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A Relationship between Unrecognized Anemia and the Development of Type 2 Diabetes Mellitus in Patient with Cardiovascular Risks

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Disclosure

- Nothing to disclose

Background

- Studies on anemia in diabetic patients are well known.

1. Thomas, M.C. et.al. Diabetes Care 2003;26:1164-1169.
2. Barbieri, J. et.al. Anemia 2015;2015:354737.

- Anemia is more common in diabetic patients than without DM, the concurrent of anemia and DM has a major impact on the quality of life along with lifespan of the patients.

McGill et.al. J Diabetes Complications 2006;20:262-72.
Gauci et.al. J Diabetes Complications 2017;31:1169-74.
Arch et.al. Intern Med 2002;162:1401-8.

Background

- However, the study for the impact of anemia on the development of the type 2 DM is very paucity.

Purpose

- We aimed to evaluate the impact of unrecognized anemia on the development of the type 2 DM and major clinical outcomes in a series of the Korean population during 5-year clinical follow-up

Methods (1)

- ## Study Population

  1, A total of 65,686 consecutive patients who visited cardiovascular center of Korea University Guro Hospital (KUGH) from January 2004 to February 2013 were retrospectively enrolled using the electronic database of KUGH.

  2. Finally, a total of 17,515 patients without DM were analyzed.

  3. The study protocol was approved by the Institutional Review Board at KUGH.

- ## Inclusion Criteria

  – All patients did, fasting glucose, hemoglobin (Hb), HbA1c level and glucose tolerance tests. Inclusion criteria included both ***HbA1c < 6.0 % and fasting glucose level < 110 mg/dL*** without diabetes medication nor diagnosis before.

Methods (2)

- Study Definition and Groups
  - The patients were divided into 2 groups according to the presence of anemia

The anemia group (n=2,907 patients)

The non-anemia group (n= 14,608 patients)

Anemia was defined as Hb levels <13 g/dL in men and <12 g/dL in women. The World Health Organization definition of anemia was used.

Methods (3)

- Study endpoints
  - Primary endpoint was **the development of DM**.
  - Type 2 DM was defined as fasting blood glucose ≥ 126 mg/dL, Hb A1c ≥ 6.5%, or the presence of a prescription for antidiabetic medication by the clinician..
  - Secondary endpoints were **Major adverse cardiac and cerebral events (MACCE)** as the composite of total death, non-fatal myocardial infarction (MI), stroke and revascularization such as PCI and CABG at 5-year follow-up.

Statistics

1. For continuous variables, differences between the two groups were evaluated using the unpaired t-test or Mann-Whitney rank test. Data were expressed as mean ± standard deviations.
2. For discrete variables, differences were expressed as counts and percentages and analyzed with the $\chi 2$ or Fisher's exact test between two groups.
3. To adjust for any potential confounders, propensity score matching (PSM) analysis was performed using the logistic regression model.
4. Matching was performed via 1:1 matching protocol using the nearest neighbor matching algorithm, with a caliper width equal to 0.01 of the standard deviation of the propensity score, yielding 2,731 well-matched pairs.
5. Various clinical outcomes up to 5 years were estimated by the Kaplan-Meier analysis, and differences between the groups were compared with the log-rank test before and after PSM.
6. For all analyses, a two-sided $p < 0.05$ was considered statistically significant. All data were processed with SPSS 20.0 (IBM Corp., Armonk, NY, USA).

Results (1)

