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## **Diabetes Medication Use and Blood Lactate Level in Type 2 Diabetics in the Atherosclerosis Risk in Communities Carotid MRI Study**

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In previous work in the ARIC Carotid MRI study, blood lactate, an indicator of oxidative capacity, is associated with prevalence of type 2 diabetes and with fasting glucose among non-diabetic persons. Lactate, a major gluconeogenic precursor, is also higher among patients who take metformin, which decreases hepatic insulin resistance and gluconeogenesis thereby increasing lactate. Therefore, we hypothesize that medications that decrease peripheral insulin resistance should be associated with lower lactate levels given their impact on glucose oxidation. To investigate this hypothesis we tested the difference in mean lactate between users and non-users of diabetes medications among ARIC Carotid MRI Study participants. This analysis included 493 adults ages 60 to 84 with type 2 diabetes. Similar to previous studies, metformin use was associated with slightly higher mean lactate level (difference in mean = 0.68 mg/dl,  $p = 0.078$ ). Thiazolidinedione (TZD) use was associated with lower blood lactate levels (-1.38 mg/dl,  $p = 0.001$ ), but use of other diabetes medications was not associated with differences in lactate (insulin: -0.52 mg/dl,  $p = 0.34$ ; sulfonylureas: 0.01 mg/dl,  $p = 0.98$ ; any diabetes medication: -0.26 mg/dl,  $p = 0.49$ ). The results were similar for linear regression models when adjusted for age, sex, race, education level, BMI, and physical activity. In this cross-sectional analysis, metformin use was associated with marginally higher levels, while TZD use was associated with lower levels of lactate. The opposite association for TZDs may be explained through their action on peripheral, and not hepatic, insulin resistance. Decreased peripheral insulin resistance may then lead to increased glucose utilization and decreased blood lactate through a number of potential pathways that require additional study. Further investigation of the role that diabetes medications play in mechanisms of insulin resistance and oxidative metabolism may provide insight into diabetes treatment.

**Table 1. Difference in mean lactate level by diabetes medication use in diabetics in the ARIC Carotid MRI study**

Diabetes Medications	Mean lactate level in mg/dl		Difference in mean lactate	P-value for difference
	User	Non-user		
Metformin	9.57	8.89	0.68	0.078
Thiazolidinediones	7.96	9.34	-1.38	0.001
Insulin	8.69	9.21	-0.52	0.339
Sulfonylureas	9.14	9.13	0.01	0.984
Any class of medication	9.02	9.28	-0.26	0.491

\* Sample size is 493 diabetics with non-missing information on diabetes medication use.

\*\* All values are survey weighted and unadjusted.