid arthritis prevalence was lower in prediabetic patients compared to that in the control group (OR, 0.64; 95% CI, 0.483–0.840; p=0.001). More frequent physical activity (≥3 days/week) was significantly associated with a reduced rheumatoid arthritis prevalence in both groups (OR, 0.28; 95% CI, 0.039–0.521; p=0.044 vs. OR, 0.15; 95% CI, 0.063–0.237; p=0.007). Additionally, a 3.8-fold higher risk of rheumatoid arthritis development was observed in prediabetic adults with less frequent baseline physical activity (≤2 days/week). Overall, in prediabetes, the prevalence of rheumatoid arthritis was associated with the frequency of physical activity and not with the fasting plasma glucose levels. **Conclusion:** More frequent physical activity is associated with a low risk of developing rheumatoid arthritis in prediabetic patients. Thus, further studies are needed to confirm the clinical outcomes of frequent physical activity in rheumatoid arthritis prevention and control.

KEYWORDS: Rheumatoid arthritis, prediabetic patients, fasting plasma glucose, physical activity

Prevalence of rheumatoid arthritis (RA) in patients with type2 diabetes mellitus (T2DM) and prediabetes was known to be higher than that of general population,[1-5] further increasing its risk for disease prevalence among adults with advanced age,[6-7] long disease duration,[6-7] and poor glycemic control.[1-2] RA is an autoimmune disease that causes chronic inflammation in the area surrounding musculoskeletal or synovial joints and connective tissues.[1-3,7-8] T2DM is significantly associated with bone, cartilage, ligament, and tendon damage.[2-3] RA development results from a multifactorial interaction of genes and the environment, including the abnormal response of anti-citrullinated protein antibodies (ACPAs) to antigens. These interactions result in synovial inflammation, bone, cartilage, and tissue damage, composed of pro-inflammatory cytokines.[4-5,8-9] Pro-inflammatory cytokines[5,9] such as interferon-gamma (IFN-γ), interleukin (IL)-1ß, IL-2, IL-5, IL-7, IL-8, and TNF-α, granulocyte macrophage-colony stimulating factor (GM-CSF), are also known to be high in overweight patients with prediabetes.[4-5,9]

With biological pharmacotherapies, modifiable behavior such as physical activity has been shown to induce the anti-inflammatory myokine IL-6,[10] which induces the release of

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IL-1 inhibitor and IL-10, a natural inhibitor of IL-1β,[11] resulting in decreased disease severity and inflammation in adults with RA, obesity, prediabetes and T2DM.[11-12] Physical activity significantly improved the joint motility, strength and functional ability in patients with either prediabetes or RA via altered pro-inflammatory muscle cytokines[13-14] and reduced the blood glucose levels, further lowering the risk for T2DM.[15]

Unfortunately, 71% of adults with RA are unable to maintain normal physical activity,[16-19] owing to arthritis related barriers to physical activity. Joint pain, joint stiffness and deformity reduced the engagement of patients with RA in physical activity.[17,20] 56.5% of adults with both RA and prediabetes are physically inactive.[20]

According to a study by the Diabetes Prevention Program (DPP), physical activity and weight loss interventions can reduce the risk of diabetes by 58%.[21-23] Physical activity and glycemic control may be beneficial in the inhibition of RA progression as well as in the reduction of its prevalence in patients with prediabetes.[24] However, T. Yates study reported that intensive physical intervention or previous physical activity level did not significantly reduce 2-h post prandial or fasting blood glucose levels[25] in adults with prediabetes and the expression of inflammatory markers[14] in patients with either RA or prediabetes. Therefore, the association between the frequency of physical activity and prevalence of RA in adults with prediabetes is unclear. Thus, this study investigated whether the frequency of physical activity was associated with RA prevalence in Korean adults with prediabetes

