Long-term Observational Study on Albuminuria and the Passive Extension Angle of Metacarpophalangeal Joints in Patients with Type 2 Diabetes

Yuji Aoki

Department of Internal Medicine, National Hospital Organization Matsumoto Medical Center, Japan

ABSTRACT

Background: Limited joint mobility (LJM) is often observed in diabetic patients and elderly people. Since our previous cross-sectional study indicated the association of LJM with diabetic nephropathy, a longitudinal study was performed. **Subjects and Methods:** A total of 71 patients with type 2 diabetes whose albuminuria, graded as normo- (<30 mg/g creatinine, Grade 0), micro- (30–300, Grade 1), and macroalbuminuria (>300, Grade 3), and the passive extension angle of metacarpophalangeal (MP) joints to quantitatively assess LJM were measured again 10–12 years later in 2015 were studied. **Results:** The angle of MP joints was smaller in males than in females and correlated with age in males but not in females at baseline. At follow-up, hemoglobin A1c (HbA1c) level increased, albuminuria worsened, and the angle of MP joints decreased. Binary logistic regression analysis demonstrated that the decreasing of the angle (>10°) could be predicted by male gender, age, body mass index, and duration of diabetes at baseline in patients with relatively normal angles of MP joints and that the worsening of albuminuria (progression from Grade 0 or 1 to Grade 1 or 2) could be predicted by age and use of insulin at baseline and HbA1c level at follow-up. **Conclusions:** Taken together with our previous report, it is inferred that the decreasing of the angle of MP joints is rather associated with arteriosclerosis than early diabetic nephropathy. It would be worth elucidating the relationship between LJM, diabetic nephropathy, and macrovascular disease, all of which are involved in advanced glycation end products.

Key words: Advanced glycation end products, diabetic nephropathy, limited joint mobility, type 2 diabetes

INTRODUCTION

Limited joint mobility (LJM) is often observed in diabetic patients and elderly people. The main pathologic mechanism of joint stiffness is considered to be the increase of collagen cross-linking, due to the non-enzymatic glycosylation of collagen with advanced glycation end product (AGE) formation.[1] AGEs produced by glycoxidation cause collagen-associated fluorescence, cross-linking, and stiffening, which are not necessarily the same products.[2,3] In addition, LJM is not well-defined because of the different subjects studied and the different methods used to assess it.[1,4]

We previously demonstrated in a cross-sectional study using a quantitative method to assess LJM that stiffening of connective tissue measured by the passive extension angle of metacarpophalangeal (MP) joints was associated with diabetic nephropathy and oxidative stress in elderly diabetic patients.[5] Here, a longitudinal observational study was performed to investigate the changes in the angle of MP joints and early diabetic nephropathy in patients with type 2 diabetes.

SUBJECTS AND METHODS

A total of 71 patients with type 2 diabetes whose albuminuria and the passive extension angle of MP joints were measured

again 10–12 years later in 2015 were studied in accordance with the Declaration of Helsinki ethical guidelines. Their clinical characteristics and laboratory data at baseline are shown by gender in Table 1. Significant differences between male and female were seen in smoking and drinking status and the angle of MP joints. The measurement of the angle of MP joints to quantitatively assess LJM is as in the previous report.[4] In brief, the angle was measured while subjects lifted their hands off the table with the fingers fixed flat on the table [Figure 1]. The mean of the angles measured on the right and left hands in individual subjects was used for assessment. Spot urine albumin-to-creatinine ratio was determined and graded as normoalbuminuria (<30 mg/g creatinine), microalbuminuria (30–300 mg/g creatinine), and macroalbuminuria (>300 mg/g creatinine). The baseline serum creatinine levels were <1.20 mg/dl.

Statistical analysis

The data are expressed as the mean ± standard deviation. Statistical analysis was performed using paired t-test, unpaired t-test, χ^2 test with Yates' correction, Pearson's correlation, multiple regression, or binary logistic regression, where appropriate, with a significant level at $P < 0.05$. In case of multiple or binary logistic regression analysis, gender was coded as 0 for female and 1 for male; smoking status was graded as 0 for non-smoker, 1 for ex-smoker, and 2 for current smoker; drinking status was graded as 0 for non-drinker, 1 for social or ex-drinker, and 2 for habitual drinker; the use of insulin was coded as 0 for "no" and 1 for "yes;" and albuminuria was graded as 0 for normoalbuminuria, 1 for microalbuminuria, and 2 for macroalbuminuria. Analyses were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd.).

