Impaired Red Blood Cell Deformability Is Associated with Diabetic Complications in Patients with Type 2 Diabetes

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Background & Aim

Red blood cells (RBCs) circulate from large artery to fine capillaries in whole body and experience a wide range of shear stress during the circulation. RBC deformability is defined as an ability to deform and elongate the shape under the shear stress to facilitate oxygen transfer and to reduce flow resistance. Particularly in diabetes, it has been considered that stiffened RBCs by chronic hyperglycemia may affect adversely to vasculature, so the hemorheologic changes in the microcirculation of diabetics may suggest a potential predictive marker. Numerous attempts have been made to measure erythrocyte deformability directly, but it has been limited for technical problems in clinical settings. Recently, a novel and new disposable-slit ektacytometer enabled to assess RBC deformability with simple technique. However, there were a few studies about the relationship between RBC deformability and diabetic complications.

For this purposes, we assessed factors affect the RBC deformability in patients with diabetes, and attempted to investigate the associations between RBC deformability and diabetic complications.

Methods

- A Cross-sectional study
- Study population (n=452)
  - Jul.1 ~ Mar. 31, 2015
  - in- & outpatients with Type 2 diabetes visited Yeungnam University Hospital(Daegu, Korea)
- Exclusion criteria
  - End stage renal disease (MDRD-eGFR < 15ml/min/1.73m2, n=4)
  - Patients who had medications for microcirculation (pentoxifyllin, n=2; ginko biloba, n=5)

- Measurement of RBC deformability
  - A microfluidic ektacytometer, RheoScan-D (Sewon Meditech, Korea)