Methods

Data sources

This study retrospectively evaluated a cohort of 264,978 adults, aged 50 to 79 years, using their medical records extracted from the centralized database of the Korean National Health Insurance Sharing Service (KNISS). Adults who met the research criteria and visited health institutions for general medical examination at least biannually in the regional areas of South Korea between January 01, 2009, and December 31, 2013, were included. Whereas subjects who were diagnosed with T1DM or T2DM, those no longer under follow-up, and those who had only one laboratory data parameter for FPG and self-questionnaire item for physical activity at baseline and during the biannual visits over the 5-year follow-up period were excluded. The data from the cohort database (DB) provided by KNISS included: individual qualification criteria DB, medical treatment DB, and health examination DB. With non-personally identifiable information only used for research, subjects were selected based on a table that was created using the database link, with person identification as a joint key according to the KNISS algorithm. Korean Classification of Disease (KCD) codes were used to identify the main sickness and sub sickness that were diagnosed by physicians. The Institutional Review Board (IRB: No. 2019-03-19-03) of Duksung Women's University approved the research protocol with a nonhuman designation, and the study was conducted in accordance with the Declaration of Helsinki.

Definition

Medical conditions were defined using KCD codes, with T1DM/T2DM subjects identified using the code E10-E11.9. Prediabetes was defined as a fasting plasma glucose (FPG) level between 100 and 125 mg/dL and the absence of a T1DM/T2DM diagnosis. RA was identified using KCD codes as follows: RA (M05.0-M05.9), other RA (M06.0.-M06.0, M06.2-M06.3, M06.8-M06.9), and other chronic postrheumatic arthropathies (M12.0-M12.0, M12.3-M12.3). RA medications, NSAIDs, and other anti-rheumatic drugs were identified using the Health Insurance Review and Evaluation Center Pharmaceutical Standards Information code 100901ACH~217004ASY. Past medical history was identified as hypertension (HTN), heart disease (HD), and hyperlipidemia, whereas family history was identified as T2DM, HTN, and HD.

Identification of RA

To evaluate RA prevalence based on FPG level at the beginning of the study, subjects were divided into two subgroups: those with impaired FPG (100-125 mg/dL) and those with normal FPG (<100 mg/dL), using the American Association of Clinical Endocrinologists (AACE) clinical guidelines (2018). RA prevalence was defined as the development of confirmed RA or chronic postrheumatic arthropathy. Additionally, to evaluate RA prevalence based on physical activity level, subjects were divided into two subgroups: those who had physical activity ≥3 times/week for at least 20-30 min/day and those who had physical activity ≤2 times a week. In this study, the indicated RA prevalence was cumulative, given that it was difficult to distinguish new RA incidence in a particular year from the duplicated RA record that would

appear in the following year in the KNISS.

Physical activity

Physical activity, which was defined as follows: walking for at least 30 min/day, lightly bicycling for at least 30 min/day, and jogging or aerobics for at least 20 min/day was assessed using a simple measurement number in the survey questionnaire, which was sub-classified into eight numbers based on the frequency of the three activity types. The eight numbers indicated the frequency of each physical activity type/week. Subjects were given a health-related questionnaire at physical examination; the subjects self-reported their daily number of activity/week in the questionnaire, and subjects who had at least 3 days of activity/week were included in the more frequent physical activity group. Those with less than 2 days of activity/week were included in the less frequent physical activity group.

