MICRO LABS LIMITED

Diabetes Update

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Dear Doctor,

Greetings from Micro Labs Limited. We are happy to bring you "DIABETES UPDATE" which contains latest and interesting news in the field of Diabetes and Endocrinology.

- Diabetic Complications and the associations between the Neutrophil-to-Lymphocyte Ratio
- CV Risk Reduction with Liraglutide: An Exploratory Mediation Analysis
- Education, Incident Type 2 Diabetes and Impact of Differential Overweight or Obese: A Danish Registry Study
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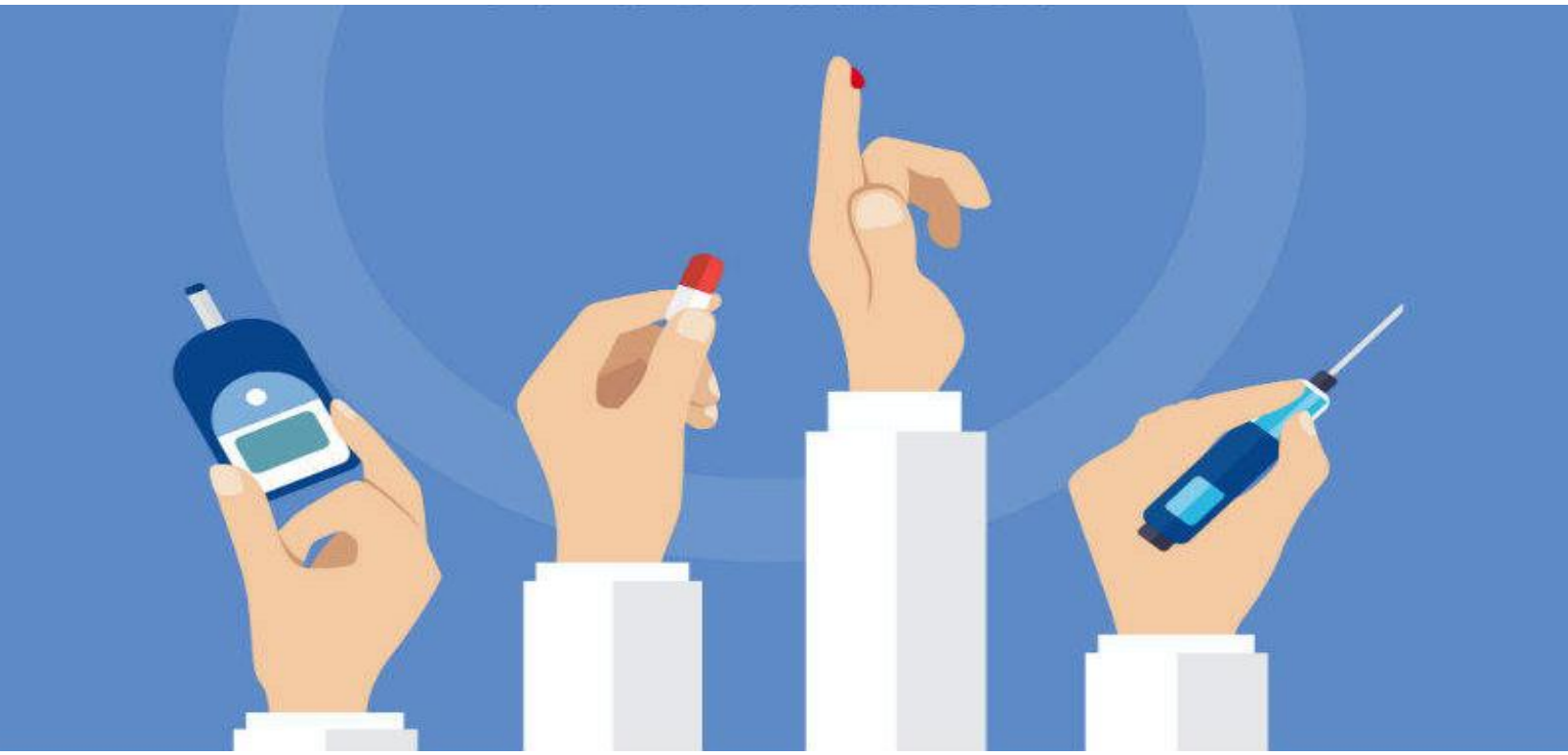
Should you require any specific article or medical information, please feel free to contact us at medicalservices@microlabs.in

Looking forward to your valuable feedback

Best Regards,
Medical Team, Micro Labs Limited



Diabetic Complications and the associations between the Neutrophil-to-Lymphocyte Ratio