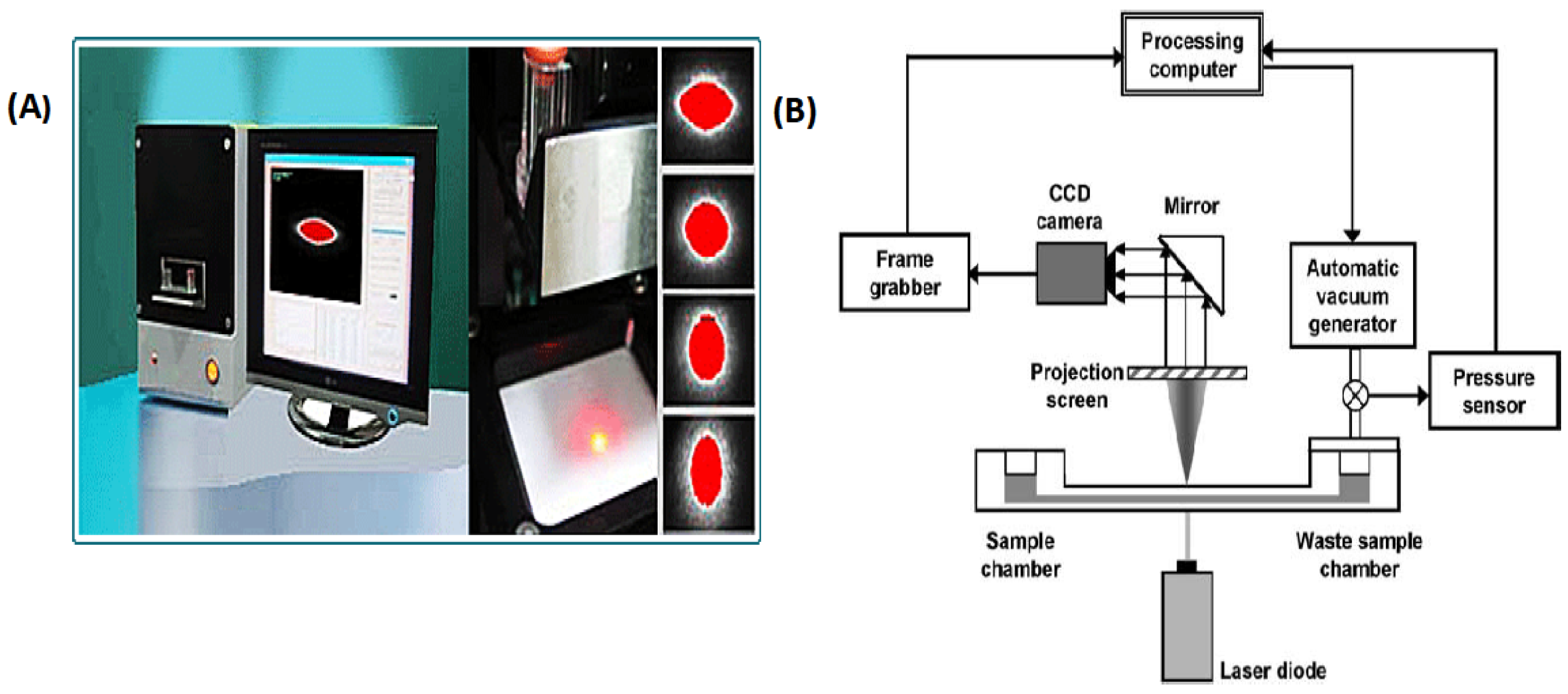

Figure 1. Measurement of RBC deformability.
(A)microfluidic ektacytometer (RheoScan-D) and laser diffraction patterns at various wall shear stresses
(B) schematics of a slit-flow ektacytometry

- **RBC deformability : Elongation index at 3Pa (EI@3Pa, %)**
  - **Defined as (A-B)/(A+B)**
  - **A : length of major axis of the ellipse, B : length of minor axis of the ellipse**

- Subjects were categorized into tertiles according to RBC deformability

	Group 1 (n=147)	Group 2 (n=147)	Group 3 (n=147)
EI@3P range (%)	25.66 ~ 30.52	30.53 ~ 31.72	31.73 ~ 34.26
EI@3P mean (%)	29.23 ± 1.06	31.11 ± 0.35	32.61 ± 0.67

Results

Table 1. Baseline characteristics of tertiles according to Elongation index(EI)

	Group 1 (n=147)	Group 2 (n=147)	Group 3 (n=147)
Age (yrs)	59.89 ± 11.61	60.19 ± 12.85	60.82 ± 11.49
Sex (M:F, % of Male)	76:70 (52%)	80:67 (54.4%)	77:70 (52.4%)
HbA1C (%)*	8.87 ± 2.53†	8.24 ± 2.25	8.13 ± 2.04
Diabetes duration (yrs)	9.17 ± 8.09	8.96 ± 7.68	8.90 ± 7.48
BMI (kg/m²)	24.16 ± 3.94	24.45 ± 4.44	24.04 ± 3.27
Smoking (n, %)	38 (30%)	35 (26%)	34 (32%)
Alcohol (n, %)	52 (41%)	39 (29%)	34 (32%)
Hb (g/dL)	13.58 ± 1.61	13.84 ± 1.57	13.93 ± 1.61
Platelet (K/uL)	257.66 ± 73.96	260.64 ± 82.78	252.37 ± 69.58
RDW*	13.45 ± 1.46†	13.18 ± 0.82	12.91 ± 0.62
MCV* (fL)	88.03 ± 4.90†,**	90.45 ± 15.05	91.51 ± 3.93
MCH (pg)	31.89 ± 22.30	30.91 ± 5.01	31.15 ± 1.42
Creatinine (mg/dL)	1.07 ± 0.30	1.02 ± 0.30	1.03 ± 0.30

Table 1. Continued

	Group 1 (n=147)	Group 2 (n=147)	Group 3 (n=147)
eGFR (ml/min/1.73m²)	76.35 ± 20.75	78.40 ± 19.39	77.89 ± 21.61
Urine ACR (mg/g)	123.63 ± 388.90	142.63 ± 504.06	113.60 ± 366.53
HOMA-IR	4.19 ± 3.36	4.18 ± 4.52	3.91 ± 2.45
HOMA-B*	32.23 ± 23.22	40.99 ± 29.63	46.55 ± 38.56
Total cholesterol(mg/dL)	185.96 ± 42.79†	188.69 ± 45.66	185.70 ± 46.20
Triglyceride (mg/dL)*	216.79 ± 170.15	170.02 ± 107.05	149.45 ± 81.31
HDL cholesterol (mg/dL)	48.08 ± 13.68	50.20 ± 13.56	51.08 ± 14.72
LDL cholesterol (mg/dL)*	93.69 ± 42.23	104.60 ± 39.61	104.55 ± 41.30
Nephropathy	57 (39%)	47 (32%)	51 (26%)
Retinopathy*	54 (37%)	47 (32%)	32 (22%)
Neuropathy*	37 (25%)	34 (23%)	25 (17%)
Coronary artery disease	13 (9%)	8 (5%)	12 (8%)
Cerebrovascular disease	15 (10%)	16 (11%)	13 (8.8%)
Any microvascular Cx*	88 (59.9%)	84 (57.1%)	71 (36%)
Any macrovascular Cx	27 (19%)	22 (15%)	21 (14.3%)

Values are n, mean ± SD or n (%). **p<0.05 for trend, **p<0.05 vs Group 2, †p<0.05 vs. Group 3 for post-hoc analysis by one-way ANOVA*

Table 2. Associations of Elongation Index (EI3@Pa) with Metabolic Variables by Univariate Linear Regression Analysis.