Data analysis

The medical records of the patients were sorted and analyzed by a professional statistician. To assess patient's baseline characteristics, continuous variables were analyzed using a proc univariate procedure and reported as mean (SD), whereas categorical variables were analyzed using proc survey freq and proc logistic procedures and reported as percentages. Based on stratified, clustered, and systematic sampling, Primary outcome of unadjusted RA prevalence was evaluated using a proc logistic procedure and a proc freq procedure; a logistic regression model was used for *p* values. Secondary outcome of risk of cumulative RA prevalence with regard to physical activity frequency was evaluated using a proc univariate procedure for mean and SD and a logistic regression for *p* value. Using logistic regression with a proc logistic procedure, the adjusted odds ratio of RA with regard to variables, including age, FPG, BMI, TG, LDL-C, and past medical history and family history, was performed to estimate potential confounding variables. A *p*-value <0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of prediabetic patients and patients without impaired fasting plasma glucose (IFG) were compared (Table 1). Of the 264,978 subjects in the KNISS database, 58,391 subjects were included and evaluated retrospectively. A total of 19,204 individuals were confirmed to have prediabetes, whereas 39,186 individuals were confirmed to be without IFG (control group). As shown in Fig. 1, over time, FPG levels were significantly higher in prediabetic RA patients than in the control group ($p<0.001$). A total of 301,294 individuals were excluded for the following reasons: 18,323 were T2DM patients, 19,129 discontinued follow-ups. 169,135 had missing FPG data and frequency of physical activity recorded at baseline and at bi-annual visits over the 5-year follow-up period. Regarding age, 69.0% adults in prediabetic and 72.8% adults in control group, respectively, were aged between 50 and 64 years. Family history of diabetes ($p<0.001$) and hypertension ($p=0.011$) were significantly higher in the prediabetes group compared with the control group. In addition, past medical history of hypertension ($p=0.001$) and dyslipidemia ($p<0.001$) were significantly higher in the prediabetes group than in the control group. Overall, chronic medical conditions were significantly higher in prediabetic patients than in the control group. The mean FPG level ($p<0.001$) was significantly higher in the prediabetes group than in the control group. Table 1 describes patients' baseline characteristics.

Prevalence of RA

RA prevalence was 66 (0.34%) (OR, 0.64; 95% CI, 0.483-0.840; $p=0.001$) in the prediabetes group and 211 (0.54%) in the control group, indicating that the risk of RA development was not associated with FPG level (Table 2).

Effect of frequency of physical activity on RA prevalence

The results showed that more frequent physical activity (≥3 days/week, ≥20-30 min/day) had a positive effect on cumulative RA prevalence in both the prediabetes (0.07%) and control (0.07%) groups (OR, 1.00; 95% CI, 0.561-2.064; $p=0.825$). Less frequent physical activity (up to 2 days/week) was found to be associated with increased RA prevalence in both groups (0.27% in the prediabetes vs. 0.47% in the control group, $p<0.001$) (Table 3).

Additionally, less frequent physical activity (up to 2 days/week) was associated with a 3.8~6.7 fold increase in RA prevalence in both groups (0.07%, $p=0.044$ in the prediabetes group, and 0.07%, $p=0.007$ in the control group), compared with more frequent physical activity (0.27 and 0.47% in the prediabetes and control groups, respectively) (Table 4).

Table 1. Baseline characteristics

Variables	Prediabetes (n=19,204)	Normoglycemia (n=39,186)	*p*-value
Age, y mean (%)			
50-64	13326 (69.0)	28,525 (72.8)	<.001
65-79	5879 (31.0)	10,661 (27.2)	<.001
Gender, n (%)			
Male	10256 (54.0)	17146 (43.8)	<.001
Female	8949 (46.0)	22040 (56.2)	<.001
Family history, n (%)			
Hypertension	2295 (19.1)	4171 (17.0)	0.011
Heart failure	578 (5.8)	1206 (4.9)	0.059
Diabetes	1405 (12.1)	2073 (8.5)	<.001
Past medical history, n (%)			
Hypertension	6524 (48.4)	9676 (37.1)	0.001
Heart failure	817 (6.0)	1318 (5.1)	<.001
Dyslipidemia	1261 (9.2)	1964 (7.6)	<.001
Physical activity, n (%)			
≥3days/week	3599 (18.7)	7192 (18.4)	0.072
Laboratory data, mean (±SD)			
Height (cm)	161.8 (±8.7)	159.5 (±8.5)	<.001
Weight (kg)	63.7 (±10.0)	60.9 (±9.6)	<.001
BMI (kg/m^2)	24.6 (±2.7)	23.9 (±2.9)	<.001
SBP (mmHg)	129 (±15.6)	125 (±15.4)	<.001
DBP (mmHg)	79 (±10.0)	77 (±10.0)	<.001
FPG (mg/dL)	108.3 (±7.6)	86.5 (±7.8)	<.001
Scr (mg/dL)	1.1 (±1.4)	1.0 (±1.1)	<.001
Total cholesterol (mg/dL)	204.2 (±39.2)	200.5 (±36.7)	<.001
Triglyceride (mg/dL)	150.2 (±95.0)	131.7 (±81.1)	<.001
HDL-C (mg/dL))	55.5 (±32.8)	56.1 (±32.0)	0.309
LDL-C (mg/dL)	121.0 (±42.1)	119.9 (±39.5)	0.001
Hemoglobin (g/dL)	13.9 (±1.4)	13.6 (±1.4)	<.001
Medication, n (%)	268 (2.8)	1222 (3.1)	0.066