Type 2 diabetes mellitus (T2DM) is a significant health burden. Chronic inflammation has been considered the potential pathogenesis responsible for the development of diabetic complications. However, the application of many inflammatory markers has been limited in daily clinical practice because of their costs and technical difficulties in measuring. It is noteworthy that the neutrophil-to-lymphocyte ratio (NLR), an easily measurable and inexpensive laboratory index calculated by routinely analyzed leukocyte characteristics, combines the negative effects of neutrophils on endothelial damage with the anti-atherosclerotic role of lymphocytes. Therefore, the NLR has been considered a convenient indicator for systemic inflammation. However, large population studies about investigating the associations of the NLR level with diabetic complications including cardiovascular and cerebrovascular diseases (CVD), diabetic kidney disease (DKD), and diabetic retinopathy (DR) in the same population were limited. The aim of our study is to evaluate the associations between the NLR level and the prevalence of CVD, DKD, and DR in adults with diabetes simultaneously.

In this cross-sectional survey, 4,813 diabetic adults were included. Persons underwent several medical examinations, including the measurement of anthropometric factors, blood pressure, routinely analyzed leukocyte characteristics, glucose, lipid profiles, urine albumin/creatinine ratio, and fundus photographs.

Compared with the first quartile of the NLR level, the odds of having CVD was significantly increased by 21% for participants in the highest quartile (OR 1.21; 95% CI 1.00, 1.47) $P<0.05$. Similarly, the

prevalence of DKD among participants in the highest quartile of the NLR level was significantly increased by 150% (OR 2.50; 95% CI 1.95, 3.19) (P<0.05). However, no association was found between the NLR level and the prevalence of DR (P<0.05). These associations were all fully adjusted.

A higher NLR level was associated with an increased prevalence of CVD and DKD, other than DR, in diabetic adults

Table: Associations between the NLR level quartiles and the prevalence of DKD.

	NLR level quartiles				*P* for trend	1SD increment of NLR
	Q 1 (≤1.38)	Q 2 (>1.38, ≤1.78)	Q 3 (>1.78, ≤2.32)	Q 4 (>2.32)		
			In total individuals			
Ln ACR	Ref.	0.18 (0.07, 0.29)	0.36 (0.25, 0.47)	0.59 (0.48, 0.70)	<0.001	0.23 (0.19, 0.27)
eGFR	Ref.	-1.07 (-2.52, 0.38)	-1.69 (-3.15, -0.24)	-6.19 (-7.65, -4.73)	<0.001	-2.35 (-2.87, -1.84)
DKD	Ref	1.60 (1.27, 2.02)	1.98 (1.58, 2.48)	2.60 (2.08, 3.24)	<0.001	1.35 (1.26, 1.45)
Ln ACR[1]	Ref.	0.12(0.01, 0.23)	0.28(0.17, 0.39)	0.43(0.32, 0.54)	<0.001	0.18(0.14, 0.22)
eGFR[2]	Ref.	-1.24 (-2.75, 0.27)	-1.81 (-3.33, -0.29)	-5.14 (-6.66, -3.63)	<0.001	-1.85 (-2.39, -1.30)
DKD[1]	Ref.	1.54 (1.20, 1.99)	2.06 (1.61, 2.65)	2.50 (1.95, 3.19)	<0.001	1.36 (1.25, 1.47)
			In individuals with normal eGFR (eGFR ≥ 90 mL/min per 1.73 m^2)			
Ln ACR[1]	Ref.	0.11 (-0.01, 0.22)	0.27 (0.15, 0.39)	0.29 (0.17, 0.41)	<0.001	0.12 (0.07, 0.16)
DKD[1]	Ref.	1.65 (1.18, 2.30)	2.11 (1.52, 2.93)	2.19 (1.58, 3.03)	<0.001	1.20 (1.08, 1.33)

Source: Wan H et al. J Diab Res. 2020. ID 6219545, 1-9.

CV Risk Reduction with Liraglutide: An Exploratory Mediation Analysis

Liraglutide is a glucagon-like peptide 1 receptor agonist (GLP-1 RA) approved for the management of hyperglycemia in type 2 diabetes and for reduction of cardiovascular (CV) risk in patients with type 2 diabetes and clinical CV disease (CVD).

The LEADER trial demonstrated a reduced risk of cardiovascular (CV) events for patients with type 2 diabetes who received the glucagon-like peptide 1 receptor agonist liraglutide versus placebo. The mechanisms behind this CV benefit remain unclear. We aimed to identify potential mediators for the CV benefit observed with liraglutide in the LEADER trial.

