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Objective

Soluble Leucine rich repeats and immunoglobulin like domains 2 (LRIG2) interact with epidermal growth factor receptor (EGFR), resulting in activation of EGFR and its downstream pathways. We previously reported the association of serum EGFR with type 2 diabetes mellitus (T2DM), and LRIG2 is also expected to be correlates with T2DM.

Aim of Study

The purpose of current study was to compare soluble LRIG2 level in T2DM and controls, and to investigate the relationship between soluble LRIG2 and glucose parameters.

Methods

A total of 240 subjects were enrolled in this study, and they were divided into three groups [80 with T2DM, 80 with prediabetes and 80 with normoglycemia (NGT)]. Blood samples were collected in the morning after an overnight fast >8 hours. Fasting (FBS) and 2-hour postprandial (PP2) plasma glucose levels, fasting insulin and C-peptide levels were measured. Fasting serum LRIG2 levels were measured using a quantitative sandwich enzyme immunoassay technique with an enzyme-linked immunosorbent assay kit (MyBioSource, China; catalog no. MBS9337066). Demographic findings and serum LRIG2 were compared among three groups, and serum LRIG2 were correlated with various clinical factors using linear regression analysis.

Results

Table 1. Baseline characteristics of total subjects

	NGT (n=80)	Prediabetes (n=80)	T2DM (n=80)	p-value
Age (mean ± SD, years)	50.7±13.7	53.5±12.1	54±12.3	0.210
Sex (male/female)	25 / 55	38 / 42	35 / 45	0.091
HTN (n, %)	16 (20.0)	14 (17.5)	33 (41.3)	0.001
Smoking (n, %)	8 (10.0)	7 (8.8)	22 (27.5)	0.001
Height (mean ± SD, cm)	161.6±8.6	163.2±8.4	163.3±9.4	0.528
Weight (mean ± SD, kg)	63.9±12.4	67.1±11.9	70.1±14.7	0.039
BMI (mean ± SD, kg/m ²)	24.3±3.3	24.8±3.2	26.2±4.4	0.020
SBP (mean ± SD, mmHg)	127.8±16.1	128.9±14.6	134.6±20.2	0.065
DBP (mean ± SD, mmHg)	79.3±12.6	77.4±10.9	81.8±11.8	0.102
Hb (mean ± SD, g/dL)	13.7±1.2	14.1±1.7	14.5±1.5	0.015
HbA1c (mean ± SD, %)	5.3±0.2	5.6±0.3	7.4±1.9	0.000
FBS (mean ± SD, mg/dL)	91.9±5	101.7±11.1	154.2±57.3	0.000
PP2 (mean ± SD, mg/dL)	105.3±19	143.3±33.5	293±101.2	0.000
Insulin, fasting (mean ± SD, mg/dL)	8.3±4.2	10±5	18±38.9	0.019
Insulin, PP2 (mean ± SD, mg/dL)	36.6±43.6	68.9±68	70.7±69.5	0.001
C-peptide, fasting (mean ± SD, ng/mL)	0.73±0.47	0.87±0.5	1.15±0.71	0.000
C-peptide, PP2 (mean ± SD, ng/mL)	3.44±2.23	4.09±2.7	6.72±24.34	0.347
TG (mean ± SD, mg/dL)	104±63.2	145.1±106.7	189.6±173	0.000
Tchol (mean ± SD, mg/dL)	191.4±30.4	196.6±39.8	192.3±46.9	0.682
HDL (mean ± SD, mg/dL)	61.7±13.7	53.7±14	49±13.4	0.000
LDL (mean ± SD, mg/dL)	113.5±29.7	121.5±34.2	116.6±45.3	0.389
BUN (mean ± SD, mg/dL)	13.7±3.6	14±3.7	14.8±4.6	0.206
Cr (mean ± SD, mg/dL)	0.73±0.15	0.75±0.18	0.72±0.19	0.496
eGFR (mean ± SD, mL/min/1.73 m ²)	103.4±18.1	104.2±24.4	112±29.4	0.061
AST (mean ± SD, U/L)	21.3±6.6	23.2±11.4	26.5±14.9	0.019
ALT (mean ± SD, U/L)	20.7±15	25±20.8	29.1±16.8	0.017

* The p-value was obtained from student t-test

† The p-value was obtained from the chi-squared test.

In baseline characteristic analysis, significant difference among the three groups were found in HTN (p=0.001), smoking (p=0.001), weight (p=0.039), BMI (p=0.020), Hb (p=0.015), HbA1c (p<0.001), fasting glucose (p<0.001), PP2 (p<0.001), fasting insulin (p=0.019), PP2 insulin (p=0.001), fasting C-peptide (p<0.001), TG (p<0.001), HDL-C (p<0.001), AST (p=0.019), and ALT (p=0.017). There was no difference in the other factors including age, sex, height, and BP (all p>0.05) (Table 1).