Data are presented as mean (SD) for continuous variables and number (percentage) for categorical variables.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Scr, serum creatinine; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

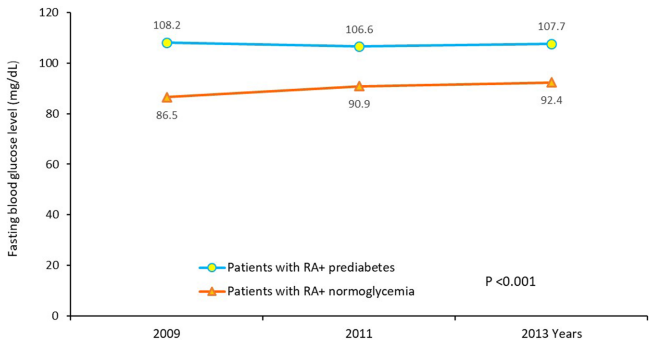

Fig. 1. Change in FPG level between adults with prediabetes and normoglycemia over time FPG level was higher in prediabetes with RA than normoglycemia with RA over time

The frequency of physical activity-adjusted risk of RA was 3.8 (95% CI, 1.601-6.199; p=0.044), which increased with less frequent physical activity in both groups. Overall, RA prevalence among Korean adults, according to the KNISS database, varied with frequency of physical activity. After adjusting for BMI, and TG and LDL-C levels and past medical history, family history, and less frequent physical activity, the analysis showed that less frequent physical activity, hypertriglyceridemia, overweight/obesity, and family history of heart disease were associated with increased risk of RA in prediabetes, only the association of less frequent physical activity was significant (Table 5).

Table 2. Unadjusted cumulative prevalence of rheumatic diseases between adults with prediabetes and control group

†Prediabetes Total case=19,204 *Rheumatic disease n (%)	§normoglycemia Total case=39,186 Rheumatic disease n (%)	Unadjusted odds ratio (95% CI) *p*-value
66 (0.34)	211 (0.54)	0.64 (0.483-0.840) 0.001

Abbreviations: CI; confidence interval.
*Rheumatoid diseases were defined by KDC code of diagnosis by physicians.
†Prediabetes was defined as fasting plasma glucose level of 100-125 mg/dL.
§Normoglycemia was defined as fasting plasma glucose level below 100 mg/dL.

Table 3. Cumulative prevalence of *rheumatic diseases according to the amount of physical activity between prediabetes group and control group

Physical exercise	†prediabetes Total=19205 n (%)	§Control group Total=39186 n (%)	OR (95% CI) *p*-value
≥3 times/week	14 (0.07)	26 (0.07)	1.00 (0.561-2.064) 0.825
≤2 times/week	52 (0.27)	185 (0.47)	0.58 (0.422-0.782) <0.001

Abbreviations: CI; confidence interval.
*Rheumatic diseases were defined as KDC code of diagnosis by physicians.
†Prediabetes was defined as fasting plasma glucose level of 100-125 mg/dL.
§control group was defined as fasting plasma glucose level below 100 mg/dL.

