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Serum adipocyte fatty acid-binding protein level predicts heart failure hospitalisation in type 2 diabetes – A prospective cohort study

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Introduction

Type 2 diabetes is associated with an increased risk of cardiovascular diseases (CVD), including heart failure (HF). The association between circulating adipocyte fatty acid-binding protein (AFABP) levels HF in type 2 diabetes has not been clearly defined. We conducted this prospective study to evaluate the association of circulating AFABP levels with incident HF hospitalisation in type 2 diabetes, and its relationship to the use of sodium glucose co-transporter 2 inhibitors (SGLT2i).

Method

Baseline serum AFABP levels were measured in 3322 participants without known cardiovascular diseases or HF recruited from the Hong Kong West Diabetes Registry. The association of baseline serum AFABP levels and incident HF hospitalisation was evaluated using multivariable Cox regression analysis, with the use of SGLT2i included as a time-dependent co-variate.

Result

Over a median follow-up of 8 years, 176 (5.3%) participants developed HF hospitalisation, while 731 (22%) were commenced on SGLT2i during the study period (Table 1). In multivariable Cox regression analysis, baseline log-transformed serum AFABP level was significantly associated with incident HF hospitalisation (HR 1.39, p=0.015), independent of the use of SGLT2i and other conventional HF risk factors (Table 2). High cumulative defined daily dose of SGLT2i was protective of incident HF hospitalisation (HR 0.10, p=0.019) (Table 1), and a dose-dependent reduction in cumulative incidence of HF hospitalisation in response to SGLT2i was more clearly observed in participants with a higher baseline AFABP level above the sex-specific median (p for trend <0.01) (Figure 1).

Conclusion

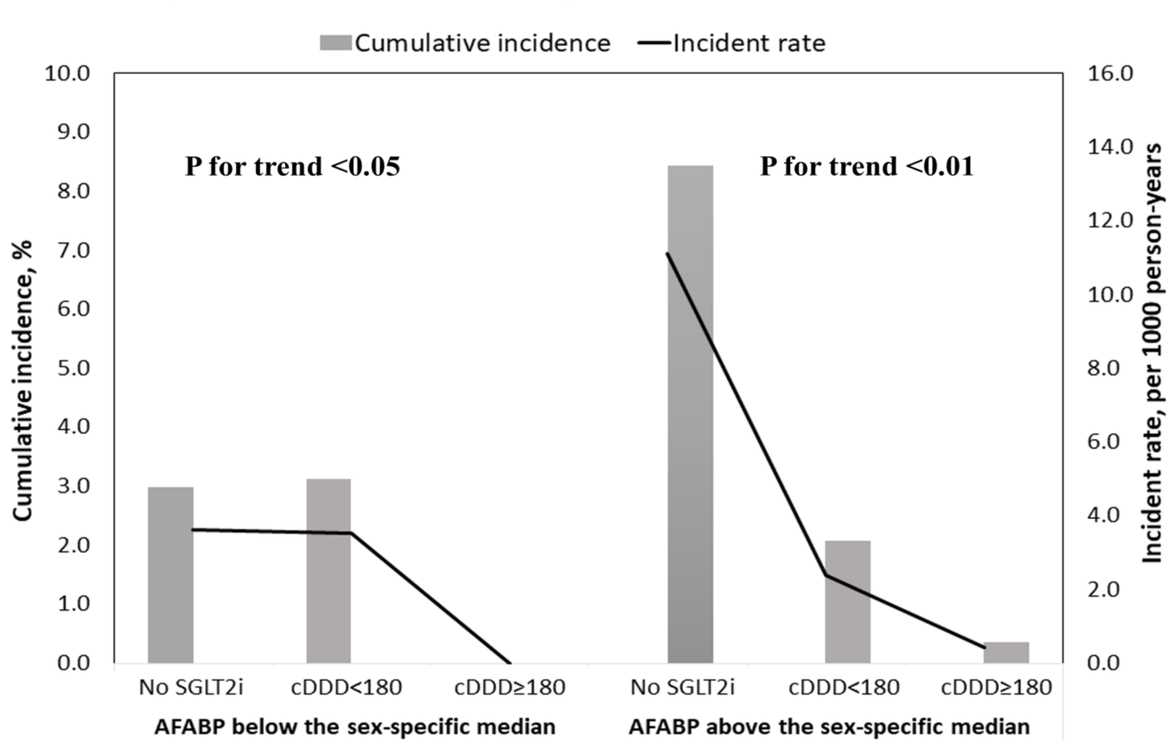
Circulating AFABP level is independently associated with incident HF hospitalisation in type 2 diabetes, and could potentially be used as a biomarker for better risk stratification for the prevention of HF hospitalisation.