Buse et al performed exploratory analyses to identify potential mediators of the effect of liraglutide on major adverse CV events (MACE; composite of CV

death, nonfatal myocardial infarction, or nonfatal stroke) from the following candidates: glycated hemoglobin (HbA1c), body weight, urinary albumin-to-creatinine ratio (UACR), confirmed hypoglycemia, sulfonylurea use, insulin use, systolic blood pressure, and LDL cholesterol. These candidates were selected as CV risk factors on which liraglutide had an effect in LEADER such that a reduction in CV risk might result. Buse et al. used two methods based on a Cox proportional hazards model and the new Vansteelandt method designed to use all available information from the mediator and to control for confounding factors.

Analyses using the Cox methods and Vansteelandt method indicated potential mediation by HbA1c (up to 41% and 83% mediation, respectively) and UACR (up to 29% and 33% mediation, respectively) on the effect of liraglutide on MACE. Mediation effects were small for other candidates. These analyses identify HbA1c and, to a lesser extent, UACR as potential mediators of the CV effects of liraglutide. Whether either is a marker of an unmeasured factor or a true mediator remains a key question that invites further investigation.

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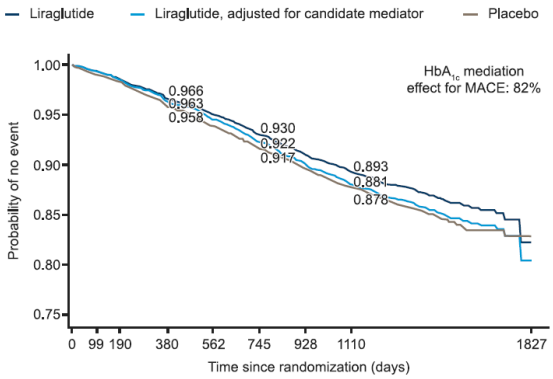
Probability of no MACE occurring in patients treated with liraglutide and placebo



Source: Buse et al. Diabetes Care 2020 May; dc192251. https://doi.org/10.2337/dc19-2251

Education and Incident Type 2 Diabetes and Impact of Differential Overweight or Obese: A Danish Registry Study

Educational inequality in type 2 diabetes incidence is evident in many high-income countries. Previous studies have shown that differential exposure to being overweight/obese across educational groups may partly explain this inequality. Whether differential susceptibility to being overweight/obese across educational groups contributes to this inequality has been investigated less frequently, even though it is a plausible mechanism. The two mechanisms may even be highly intertwined. In this longitudinal cohort study, we investigated the simultaneous contribution of differential exposure and differential susceptibility to being overweight/obese to educational inequality in type 2 diabetes incidence.

The study population comprised 53,159 Danish men and women aged 50–64 years at baseline who were followed for a mean of 14.7 years. We estimated rate differences of type 2 diabetes by education level per 100,000 person-years. Using counterfactual mediation analysis, these rate differences were decomposed into proportions attributable to differential exposure, differential susceptibility and all other pathways, respectively. We compared this approach with conventional approaches to mediation and interaction analysis.

Compared with a high level of education, a low education level was associated with 454 (95% CI 398, 510) additional cases of type 2 diabetes, and a medium education level with 316 (CI 268, 363) additional cases. Differential exposure to being overweight/obese accounted for 37% (CI 31%, 45%) of the additional cases among those with a low education level and 29% (CI 24%, 36%) of the additional cases among those with a medium education level. Differential susceptibility accounted for 9% (CI 4%, 14%) and 6% (CI 3%, 10%) of the additional cases among those with a low and medium education level, respectively. Compared with the counterfactual approach, the conventional approaches suggested stronger effects of both mechanisms.

Differential exposure and susceptibility to being overweight/obese are both important mechanisms in the association between education and type 2 diabetes incidence.

Variable	RD (95% CI)	Proportion of total effect (95% CI)
High→medium level of education		
Total effect of education level	316 (268, 363)	100%
Differential exposure to being overweight/obese	92 (83, 102)	29% (24, 36)
Differential susceptibility to being overweight/obese	20 (8, 32)	6% (3, 10)
Other pathways (direct effect)	204 (158, 249)	65% (59, 69)
High→low level of education		
Total effect of education level	454 (398, 510)	100%
Differential exposure to being overweight/obese	168 (149, 186)	37% (31, 45)
Differential susceptibility to being overweight/obese	41 (17, 64)	9% (4, 14)
Other pathways (direct effect)	246 (193, 298)	54% (48, 59)

Mathisen J, Diabetologia. 2020;10.1007/s00125-020-05150-3. [published online ahead of print, 2020 May 3].