Table 4. Cumulative prevalence of *rheumatic diseases according to the amount of physical activity between each group

Physical exercise	Physical exercise ≥3 times/week n (%)	Physical exercise ≤2 times/week n (%)	OR (95% CI) *p*-value
†prediabetes	14 (0.07)	52 (0.27)	0.28 (0.039-0.521) 0.044
§Control group	26 (0.07)	185 (0.47)	0.15 (0.063-0.237) 0.007

Abbreviations: CI; confidence interval.
*Rheumatic diseases were defined as KDC code of diagnosis by physicians.
†Prediabetes was defined as fasting plasma glucose level of 100-125 mg/dL.
§control group was defined as fasting plasma glucose level below 100 mg/dL.

Table 5. Effect of variables on progression of rheumatic arthritis in patients with prediabetes or normoglycemia

Variables	*RA and †Prediabetes (n=19,204)	RA and §Normoglycemia (n=39,186)
	Odds Ratio 95 % CI, *p*-value	Odds Ratio 95 % CI, *p*-value
Age (years, 5 years increments)	1.05 (0.833-1.323) 0.680	1.04 (0.877-1.243) 0.630
Physical exercise (<3 times/week)	3.86 (1.601-6.199) 0.044	6.71 (3.532-9.868) 0.007
BMI (≥23 kg/m^2)	1.65 (0.538-5.036) 0.382	1.24 (0.834-1.854) 0.285
Past medical history Hypertension	1.04 (0.403-2.695) 0.933	1.05 (0.431-2.573) 0.911
Family history Cardiovascular disease	2.44 (0.737-8.079) 0.144	1.46 (0.639-3.358) 0.366
Triglyceride (≥200 mg/dL)	1.95 (0.448-8.482) 0.374	1.77 (0.756-4.150) 0.188
LDL_C (≥130 mg/dL)	0.79 (0.383-1.648) 0.536	0.70 (0.464-1.064) 0.095

Data are presented as mean (SD) for continuous variables and number (percentage) for categorical variables.
Abbreviations: BMI, body mass index; CI; confidence interval; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; Scr, serum creatinine.
*Rheumatic arthritis was defined as KDC code of diagnosis by physicians.
†Prediabetes was defined as fasting plasma glucose level of 100-125 mg/dL.
§Normoglycemia was defined as fasting plasma glucose level below 100 mg/dL.

Discussion

In this cohort observational study, the association between frequency of physical activity and RA prevalence in prediabetic adults was assessed. The results showed that the cumulative prevalence of RA was significantly lower in

prediabetic subjects with frequent physical activity (≥3 days/week). This cohort study highlights the importance of frequent physical activity in preventing the development of inflammatory RA in prediabetic adults. The prevalence of RA in the US reportedly ranges from 0.41 to 0.54%.[26] In China and Japan, it is lower, but it varies with gender and age.[27] In the present study, RA was observed in 0.07% of Korean prediabetic subjects with frequent physical activity (≥3 days/week for at least ~20-30 min/day), compared with those with less frequent physical activity. This finding suggests that the lower risk of RA development may be an evidence of the mechanism of previously observed outcomes.

Several previous studies have assessed the association between physical activity and chronic disease. In one study, the prevalence of physical inactivity and obesity among US adults with prediabetes and arthritis was found to be 56.5 and 50.1%, respectively, higher than that in adults without prediabetes and arthritis.[20] Physical inactivity is reportedly associated with the risk of progression to chronic diseases including obesity, prediabetes, T2DM, coronary heart disease, and RA.[15,21,28] Conversely, physical activity reduces pro-inflammatory markers by IL-6 production, hence inhibiting chronic disease development.[24,30] It induces IL-10-mediated anti-inflammatory response and IL-1ß inhibition.[23-24] This study confirmed the results of previous studies.

In accordance with the physical activity recommendations of the American Diabetes Association, most adults with T2DM should engage in moderate-to-vigorous intensity aerobic activity at least 3 days/week (150 min/week), with no more than 2 consecutive days without activity.[21] Because activity-induced improvement in insulin activity (decreased rapidly) is dependent on the duration and intensity of previous activity, adults should participate in aerobic activity at least 3 days/week with no more than 2 consecutive days without activity.[20,31]

As the prevalence and incidence of diabetes increase worldwide,[32] regular physical activity could play an important role in the reduction of the risk of developing of T2DM and RA in prediabetic adults.[33] Additionally, US adults with metabolic syndromes are reportedly associated with a 2-fold risk of developing T2DM and CVD.[19,34] Moreover, owing to several hypotheses, it is advisable to consider RA development in adults with obesity, as they might have metabolic syndrome (MS) and/or chronic inflammatory diseases.