	Men	p	Women	p
HbA1c	-0.096±0.042	0.022	-0.143±0.056	0.011
TG	-0.004±0.001	0.000	-0.004±0.001	0.000
HDL-C	0.018±0.008	0.021	0.006±0.008	0.419
FPG	-0.006±0.002	0.002	-0.003±0.002	0.217
HOMA-B	0.013±0.006	0.027	0.006±0.004	0.122

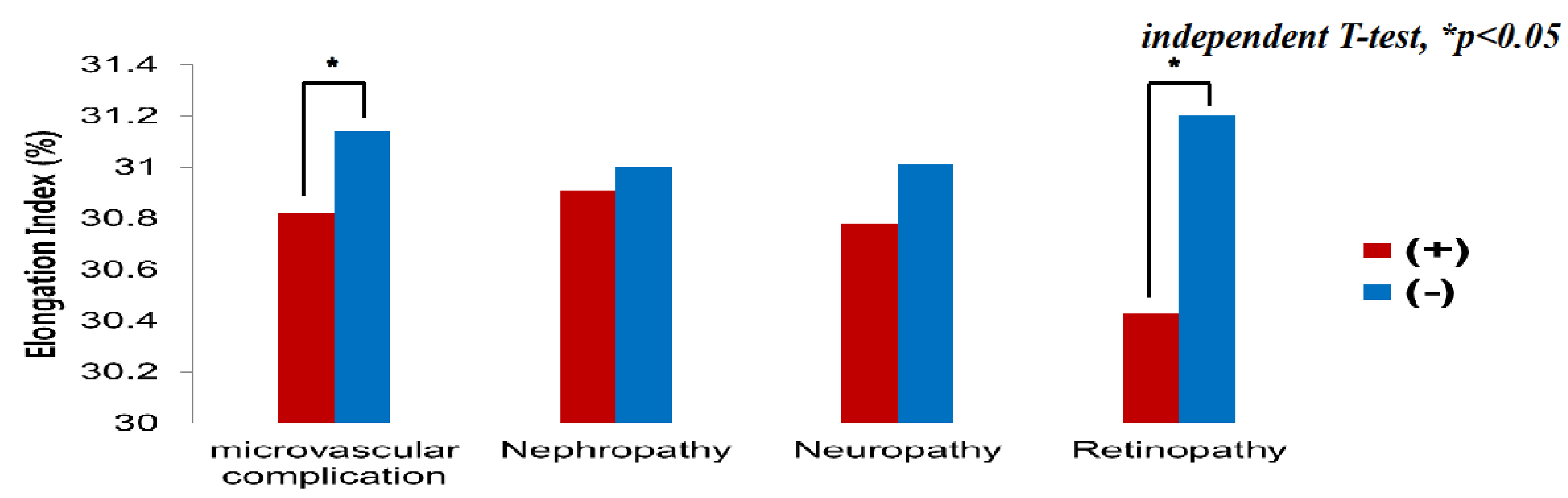

Figure 2. Comparison of RBC Deformability between group with and without diabetic microvascular complications

Table 3. Odds ratio of RBC deformability for Diabetic Retinopathy

EI3@Pa	β Coefficient	OR (95% CI)	p-value
Group 3 (Reference)			
Group 1	0.857	2.355 (1.126 – 4.926)	0.023
Group 2	0.728	2.071 (1.015 – 4.223)	0.045

By multiple logistic regression analysis adjusted for age, gender, hypertension, smoking, duration of diabetes, HbA1c, GFR, Triglyceride, LDL-cholesterol

Summary & Conclusion

- **Lower EI@3Pa group showed**
  - ✓ **poorer glycemic control and decreased insulin secretory function (HOMA-B)**
  - ✓ **higher incidence of microvascular complications, especially in diabetic retinopathy**
- **Patients with diabetic retinopathy present significant lower EI@3Pa than those without retinopathy.**

These results suggest poor RBC deformability would contribute in developing diabetic microangiopathy, especially in diabetic retinopathy.

- The limitation of this study
  - ✓ Cross-sectional study design
  - ✓ data on fibrinogen are lacking

Reference:
1) JS Moon, JH Kim, JH Kim, IR Park, JH Lee et al. Impaired RBC deformability is Associated with Diabetic Retinopathy in Patients with Type 2 diabetes. Diabetes Metab. 2016 (in press)
2) Clinton D. Brown et al. Association of reduced red blood cell deformability and diabetic Nephropathy. Kidney Int. 2005 May;67(5):2066