RESULTS

As in Table 1, the passive extension angle of MP joints at baseline was significantly ($P < 0.05$) smaller in males

than in females. The angle of MP joints were significantly correlated with age in males ($r = -0.350$, $P = 0.034$) but not in females ($r = 0.022$, $P = 0.903$). Table 2 shows multiple regression analysis of the angle of MP joints or the grade of albuminuria as a target variable at baseline. The partial regression coefficient for use of insulin ("yes") was only significant ($P < 0.05$) when the grade of albuminuria was set as a target variable. The best fitting multiple regression equation by the stepwise method with $P = 0.2$ was the angle of MP joints = $-8.496 \times$ male gender ($P = 0.021$) $-0.389 \times$ age ($P = 0.062$) $+ 5.125 \times$ grade of albuminuria ($P = 0.134$) $+ 76.065$ (adjusted $R^2 = 0.103$, $P = 0.016$) and the grade of albuminuria = $0.011 \times$ age ($P = 0.116$) $+ 0.034 \times$ body mass index ($P = 0.056$) $+ 0.312 \times$ use of insulin ($P = 0.054$) $+ 0.006 \times$ angle of MP joints ($P = 0.159$) -1.503 (adjusted $R^2 = 0.088$, $P = 0.038$). Data assessed at follow-up in comparison with those at baseline are shown in Table 3. There were significant differences between them in hemoglobin A1c (HbA1c) level, albuminuria, and angle of MP joints; HbA1c level increased, albuminuria worsened, and the angle of MP joints decreased at follow-up.

Excluding two patients with macroalbuminuria at baseline, the remaining patients were divided into two groups by "yes" or "no" for the worsening of the
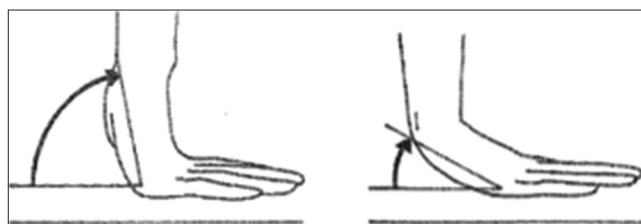
Figure 1: The method for measuring the passive extension angle of metacarpophalangeal joints while subjects lift their hands off the table with the fingers fixed flat on the table

Table 1: Clinical characteristics of type 2 diabetic patients at baseline		
	Male	**Female**
n	37	34
Age (years)	62.6±9.0	62.6±8.9
Body mass index (kg/m²)	24.2±3.2	23.6±3.9
Non-/ex-/current smoker (n)	10/15/12	29/1/4**
Non-/social or ex-/habitual drinker (n)	3/18/16	28/4/2**
Mean blood pressure (mmHg)	99.1±10.9	96.6±11.0
Duration of diabetes (years)	10.5±8.0	12.9±9.8
HbA1c level (%)	7.6±0.9	7.5±1.0
Use of insulin (n)	7	6
Normo-/micro-/macroalbuminuria (n)	25/11/1	22/11/1
Extension angle of MP joints (degrees)	45.0±18.0	53.7±12.3*

Mean±SD; *P<0.05, **P<0.01 by unpaired t test or χ^2 test with Yates' correction, MP: Metacarpophalangeal, HbA1c: Hemoglobin A1c, SD: Standard deviation

Table 2: Multiple regression analysis of the passive extension angle of MP joints or the grade of albuminuria as a target variable at baseline

Target variable	Angle of MP joints		Albuminuria	
Explanatory variables	*b* (95% CI)	*P* value	*b* (95% CI)	*P* value
Male gender	−7.794 (−19.154, 3.567)	0.175	−0.048 (−0.438, 0.341)	0.805
Age	−0.383 (−0.858, 0.113)	0.130	0.013 (−0.003, 0.030)	0.108
Body mass index	−0.095 (−1.313, 1.124)	0.877	0.029 (−0.011, 0.070)	0.153
Smoking status	3.212 (−2.587, 9.011)	0.272	−0.044 (−0.242, 0.153)	0.654
Drinking status	−2.405 (−9.187, 4.377)	0.481	0.051 (−0.179, 0.280)	0.661
Mean blood pressure	−0.012 (−0.403, 0.380)	0.953	0.001 (−0.012, 0.015)	0.843
Duration of diabetes	0.145 (−0.387, 0.675)	0.588	−0.010 (−0.028, 0.007)	0.244
HbA1c level	−0.883 (−5.139, 3.373)	0.680	−0.017 (−0.161, 0.127)	0.812
Use of insulin	0.507 (−10.638, 11.653)	0.175	0.389 (0.026, 0.751)	0.036
Albuminuria	5.303 (−2.227, 12.833)	0.175	–	–
Angle of MP joints	–	–	0.006 (−0.003, 0.015)	0.164
Constant	82.680		−1.400	

