



## Minimally Invasive Surgery

Presented at the Academic Surgical Congress 2019

# Plasma lactate as a marker of metabolic health: Implications of elevated lactate for impairment of aerobic metabolism in the metabolic syndrome



Terry E. Jones, PhD<sup>a,\*</sup>, Walter J. Pories, MD<sup>b</sup>, Joseph A. Houmard, PhD<sup>c,d</sup>, Charles J. Tanner, MS<sup>c,d</sup>, Donghai Zheng, PhD<sup>c,d</sup>, Kai Zou, PhD<sup>f</sup>, Paul M. Coen, PhD<sup>g</sup>, Bret H. Goodpaster, PhD<sup>g</sup>, William E. Kraus, MD<sup>h</sup>, G. Lynis Dohm, PhD<sup>e</sup>

<sup>a</sup> Department of Physical Therapy, East Carolina University, Greenville, NC<sup>b</sup> Department of Surgery, East Carolina University, Greenville, NC<sup>c</sup> Department of Kinesiology, East Carolina University, Greenville, NC<sup>d</sup> Human Performance Laboratory, East Carolina University, Greenville, NC<sup>e</sup> Department of Physiology, East Carolina University, Greenville, NC<sup>f</sup> Department of Exercise and Health Sciences, University of Massachusetts Boston, Boston, MA<sup>g</sup> Translational Research Institute for Metabolism and Diabetes, Florida Hospital, Orlando, FL<sup>h</sup> Division of Cardiology, Duke University Medical Center, Durham, NC

## ARTICLE INFO

## Article history:

Accepted 24 April 2019

Available online 25 June 2019

## ABSTRACT

**Background:** Fasting lactate is elevated in metabolic diseases and could possibly be predictive of the risk of developing the metabolic syndrome.

**Methods:** Plasma samples were analyzed for fasting lactate to compare lean subjects, nondiabetic subjects with severe obesity, and metabolically impaired subjects. Subjects with severe obesity were studied 1 week before and 1 week to 9 months after gastric bypass surgery. Subjects with components of the metabolic syndrome were studied before and after 6 months of an exercise intervention.

**Results:** Metabolically impaired subjects had higher fasting lactate concentrations ( $P < .0001$ ) and respond to a glucose or insulin challenge with higher lactates than non-obese subjects ( $P < .004$ ). Lactate was significantly reduced a week after gastric bypass surgery ( $P < .05$ ) and further reduced 1 to 9 months after surgery ( $0.95 \pm 0.04$  mM in non-obese,  $1.26 \pm 0.12$  mM in subjects with severe obesity, and  $0.68 \pm 0.03$  mM 1–3 months after gastric bypass). Six months of chronic exercise resulted in a 16% reduction ( $P = .028$ ) in fasting lactate.

**Conclusion:** Fasting plasma lactate was elevated in obese subjects with the metabolic syndrome compared with healthy lean individuals. Lactate was reduced by exercise and bariatric surgery, interventions that improve metabolic health and risk for subsequent disease. The results of this study and those previously published by our research group suggest that elevated lactate may be caused by an impairment in aerobic metabolism and may offer a metric assessing the severity of the metabolic syndrome.

© 2019 Elsevier Inc. All rights reserved.

## Introduction

Fasting lactate concentration has long been used to indicate the severity of acute illnesses and as a useful predictor of clinical outcomes.<sup>1</sup> In addition to the increase in lactate in tissue hypoxia and hypoperfusion associated with conditions such as shock and sepsis, it is also elevated in burns, diabetic ketoacidosis, malignancy, and by some toxins. Several studies suggest that fasting lactate may also be a useful indicator of chronic metabolic diseases. Plasma lactate concentrations were elevated in obesity and yet higher in type 2

Supported by grants from the National Institutes of Health (HL-57354 to WK and DK078192 to BG).

Presented by Dr Walter J. Pories at the 14th Annual Academic Surgical Congress in Houston, Texas on February 6, 2019.

\* Reprint requests: Terry E. Jones, PhD, Department of Physical Therapy, College of Allied Health Sciences, East Carolina University, Greenville, NC 27834.

E-mail address: [joneste@ecu.edu](mailto:joneste@ecu.edu) (T.E. Jones).

