Serum ferritin level is positively associated with microalbuminuria in Type 2 Diabetes of Taiwan

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AIMS

Serum ferritin has been found closely related with diabetes and glucose metabolism, but its impacts on diabetic nephropathy remains unknown. This study aimed to explore the association between serum ferritin and microalbuminuria in type 2 diabetes

METHODS

Eight hundred and fifty one type 2 diabetes subjects were selected from a cohort participating in a glycemic control study in Taiwan in 2008. We used urine albumin-to-creatinine ratio to define microalbuminuria; serum ferritin was divided into quartiles for analysis. Logistic regression and trend tests were used to delineate the association between serum ferritin and microalbuminuria.

RESULTS

Diabetes subjects with higher ferritin tended to have earlier diabetes onset, more metabolic disorders, higher high-sensitivity C-reactive protein (hsCRP), and higher prevalence of microalbuminuria. Compared with those in the lowest quartile, diabetes subjects in the highest ferritin quartile were 53% (P=0.032) more likely to develop microalbuminuria. After controlling for demographics, metabolic profiles, and other inflammatory markers, the effect of serum ferritin levels on microalbuminuria remained significant (P for trend < 0.001). This independent relationship was not changed either for those who had better glycemic control or those who had not used an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

Table 1 Demographics and biochemical characteristics of study subjects by quartile of serum ferritin concentration

	Ferritin quartile				
Variables	1st	2nd	3rd	4th	*P**
Ferritin, pmol/l	<186.5	186.5–350.4	350.5–610.4	≧610.5	
Median of ferritin, pmol/l	118.9	263.1	467.8	863.5	
Male, n (%)	58 (27.2)	87 (41.0)	117 (54.9)	144 (67.3)	<0.001
Education ≤ 6 years, n (%)	117 (55.5)	119 (56.1)	118 (55.4)	110 (51.6)	0.769
Age in year 2008, years	59.3 ± 9.5	60.5 ± 7.9	60.9 ± 7.9	58.3 ± 8.6	0.007
Duration of diabetes, years	7.8 ± 3.2	8.0 ± 4.0	7.2 ± 2.3	6.9 ± 2.7	0.002
Smoking status, n (%)					<0.001
Non-smoker	173 (81.2)	159 (75.0)	142 (66.7)	122 (57.3)	
Ex-smoker	12 (5.6)	22 (10.4)	27 (12.7)	23 (10.8)	
Current smoker	26 (12.2)	32 (15.1)	44 (20.7)	69 (32.4)	
Drinking status, n (%)					<0.001
Non-drinker	198 (93.8)	190 (89.2)	188 (88.3)	168 (78.5)	
Moderate drinker	8 (3.8)	16 (7.5)	11 (5.2)	28 (13.1)	
Heavy drinker	5 (2.4)	7 (3.3)	14 (6.6)	18 (8.4)	
BMI, kg/m^2	26.5 ± 3.9	25.8 ± 4.1	26.0 ± 3.8	26.2 ± 3.3	0.308
Waist circumference, cm	90.2 ± 10.9	87.8 ± 10.8	89.9 ± 9.4	91.1 ± 9.2	0.687
eGFR, ml min^{-1} 1.73 m^{-2}	83.9 ± 22.8	82.9 ± 20.6	82.8 ± 20.7	81.5 ± 26.2	0.752
eGFR< 60 ml min^{-1} 1.73 m^{-2}, n (%)	34 (16.0)	31 (14.6)	35 (16.4)	40 (18.8)	0.396
Albumin:creatinine ratio (mg/mmol)	17.6 ± 68.7	24.2 ± 66.2	28.4 ± 82.0	32.5 ± 91.8	0.007
Prevalence of microalbuminuria, n (%)	103 (48.8)	109 (50.9)	117 (54.9)	128 (59.8)	0.016
Triglycerides, mmol/l	1.7 ± 1.0	1.6 ± 0.8	1.7 ± 1.1	2.1 ± 1.4	<0.001
HDL cholesterol, mmol/l	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	0.9 ± 0.2	<0.001
Hypertension, n (%)	134 (62.9)	133 (62.7)	147 (69.0)	144 (67.6)	0.437
Systolic blood pressure, mmHg	136.3 ± 19.0	135.2 ± 18.3	137.7 ± 20.0	137.0 ± 20.3	0.582
Diastolic blood pressure, mmHg	79.0 ± 10.1	78.1 ± 10.3	79.7 ± 10.9	81.5 ± 12.3	0.775
HbA1c, mmol/mol (mean ± SD, %)	62 (7.8±1.4)	64 (8.0±1.5)	64 (8.0± .4)	64 (8.0±1.5)	0.239
White blood cells, × 10^3	6.8 ± 1.8	6.7 ± 1.9	6.8 ± 1.7	7.1 ± 2.3	0.224
hsCRP, nmol/l	2.2 ± 2.3	2.4 ± 3.6	3.1 ± 5.8	4.6 ± 16.7	0.078