Categorical variables were coded as in the "statistical analysis" section, *b*: Unstandardized partial regression coefficient, CI: Confidence interval. MP: Metacarpophalangeal, HbA1c: Hemoglobin A1c

Table 3: Clinical and laboratory data assessed at baseline and follow-up

	Baseline	Follow-up
n	71	71
Age (years)	62.6±8.9	74.1±8.9**
HbA1c level (%)	7.5±0.9	7.9±1.1*
Use of insulin (n)	13	17
Normo-/micro-/macroalbuminuria (n)	47/22/2	38/21/12*
Extension angle of MP joints (degree)	49.2±16.0	39.4±16.4**

Mean±SD; *$P<0.05$, **$P<0.01$ by paired *t* test or χ^2 test with Yates' correction, MP: Metacarpophalangeal, HbA1c: Hemoglobin A1c, SD: Standard deviation

grade (0 or 1–1 or 2) of albuminuria at follow-up. Table 4 shows clinical and laboratory data at baseline and follow-up, including interval changes (per year) in the extension angle of MP joints in two groups. Patients with the worsening of albuminuria were significantly ($P < 0.05$) older than patients without and tended to have smaller angles of MP joints and higher frequencies of insulin use at baseline and follow-up. When the worsening of albuminuria (1 for "yes" and 0 for "no") was predicted by binary logistic regression analysis using the stepwise method with $P = 0.2$, partial regression coefficients were significant ($P < 0.05$) for age, duration of diabetes, use of insulin at baseline, and HbA1c level at follow-up [Table 5]. The explanatory variables of the extension angle of MP joints at baseline and follow-up and its interval change were excluded.

When patients were divided by the median value of the angle of MP joints at baseline (45° for male and 50° for female), patients with smaller angles of MP joints than the median value tended to have a higher frequency of the worsening of albuminuria (12/24 [50.0%]) than the other patients (12/45 [26.7%]) ($P = 0.053$, χ^2 test). Among patients with the angle of MP joints at baseline ≥45° for males and 50° for females, the worsening of the angle of MP joints, which was regarded as the decrease of the angle >10° at follow-up (1 for "yes" and 0 for "no"), was predicted by binary logistic regression analysis using the stepwise method with $P = 0.2$. Partial regression coefficients were significant ($P < 0.05$) for the duration of diabetes and body mass index at baseline [Table 6]. The explanatory variables of albuminuria at baseline and follow-up and the worsening of albuminuria were excluded.

DISCUSSION

In general, joint ranges of motion are affected by age and gender, depending on the segments of joints.[6,7] The present study in patients with type 2 diabetes, similar to the results

Table 4: Clinical and laboratory data at baseline and follow-up with interval changes in the passive extension angle of MP joints in patients with or without the worsening of albuminuria

Worsening of albuminuria Normo-/Micro-/Macroalbuminuria (n) at baseline at follow-up	No 45 34/11/0 37/8/0	Yes 24 13/11/0 0/13/11
Baseline data		
Male/female	22/23	14/10
Age (years)	60.7±8.5	65.8±9.1*
Body mass index (kg/m^2)	23.9±3.6	23.8±3.3
Non-/ex-/current smoker (n)	25/11/9	12/5/7
Non-/social or ex-/habitual drinker (n)	20/16/9	10/5/9
Mean blood pressure (mmHg)	98.3±12.3	97.0±8.1
Duration of diabetes (years)	11.9±8.5	10.7±9.3
HbA1c level (%)	7.5±0.8	7.6±1.2
Use of insulin (n)	5	7
Extension angle of MP joints (degrees)	50.3±16.5	46.7±15.6
Follow-up data		
HbA1c level (%)	7.9±1.0	8.0±1.4
Use of insulin (n)	7	9
Extension angle of MP joints (degrees)	41.9±15.9	34.4±16.6
Interval change of the angle (degrees per year)	−0.74±0.79	−1.07±0.79

Mean±SD; *$P<0.05$ by unpaired t test or χ^2 test with Yates' correction. MP: Metacarpophalangeal, HbA1c: Hemoglobin A1c

Table 5: Worsening of albuminuria predicted by binary logistic regression analysis using the stepwise method with $P=0.2$