The results of the Bianchi G. study showed that a high $VO2_{max}$ level was associated with both good health and morbidity prevention. It showed that a 2.5-fold higher $VO2_{max}$ variance existed in the sedentary population,[35] attributed to phenotype-individualized variation of genes for responsiveness to aerobic activity and disease susceptibility. Pharmacologically, physical activity may interact with drug efficacy and organ functions.[36] Additionally, the results of the Bianchi G study showed that physical inactivity, which is a risk factor of MS,[37] as well as dyslipidemia, hypertension, hyperglycemia, and obesity, is associated with increased risk of T2DM.[37,38] It also showed that physical inactivity is associated with reduced skeletal muscle blood flow, as well as reduced vascular endothelial nitric oxide synthase expression.[19]

Between 2009 and 2013, the prevalence of diabetes and prediabetes among Korean adults aged >30 years was 5 million (14.4%) and 8.7 million (25.3%).[40-41] RA prevalence among Korean adults aged ≥19 years was 2.0% in 2005.[42] Additionally, the Origuchi T study reported a high RA incidence (4.3%) in adults with DM and prediabetes, but low (2.0%) incidence in adults with normal blood glucose levels aged ≥46 years in Japan.[4] These studies showed a wide variation in RA prevalence, which can be attributed to the difference in their sample stratification and methods for estimating RA prevalence. The Origuchi T study[4] collected data on subjects with prediabetes, including patients on DM drug treatment. Thus, the higher RA incidence reported may be due to subject selection bias. Additionally, the Hur NW. study[42] surveyed only a major chronic disease associated with musculoskeletal diseases, individually interviewing different household members; however, patients with sub-sicknesses of musculoskeletal disease seem to be omitted from the subjects, making it difficult for the results to reflect the exact number of RA patients. Therefore, during studies, it is necessary to estimate RA prevalence by stratification of homogeneous populations. To avoid selection bias, omission bias, and interviewer bias, the present study included both main-sickness and sub-sickness codes for RA, excluded diabetic patients, and confirmed RA status in prediabetic Korean patients. Thus, the results reflect lower RA prevalence[26] among prediabetic subjects, than that reported in previous studies.

This study had some strengths. Firstly, all the data regarding frequency of physical activity, in relation to RA outcomes, were derived from large population-based survey cohort data, and frequency of physical activity was estimated using a simple frequency measurement number in the survey questionnaire.

Additionally, the collected physical activity data can be used to identify the exact frequency of physical activity and number of individuals involved. The additional benefits of using this survey questionnaire were that it minimized measurement error and the cost associated with collecting clinical data. However, it also had some limitations. Firstly, there might have been a response bias in the self-reporting of frequency of physical activity measurement,[43] to impress management.[45] Further, this study was designed to evaluate the association between RA and frequency of physical activity. Of the rheumatic conditions, neuropathic arthropathy, carpal tunnel syndrome, diffuse idiopathic skeletal hyperostosis, and tendinopathy were excluded. Thus, the RA outcomes in this study may not reflect the prevalence of other rheumatic conditions among prediabetic Korean adults.

Despite these limitations, this study supports the association that RA prevalence is lower in prediabetic adults with more frequent physical activity, compared with those with less frequent physical activity, and that lack of physical activity causes chronic diseases,[39] including diabetes, RA, and prediabetes.

Conclusion

RA prevalence is associated with frequency of physical activity and not fasting plasma glucose level in prediabetes. Over time, a sedentary lifestyle affected the development of RA in both groups. Physical activity plays an important role in the reduction of the risk of RA development in prediabetic Korean adults.

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Conflicts of Interest

The author has no institutional interest or conflicts.

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