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Advantages of metformin therapy for the prevention and mitigation of diabetic foot ulcer in patients with diabetic kidney disease: A real-world evidence from large-scale cohort

Soie Kwon[1], Dong Ki Kim[1], Yon Su Kim[1], Chun Soo Lim[2], Jung Pyo Lee[2]
[1]Department of Internal Medicine-Nephrology, Seoul National University Hospital, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, SMG-SNU Boramae Medical Center, Korea, Republic of

Objectives: Diabetic foot ulcer (DFU) and diabetic kidney disease (DKD) are diabetes-related microvascular complications strongly correlated with high morbidity and mortality. Metformin potentially confers a wound-healing advantage, although there are no well-established evidence. We first time investigated the effect of metformin on DFU among large retrospective cohort of DKD patients.

Methods: This retrospective cohort study enrolled DKD patients from two South Korean tertiary-referral centers. Antidiabetic medication history was reviewed. Primary outcomes were all-cause mortality and DFU events; secondary outcomes included hospitalization, amputation, composite of amputation or vascular intervention, and Wagner Grade >3. Multivariate cox analysis and Propensity score matching (PSM) was used to balance baseline intergroup differences between metformin users and metformin non-users.

Results: Among 10,832 patients (4,748 metformin users; 6,084 metformin non-users), the 117·5±66·9 months follow-up period, all-cause mortality rate and DFU incidence were, 37·1%, and 5·2%, respectively. Fully adjusted multivariate Cox analysis showed that metformin users had a lower all-cause mortality (adjusted hazard ratio 0·63; 95% confidence interval 0·58–0·68; p<0·001) and DFU events (0·39; 0·31–0·48; p<0·001). After PSM, metformin users showed lower all-cause mortality (0·61; 0·55–0·67; p<0·001), DFU events (0·42; 0·32 –0·56; p<0·001), and secondary outcomes (hospitalization, amputation, composite of amputation or vascular intervention, and DFU with Wagner Grade >3).

Conclusions: Metformin therapy in DKD patient can lower all-cause mortality, DFU incidence, and DFU progression.

Table 1. Survival analysis of primary and secondary outcomes

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	All cause mortality			DM Foot		
	HR	95% CI	p value	HR	95% CI	p value
Univariate	0.4131	0.3863-0.4418	<0.001	0.3767	0.3134-0.4528	<0.001
Model 1	0.4578	0.4277-0.4901	<0.001	0.4324	0.3585-0.5217	<0.001
Model 2	0.536	0.4983-0.5765	<0.001	0.4666	0.3812-0.5710	<0.001
Model 3	0.626	0.5781-0.6778	<0.001	0.3874	0.3114-0.4820	<0.001
Model 4	0.6113	0.5537-0.6748	<0.001	0.4197	0.3167-0.5560	<0.001

	Admission			Amputation			Composite (Ampu, Vascular)			Wagner Gr3		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Univariate	0.3187	0.2533-0.4010	<0.001	0.3411	0.2558-0.4549	<0.001	0.3713	0.2927-0.4712	<0.001	0.3545	0.2736-0.4592	<0.001
Model 1	0.3816	0.3018-0.4826	<0.001	0.4299	0.3197-0.5781	<0.001	0.4363	0.3418-0.5569	<0.001	0.4459	0.3417-0.5819	<0.001
Model 2	0.4116	0.3194-0.5305	<0.001	0.4842	0.3505-0.6689	<0.001	0.5131	0.3945-0.6673	<0.001	0.5169	0.3877-0.6891	<0.001
Model 3	0.3488	0.2656-0.4580	<0.001	0.3999	0.2826-0.5658	<0.001	0.4316	0.3254-0.5726	<0.001	0.4306	0.3158-0.5872	<0.001
Model 4	0.4058	0.2866-0.5744	<0.001	0.4581	0.2998-0.7001	0.0003	0.4849	0.3410-0.6895	<0.001	0.4823	0.3285-0.7081	<0.001

[a]Unadjusted. [b]Adjusted for age, gender and comorbidities (hypertension, liver disease, dyslipidemia, cardiovascular disease, cerebrovascular disease and previous diabetic foot event). [c]Adjusted for age, gender, comorbidities and initial laboratory findings (serum creatinine, serum HbA1c and serum albumin). [d]Adjusted for age, gender, comorbidities, initial laboratory findings and medication usage (sulfonylurea, DPP4, insulin and renin-angiotensin system blocker). [e]Propensity score matching (adjusted for age, gender, previous diabetic foot, initial creatinine, initial HbA1c and medications).