Explanatory variables	b	Odds ratio (95% CI)	P value
Age	0.142	1.152 (1.055, 1.259)	0.002
Mean blood pressure	−0.067	0.935 (0.872, 1.002)	0.058
Duration of diabetes	−0.095	0.910 (0.833, 0.993)	0.035
HbA1c level at baseline	−0.553	0.575 (0.283, 1.171)	0.127
Use of insulin at baseline	2.148	8.567 (1.500, 48.923)	0.016
Albuminuria at baseline	0.919	2.507 (0.654, 9.613)	0.180
HbA1c level at follow-up	0.583	1.791 (0.992, 3.233)	0.002
Constant	−3.189		

The worsening of albuminuria was regarded as the worsening of the grade (0–2) of albuminuria at follow-up (1 for "yes" [$n=24$] and 0 for "no" [$n=45$]). Categorical variables were coded as in the "statistical analysis" section, b: Unstandardized partial regression coefficient. CI: Confidence interval, HbA1c: Hemoglobin A1c

of another study population in our previous report,[5] demonstrated that the passive extension angles of MP joints were smaller in males than in females and correlated negatively with age in males but not in females. The influence of age on the passive range of motion of peripheral joints seems to be little in females.[8] A multiple regression analysis was performed using 10 explanatory variables including age and gender to predict the angle of MP joints or the grade of albuminuria at baseline. When using all 10 explanatory variables, the partial regression coefficient for

the use of insulin was only significant in case of the grade of albuminuria as a target variable. When using the stepwise method, the partial regression coefficient for male gender was only significant in case of the angle of MP joints as a target variable. At 10–12-year follow-up, it was apparently observed that the passive extension angles of MP joints decreased and the grades of albuminuria progressed. Patients whose grades of albuminuria worsened were significantly older and tended to have smaller angles of MP joints compared with patients without the worsening of albuminuria. Binary logistic

Table 6: Worsening of the passive extension angle of MP joints predicted by binary logistic regression analysis using the stepwise method with *P*=0.2

Explanatory variables	*b*	Odds ratio (95% CI)	*P* value
Duration of diabetes	0.085	1.089 (1.003, 1.181)	0.042
Body mass index	0.212	1.236 (1.005, 1.521)	0.045
Angle of the joints at baseline	0.055	1.057 (0.986, 1.132)	0.118
Constant	−9.063		

The worsening of the angle of MP joints was regarded as the decrease of the angle >10° at follow-up (1 for "yes" [*n*=24] and 0 for "no" [*n*=21]). MP: Metacarpophalangeal, *b*: Unstandardized partial regression coefficient, CI: Confidence interval

regression analysis using the stepwise method demonstrated that the worsening of albuminuria could be predicted by age, duration of diabetes (negatively), and use of insulin at baseline and HbA1c level at follow-up. Similarly, it was demonstrated that the decreasing (>10°) of the angle of MP joints could be predicted by duration of diabetes and body mass index at baseline. In this case, patients whose angles of MP joints were equal to or larger than the median value of 45° for males and 50° for females were analyzed. There is a report[9] describing that the passive extension angle of MP joints >60° or <45° was regarded as normal or definitely abnormal.

Thus, the present long-term observation study suggested that the passive extension angle of MP joints to quantitatively assess LJM was affected by male gender, aging, high body mass index, and long duration of diabetes but did not well predict the progression of early diabetic nephropathy. The progression of early diabetic nephropathy was suggested to be associated with aging, use of insulin, and poor glycemic control but not long duration of diabetes. Taken together with the results of our previous report[5] (possible common factors contributing the decreased angle and arteriosclerosis), it is inferred that the decreasing of the angle of MP joints is rather associated with arteriosclerosis than early diabetic nephropathy. Other follow-up studies using common methods to identify LJM in type 1 diabetes have demonstrated inconsistent results on the relationship between LJM and diabetic nephropathy.[10-13] In contrast to our study, a cross-sectional study in younger patients with type 1 (age, 31.7 ± 10.5 years) indicated that microalbuminuria, but not LJM, was associated with risk factors of cardiovascular disease.[14] In patients with type 2 diabetes, it was reported that age, duration of diabetes, and occupation, but not microvascular complications, correlated with LJM.[15] It would be worth elucidating further the relationship between LJM, diabetic nephropathy, and macrovascular disease, all of which are involved in AGEs.[1,16-18]

CONCLUSIONS

Taken together with our previous report, it is inferred that the decreasing of the angle of MP joints is rather associated with arteriosclerosis than early diabetic nephropathy. It would

be worth elucidating the relation between LJM, diabetic nephropathy, and macrovascular disease, all of which are involved in AGEs.

COMPETING INTEREST

Author declares that he has no conflicts of interest.

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