Figure 1. Comparison of Soluble LRIG2 levels

Serum LRIG2 levels in T2DM group (16.73±8.01 ng/mL) was significantly higher than those of preDM (13.18±5.83 ng/mL, p=0.002) and control group (12.29±5.27 ng/mL, p<0.001). For subgroup analysis, preDM group was divided into 3 groups as impaired fasting glucose (IFG, n=26), impaired glucose tolerance (IGT, n=26), and IFG + IGT (n=28). There were no significant differences in serum LRIG2 levels between groups (p=0.099) (Fig. 1).

Table 2. Correlation between LRIG2 and clinical factors

	Total		NGT		PreDM		T2DM	
	r	p	r	p	r	p	r	p
Age	-0.065	0.317	0.122	0.280	-0.160	0.157	-0.211	0.060
Height	0.122	0.103	0.035	0.806	-0.113	0.422	0.247	0.034
weight	0.175	0.019	-0.057	0.690	0.043	0.759	0.239	0.040
BMI	0.139	0.065	-0.107	0.454	0.090	0.525	0.146	0.219
SBP	0.179	0.016	0.270	0.055	-0.088	0.528	0.185	0.114
DBP	0.216	0.004	0.236	0.096	0.153	0.269	0.197	0.092
Hb	0.109	0.128	-0.006	0.962	0.006	0.966	0.110	0.396
HbA1c	0.305	0.000	0.021	0.856	0.060	0.603	0.239	0.037
FBS	0.319	0.000	-0.068	0.547	-0.181	0.107	0.298	0.007
PP2	0.320	0.000	0.157	0.165	0.167	0.138	0.181	0.109
Insulin, FBS	0.073	0.260	-0.224	0.047	-0.062	0.590	0.051	0.656
Insulin, PP2	-0.004	0.955	-0.065	0.589	0.078	0.519	-0.146	0.198
C-peptide, FBS	0.144	0.034	0.014	0.909	0.090	0.453	0.061	0.603
C-peptide, PP2	-0.001	0.988	0.107	0.376	0.136	0.259	-0.062	0.606
TG	0.176	0.007	0.070	0.540	-0.001	0.995	0.168	0.153
TC	-0.024	0.715	-0.086	0.452	-0.132	0.253	0.075	0.526
HDL-C	-0.125	0.059	-0.253	0.025	0.027	0.814	0.067	0.574
LDL-C	-0.074	0.264	0.003	0.978	-0.164	0.154	-0.071	0.555
BUN	0.101	0.131	0.005	0.963	0.088	0.449	0.093	0.441
Cr	0.096	0.152	0.096	0.401	0.087	0.453	0.145	0.228
eGFR	0.033	0.623	-0.102	0.370	-0.002	0.984	0.013	0.914
AST	0.118	0.076	-0.068	0.553	-0.023	0.844	0.167	0.165
ALT	0.113	0.089	-0.056	0.625	0.106	0.359	0.108	0.369

In pearson correlation analysis, serum LRIG2 was significantly correlated with HbA1c (r=-0.305, p<0.001), FBS (r=0.319, p<0.001) and PP2 (r=0.320, p<0.001) (Table 2).

Figure 2. Change of LRIG2 levels after metformin treatment.

Table 3. Association between serum LRIG2 change and change in clinical factors

	r	p-value
HbA1c changes	-0.006	0.967
FBS changes	0.265	0.431
Weight changes	0.076	0.609
BMI changes	0.063	0.669
TG changes	-0.072	0.666
TC changes	-0.132	0.356
HDL changes	-0.124	0.386
LDL changes	0.084	0.553

A total of 53 subjects with T2DM were additionally enrolled and treated with metformin monotherapy. Serum LRIG2 levels before (10.90±9.50) and after 6 months (11.25±5.42) of treatment did not show any significant difference (n=53, p=0.524). And these trends were also obtained in the 31 subjects who were followed up 1-year (11.59±6.38, p=0.681) (Fig. 2). In addition, no significant correlation was found between the changes of LRIG2 and clinical factors (Table 3).

Conclusion

Serum LRIG2 levels were highest in the T2DM group and higher in the prediabetes group than in the NGT group. And there were no significant changes in serum LRIG2 levels after 6 or 12 months of metformin treatment. The results of our study suggest a possible association of EGFR signaling with T2DM and serum LRIG2 might be a novel biomarker in diagnosis of T2DM.