Table. Baseline Characteristics in Entire Cohort and Propensity-Matched Groups

Variables, N (%)	Entire cohort				Matched cohort			
	Anemia (n=2,907)	No anemia (n=14,608)	P value	S.diff	Anemia (n=2,731)	No anemia (n=2,731)	P value	S.diff
Sex, men	874 (30.1)	7422 (50.8)	< 0.001	3.27	819 (30.0)	760 (27.8)	0.078	-0.40
Age, years	59.1 ± 15.9	52.5 ± 14.3	< 0.001	0.44	58.3 ± 15.8	58.2 ± 13.4	0.726	0.01
Body mass index, kg/m^2	24.2 ± 3.1	24.3 ± 3.3	0.103	-0.05	24.2 ± 3.1	24.0 ± 3.1	0.113	0.06
Patient's risk								
Hypertension	1142 (39.3)	5911 (40.5)	0.236	0.19	1060 (38.8)	1057 (38.7)	0.934	-0.02
Coronary artery disease	415 (14.3)	1300 (8.9)	< 0.001	-1.58	328 (12.0)	333 (12.2)	0.836	0.05
Myocardial infarction	100 (3.4)	242 (1.7)	< 0.001	-1.12	78 (2.9)	71 (2.6)	0.561	-0.16
PCI	288 (9.9)	572 (3.9)	< 0.001	-2.28	212 (7.8)	212 (7.8)	> 0.99	0.00
Angina pectoris	581 (20.0)	3057 (20.9)	0.254	0.21	537 (19.7)	554 (20.3)	0.565	0.14
Stroke	386 (13.3)	1406 (9.6)	< 0.001	-1.08	346 (12.7)	337 (12.3)	0.713	-0.09
Heart failure	125 (4.3)	506 (3.5)	0.027	-0.42	110 (4.0)	105 (3.8)	0.728	-0.09
Chronic kidney disease	69 (2.4)	21 (0.1)	< 0.001	-1.99	8 (0.3)	12 (0.4)	0.370	0.24
Arrhythmia	197 (6.8)	961 (6.6)	0.695	-0.08	183 (6.7)	212 (7.8)	0.130	0.40
Arterial fibrillation	120 (4.1)	495 (3.4)	0.048	-0.38	111 (4.1)	116 (4.2)	0.735	0.09

Data are presented as N (%) or mean ± standard deviation. S.diff indicates a standardized difference, PCI: percutaneous coronary intervention, ARB: angiotensin receptor blockers, ACEI: angiotensin-converting enzyme inhibitors, CCB: calcium channel blockers.

Results (2)

Table. Baseline Characteristics in Entire Cohort and Propensity-Matched Groups

Variables, N (%)	Entire cohort				Matched cohort			
	Anemia (n=2,907)	No anemia (n=14,608)	P value	S.diff	Anemia (n=2,731)	No anemia (n=2,731)	P value	S.diff
Laboratory finding s								
Hemoglobin, mg/dL	11.3 ± 1.1	14.1 ± 1.2	< 0.001	-2.29	11.3 ± 1.1	13.6 ± 1.0	< 0.001	-2.02
A1c, %	5.55 ± 0.31	5.52 ± 0.29	< 0.001	0.10	5.56 ± 0.31	5.56 ± 0.28	0.610	-0.01
Fasting glucose, mg/dL	92.1 ± 8.7	94.3 ± 7.8	< 0.001	-0.27	92.3 ± 8.4	92.5 ± 8.0	0.408	-0.02
Creatinine, mg/dL	0.86 ± 0.84	0.80 ± 0.25	< 0.001	0.10	0.77 ± 0.31	0.76 ± 0.32	0.286	0.03
Medications								
Statins	612 (21.1)	2684 (18.4)	0.001	-0.60	548 (20.1)	573 (21.0)	0.402	0.20
ARBs	488 (16.8)	2485 (17.0)	0.769	0.05	452 (16.6)	446 (16.3)	0.827	-0.05
ACEIs	158 (5.4)	702 (4.8)	0.151	-0.28	132 (4.8)	136 (5.0)	0.802	0.07
CCBs	808 (27.8)	4022 (27.5)	0.773	-0.05	753 (27.6)	737 (27.0)	0.627	-0.11
ß-blockers	434 (14.9)	1713 (11.7)	< 0.001	-0.88	384 (14.1)	387 (14.2)	0.907	0.03
Diuretics	467 (16.1)	1904 (13.0)	< 0.001	-0.80	423 (15.5)	421 (15.4)	0.940	-0.02
Nitrates	586 (20.2)	2104 (14.4)	< 0.001	-1.39	518 (19.0)	515 (18.9)	0.917	-0.03
Proton pomp inhibitors	79 (2.7)	183 (1.3)	< 0.001	-1.04	66 (2.4)	64 (2.3)	0.859	-0.05

Data are presented as N (%) or mean ± standard deviation. S.diff indicates a standardized difference, PCI: percutaneous coronary intervention, ARB: angiotensin receptor blockers, ACEI: angiotensin-converting enzyme inhibitors, CCB: calcium channel blockers.