Results are presented as mean SD, unless otherwise noted.
**P*-value: the chance to reject null hypotheses that there is no difference between those in different ferritin quartiles, by using v2- tests (for categorical data), t-tests (for continuous data) or Kruskal–Wallis tests (for not-normally distributed variables albumin:creatinine ratio and hsCRP).
eGFR, estimated glomerular filtration rate [by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation]; hsCRP, high-sensitivity C-reactive protein.

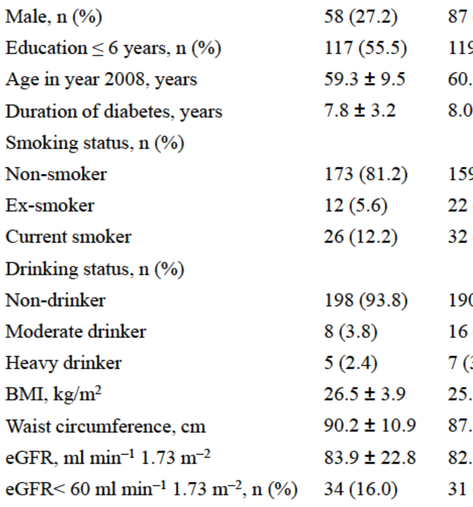

Figure 1 Adjusted odds ratios for risk of microalbuminuria in those with HbA1c < 53 mmol/mol (7%) (left) and in those without angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use (right), by quartile of serum ferritin concentration. All logistic regression models have been adjusted for sex, education level, diabetes duration, smoking status, drinking status, blood pressure, waist circumference, HbA_{1c}, eGFR, triglycerides and HDL.

Table 2 Risk factors associated with development of microalbuminuria in subjects with Type 2 diabetes