Table 1 Use of sodium glucose co-transporter 2 inhibitors and incident HF hospitalisation

	No incident HF hospitalisation	Incident HF hospitalisation	Unadjusted HR (95% CI)	p-value
N	3146	176	--	--
Use of SGLT2i	727	4 (2.3%)	0.24 (0.04-0.74)	**0.014**
Canagliflozin	3 (0.4%)	0 (0%)		
Dapagliflozin	320 (44.0%)	3 (75%)		
Empagliflozin	402 (55.3%)	1 (25%)		
Ertugliflozin	2 (0.3%)	0 (0%)		
cDDD of SGLT2i (n=731)	686 (299-1163)	139 (124-231)	0.991 (0.985-0.997)	**0.002**
cDDD			0.996 (0.994-0.999)	**<0.001**
No SGLT2i	2419 (76.9%)	172 (97.7%)	Referent	--
<180	110 (3.5%)	3 (1.7%)	1.26 (0.40-3.99)	0.690
≥ 180	617 (19.6%)	1 (0.6%)	0.08 (0.01-0.55)	**0.010**

HF, heart failure; HR, hazard ratio; 95%CI, 95% confidence interval; SGLT2i, sodium-glucose transport protein 2 inhibitors; cDDD, cumulative daily defined dose.

Figure 1 Cumulative incidence of HF hospitalisation in study participants stratified by their baseline circulating AFABP levels and use of SGLT2i



HF, heart failure; AFABP, adipocyte fatty acid-binding protein; SGLT2i, sodium glucose co-transporter 2 inhibitors; cDDD, cumulative daily defined dose.

Table 2 Multivariable Cox regression analysis showing the associations between baseline circulating AFABP levels and incident HF hospitalisation

	Model 1		Model 2	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Men	1.42 (0.97-2.08)	0.075	1.44 (0.98-2.12)	0.06
Age, years	1.05 (1.03-1.07)	**<0.001**	1.05 (1.03-1.07)	**<0.001**
BMI, kg/m^2	1.03 (0.99-1.07)	0.202	1.03 (0.99-1.07)	0.172
Ever-smoker	0.90 (0.62-1.31)	0.572	0.89 (0.61-1.31)	0.566
Duration of diabetes, years	1.03 (1.01-1.04)	**0.007**	1.03 (1.01-1.04)	**0.012**
Hypertension	1.42 (0.67-3.01)	0.355	1.40 (0.66-2.96)	0.377
Dyslipidaemia	1.43 (0.77-2.67)	0.260	1.07 (0.94-1.22)	0.266
Atrial fibrillation	1.78 (1.12-2.83)	**0.015**	1.85 (1.13-3.04)	**0.015**
eGFR <60 ml/min/1.73m^2	1.44 (0.96-2.16)	0.075	1.38 (0.92-2.05)	0.118
Albuminuria	2.23 (1.54-3.22)	**<0.001**	2.22 (1.52-3.22)	**<0.001**
HbA1c, %	1.07 (0.96-1.97)	0.227	1.07 (0.94-1.22)	0.292
Metformin	1.53 (1.03-2.29)	**0.035**	1.57 (1.01-2.42)	**0.044**
SGLT2i†	-	-		
No SGLT2i	-	-	Referent	
cDDD <180	-	-	1.39 (0.43-4.52)	0.582
cDDD ≥180	-	-	0.10 (0.01-0.68)	**0.019**
Insulin	1.40 (1.00-1.97)	0.052	1.39 (0.98-1.96)	0.063
Aspirin	1.25 (0.90-1.73)	0.188	1.26 (0.90-1.77)	0.174
Furosemide	2.28 (1.37-3.79)	**0.002**	2.29 (1.35-3.88)	**0.002**
hsCRP*, mg/ml	1.09 (0.96-1.24)	0.174	1.09 (0.96-1.24)	0.202
A-FABP*, ng/ml	1.37 (1.05-1.79)	**0.021**	1.39 (1.07-1.81)	**0.015**

*Log-transformed before analysis. †Time-dependent covariate AFABP, adipocyte fatty acid-binding protein; HF, heart failure; HR, hazard ratio; 95%CI, 95% confidence interval; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; FG, fasting glucose; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; LDL-C low density lipoprotein-cholesterol; SGLT2i, sodium glucose co-transporter 2 inhibitors; cDDD, cumulative defined daily dose; DPP4i, dipeptidyl peptidase-4 inhibitor; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; hsCRP, high-sensitivity C-reactive protein. Hypertension was defined as blood pressure ≥ 140 / 90 mmHg or on anti-hypertensive medications; Dyslipidaemia was defined as fasting triglycerides (TG) ≥ 1.69 mmol/L, high density lipoprotein cholesterol (HDL-C) <1.04 mmol/L in men and <1.29 mmol/L in women, low density lipoprotein cholesterol (LDL-C) ≥ 2.6 mmol/L or on lipid-lowering agents; Albuminuria was defined as urine albumin to creatinine ratio ≥30mg/g (i.e. A2 or A3).

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