Results (3)

Table. Various Clinical Outcomes by Kaplan-Meier Curved Analysis and Log-Rank Test

Incidence (%)	Anemia	No anemia	Log-rank (Mantel-Cox)	Hazard ratio (95% C.I.)	P value
Entire cohort	**(n=2,907)**	**(n=14,608)**			
Type 2 diabetes	122 (11.5)	456 (7.9)	0.002	1.373 [1.124 - 1.677]	0.002
MACCE	104 (8.1)	262 (4.1)	< 0.001	2.010 [1.601 - 2.523]	< 0.001
Total death	42 (3.0)	52 (0.8)	< 0.001	4.031 [2.684 - 6.055]	< 0.001
Cardiac death	16 (1.1)	16 (0.2)	< 0.001	4.974 [2.487 - 9.948]	< 0.001
Myocardial infarction	19 (1.3)	29 (0.4)	< 0.001	3.274 [1.835 - 5.839]	< 0.001
PCI	58 (4.8)	158 (2.4)	< 0.001	1.859 [1.376 - 2.512]	< 0.001
Stroke	15 (1.5)	73 (1.3)	0.862	1.050 [0.602 - 1.831]	0.862
Matched cohort	**(n=2,731)**	**(n=2,731)**			
Type 2 diabetes	107 (10.7)	86 (7.7)	0.035	1.356 [1.021 - 1.802]	0.035
MACCE	86 (7.2)	71 (5.5)	0.132	1.272 [0.929 - 1.742]	0.133
Total death	35 (2.6)	15 (1.2)	0.003	2.449 [1.337 - 4.485]	0.004
Cardiac death	15 (1.0)	6 (0.5)	0.040	2.605 [1.010 - 6.716]	0.048
Myocardial infarction	17 (1.3)	4 (0.4)	0.003	4.474 [1.505 - 13.29]	0.007
PCI	47 (4.3)	47 (3.6)	0.784	1.058 [0.706 - 1.585]	0.784
Stroke	16 (1.4)	13 (1.4)	0.718	0.874 [0.420 - 1.817]	0.719

Data are presented as incidence (%). HR: hazard ratio, CI: confidence interval, MACCE indicates major adverse cardiac and cerebral events, PCI: percutaneous coronary intervention.

Results (3)