		Model 1	Model 2	Model 3
	Univariate odds ratio (95% CI) *P*	Multivariates odds ratio (95% CI) *P*	Multivariates odds ratio (95% CI) *P*	Multivariates odds ratio (95% CI) *P*
Male	0.78 (0.59–1.02) 0.073	- 0.65 (0.45–0.94) 0.021	- 0.74 (0.50–1.08) 0.119	- 0.77 (0.52–1.14) 0.194
Education ≤ 6 years	1.34 (1.02–1.77) 0.035	1.19 (0.89–1.60) 0.249	1.23 (0.90–1.67) 0.188	1.24 (0.91–1.69) 0.180
Duration of diabetes	1.05 (1.00–1.10) 0.045	1.06 (1.01–1.11) 0.024	1.05 (1.00–1.10) 0.066	1.06 (1.00–1.11) 0.033
Smoking status				
Ex-smoker/non-smoker	0.69 (0.43–1.09) 0.113	0.82 (0.48–1.39) 0.451	0.78 (0.45–1.35) 0.372	0.75 (0.43–1.30) 0.308
Current smoker/non-smoker	1.20 (0.85–1.70) 0.310	1.38 (0.92–2.08) 0.117	1.31 (0.86–1.99) 0.207	1.14 (0.74–1.77) 0.553
Drinking status				
Moderate drinker/non-drinker	1.06 (0.63–1.79) 0.820	1.18 (0.68–2.05) 0.569	1.15 (0.65–2.03) 0.630	1.20 (0.67–2.12) 0.540
Heavy drinker/non-drinker	1.34 (0.71–2.51) 0.364	1.48 (0.76–2.86) 0.248	1.31 (0.66–2.60) 0.444	1.42 (0.71–2.84) 0.317
Large waist circumference*	1.51 (1.14–2.01) 0.004		1.23 (0.90–1.69) 0.200	1.15 (0.83–1.59) 0.403
GFR < 60 ml min^{-1} m^{-2}	1.55 (1.06–2.25) 0.022		1.30 (0.87–1.95) 0.206	1.18 (0.78–1.78) 0.435
Triglycerides > 1.7 mmol/l	1.91 (1.44–2.54) <0.001		1.64 (1.20–2.23) 0.002	1.60 (1.17–2.19) 0.003
Low HDL cholesterol†	1.18 (0.84–1.66) 0.341		0.98 (0.67–1.43) 0.914	0.94 (0.64–1.37) 0.729
Blood pressure > 130/80 mmHg	1.83 (1.37–2.45) <0.001		1.64 (1.20–2.23) 0.002	1.62 (1.19–2.22) 0.003
HbA_{1c} ‡				
53–75 vs. < 53 mmol/mol	1.34 (0.97–1.85) 0.075		1.20 (0.85–1.69) 0.293	1.17 (0.83–1.65) 0.377
> 75 vs. < 53 mmol/mol	2.37 (1.56–3.58) <0.001		1.94 (1.24–3.01) 0.004	1.78 (1.13–2.78) 0.013
hsCRP				
Quartile 2/quartile 1	1.21 (0.83–1.79) 0.325			0.98 (0.64–1.49) 0.923
Quartile 3/quartile 1	1.57 (1.06–2.31) 0.024			1.19 (0.77–1.82) 0.437
Quartile 4/quartile 1	2.06 (1.39–3.05) <0.001			1.36 (0.87–2.14) 0.178
White blood cell count				
Quartile 2/quartile 1	1.31 (0.89–1.94) 0.174			1.25 (0.82–1.89) 0.298
Quartile 3/quartile 1	1.47 (0.99–2.18) 0.054			1.33 (0.87–2.03) 0.194
Quartile 4/quartile 1	1.99 (1.34–2.95) 0.001			1.54 (0.98–2.42) 0.059
Ferritin				
Quartile 2/quartile 1	1.08 (0.73–1.59) 0.694	1.12 (0.75–1.66) 0.578	1.17 (0.78–1.76) 0.460	1.17 (0.78–1.77) 0.454
Quartile 3/quartile 1	1.25 (0.85–1.84) 0.261	1.40 (0.93–2.09) 0.103	1.34 (0.88–2.03) 0.170	1.33 (0.87–2.03) 0.187
Quartile 4/quartile 1	1.55 (1.05–2.28) 0.029	1.76 (1.16–2.67) 0.008	1.65 (1.07–2.55) 0.024	1.61 (1.04–2.50) 0.034
	P for trend 0.016	*P* for trend <0.001	*P* for trend <0.001	*P* for trend <0.001

*Waist circumference (large): > 80 cm for women, > 90 cm for men.
†HDL cholesterol (low): < 1.30 mmol/l for women, < 1.04 mmol/l for men.
‡HbA1c: 53 and 75 mmol/mol in International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units are equivalent to 7 and 9% in Diabetes Control and Complications Trial
(DCCT) units, respectively.
eGFR, estimated glomerular filtration rate [by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation]; hsCRP, high-sensitivity C-reactive protein.

CONCLUSIONS

The current study shows an independent dose–response effect of serum ferritin on microalbuminuria in type 2 diabetes patients.

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