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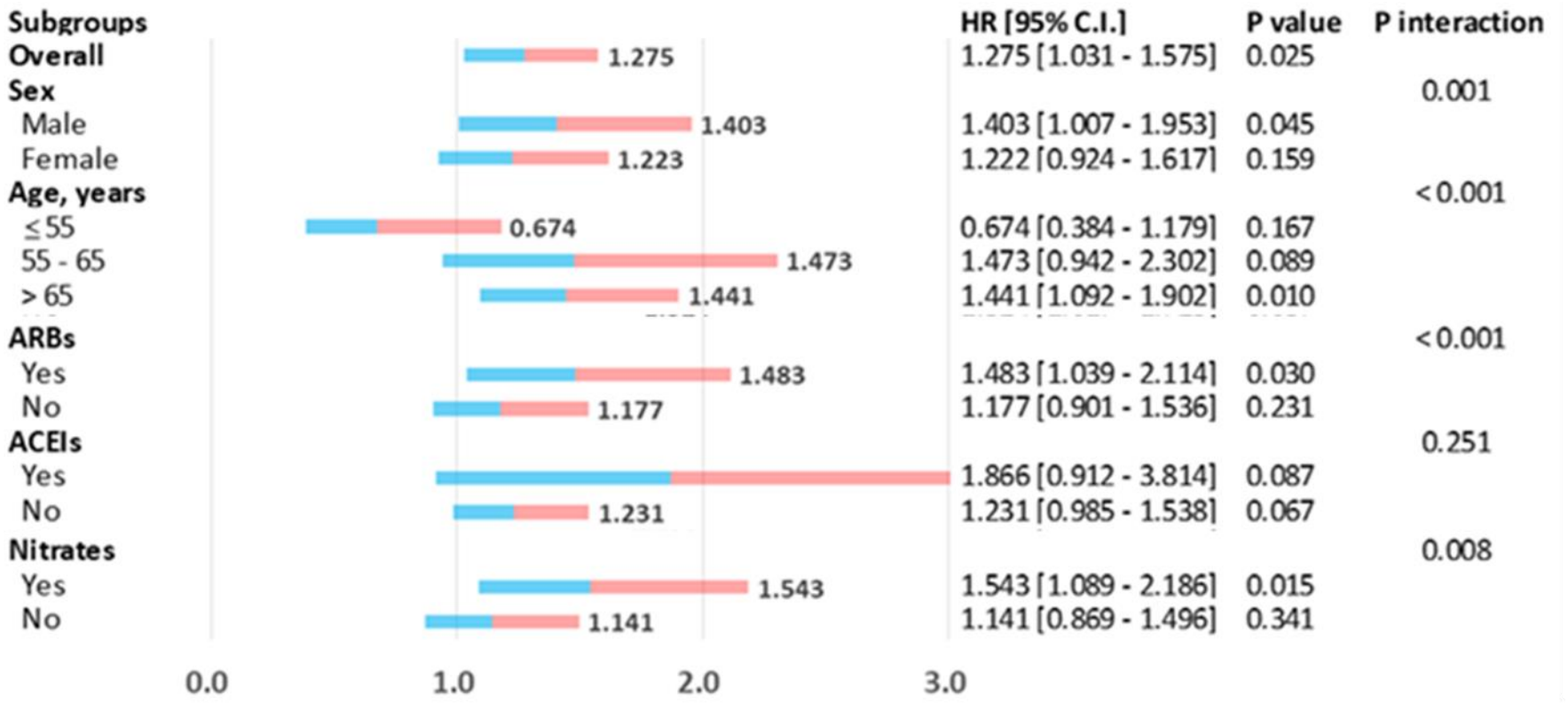
Subgroup Analysis for Impact of Anemia on New-onset Diabetes Mellitus at 5-Year Follow-Up by Cox-Proportional Hazard Ratio Analysis Adjusted Propensity-Score.



Figures are showing the cumulative incidences of new-onset type 2 diabetes in crude population (left) and matched population (right).

Summary

1) Anemia was associated not only with mortality and MI but also the development of type 2 DM in patients with cardiovascular risk factors

2) Anemia and the development of type 2 DM was related to sex, aging, and the use of ARB or nitrates.

Limitations

- This was a retrospective single-center study. Propensity score matching was performed to minimize confounding factors. However, we could not adjust for all limiting factors not shown in medical records.

- This study included subjects with cardiovascular risks, so the results of this study cannot be generalized to everyone.

Conclusion

- Unrecognized anemia can be an important risk factor for the development of type 2 diabetes in patients with cardiovascular risk and without diabetes. Therefore, in those population, treatment and prevention of diabetes and anemia can be an important strategy for optimal treatment.

- A well-designed, a randomized trial is needed to the final conclusion.

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Plausible Mechanisms (1)

- Anti-hypertensive medications such as ACE inhibitors or ARB are known to be associated with a development anemia.

  Sahay et. al. Diabetes Metab Syndr 2017;11 Suppl 2:S685-S95.

- Angiotensin II is a key regulator of erythropoiesis and also an important factor for the growth of erythroid precursors.

- The use of ACE inhibitors or ARB may influence the erythropoietin action of angiotensin and contributes to the development of anemia.

Plausible Mechanisms (2)

- **Nitric oxide** is a key mediator of the majority of glucose extraction by skeletal muscle, nitric oxide synthase inhibition decreased glucose uptake.

Kingwell et. al. Diabetes 2002;51:2572-80..

- In the present study, patients with nitrates may be patients with impaired nitric oxide synthase.

Kugiyama et. al. Circulation 1996;94:266-71.
Kugiyama et. al. J Am Coll Cardiol 1997;30:920-6.

Plausible Mechanisms (3)

- Anemia maybe like a systemic ischemia condition.

- Anemia-induced tissue hypoxia may increase production of oxidative stress boosters which may have a role in the development of type 2 DM.

Singh et. Al. Nat Rev Endocrinol 2009;5:204-10.

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