<https://doi.org/10.1016/j.surg.2019.04.017>

0039-6060/© 2019 Elsevier Inc. All rights reserved.

diabetics compared with lean controls subjects.<sup>2</sup> In the Atherosclerosis Risk in Communities (ARIC) Carotid magnetic resonance imaging trial, 1,709 older adults (mean age 70.4 years) were studied for an association between lactate and type 2 diabetes (T2D). The quartile with the lowest lactate concentrations had 12% incidence of T2D, whereas 30% of the highest quartile exhibited T2D. Lactate was still linked with T2D after adjustments for factors such as age, sex, ethnicity, body mass index (BMI), and waist circumference.<sup>3</sup> In a case-cohort analysis of 544 incident cases of T2D and 533 non-cases (ARIC subjects at year 9 of follow-up), lactate at baseline predicted incident T2D development.<sup>4</sup> Another data analysis from the ARIC study (8,045 subjects without diabetes at baseline and median follow-up of 12 years) showed that elevated lactate preceded T2D.<sup>5</sup> These studies demonstrate the strong association between fasting plasma lactate and T2D and suggest that lactate may be a useful predictor of patients at risk for development of T2D and other metabolic diseases.

Plasma lactate may also be predictive of other aspects of the metabolic syndrome. In the ARIC study, elevated lactate was found to be associated with higher triglycerides, lower HDL, and higher fasting glucose among nondiabetics.<sup>3</sup> In a metabolomics analysis of plasma samples from the Framingham Heart Study ( $n = 650$ ) and the BioImage study ( $n = 670$ ), lactate was the top organic acid biomarker for obesity, dyslipidemia, and dysglycemia.<sup>6</sup> Juraschek et al<sup>4</sup> reported that fasting lactate at baseline in 5,554 ARIC study subjects with no subclinical or diagnosed hypertension was a strong predictor of hypertension development during an 11.9-year median follow-up.

Two studies investigated the effects of weight loss on plasma lactate concentrations with respect to metabolic health. Chondronikola et al<sup>7</sup> studied subjects after 5%, 11%, and 16% weight loss and found that fasting plasma lactate was correlated with weight loss. Crawford et al<sup>8</sup> measured fasting lactate in subjects with obesity and the metabolic syndrome, subjects with obesity but without the metabolic syndrome, and lean controls. Lactate concentrations were higher in the subjects with obesity, with or without metabolic syndrome, than in lean subjects. The metabolic syndrome subjects were placed on a 12 to 20 week very low-calorie diet intervention that reduced lactate by 31%, with concurrent improvements in diastolic blood pressure, systolic blood pressure, glucose, insulin, and triglycerides.

Based on existing literature and our own experience, we hypothesized that individuals at risk of metabolic diseases, such as hypertension, diabetes, dyslipidemia, and cardiovascular disease, would have elevated fasting plasma lactate concentrations. In addition, we postulated that interventions that are known to ameliorate metabolic diseases would reduce fasting plasma lactate. To test this hypothesis, we relied on previous studies that our research group had conducted and additional studies before and after gastric bypass surgery.

The ultimate purpose of the present study was to determine whether fasting plasma lactate is related to metabolic status. If lactate is a valid marker of risk for development or progression of metabolic disease, a physician could use this for recommendation of lifestyle modifications that would reduce the risk, which could then be confirmed by a follow-up fasting plasma lactate.

## Methods

### Subjects

Studies were approved by the University and Medical Center Institutional Review Board at East Carolina University, the Duke Health Institutional Review Board, and University of Pittsburgh Institutional Review Board. All subjects provided informed consent.

Fasting plasma samples from two previously reported studies were analyzed for lactate: STRRIDE<sup>9</sup> and POWER.<sup>10</sup> Additional non-obese subjects ( $n = 39$ ) and nondiabetic subjects with severe obesity ( $n = 13$ ) were recruited. Sex, age, and BMI of subjects are given in the figure legends.

In the Studies of a Targeted Risk Reduction Intervention through Defined Exercise trial (STRRIDE) subjects were chosen who were sedentary and overweight with mild to moderate lipid abnormalities.<sup>9,11</sup> These characteristics are clearly consistent with increased risk of metabolic diseases and we have chosen to term their condition as metabolically impaired. Metabolically impaired subjects were first tested and then subjected to 1 of 2 exercise programs of different exercise intensity. After 6 months, they were studied again. STRRIDE was the ideal design to test our hypothesis and plasma samples were available for lactate analysis.

A second opportunity to test our hypothesis was provided by subjects in the Post-Operative Wellness and Exercise Regimen (POWER) study, who had undergone gastric bypass surgery.<sup>10</sup> Patients with severe obesity have a high incidence of metabolic diseases that are ameliorated after gastric bypass surgery. In the Longitudinal Assessment of Bariatric Surgery study, 33% of the subjects with severe obesity had diabetes at baseline, whereas 63% had dyslipidemia and 68% had hypertension.<sup>12</sup> Our group was the first to report remission of diabetes within a few days after gastric bypass.<sup>13</sup> Many other groups have confirmed and extended this finding; in the Longitudinal Assessment of Bariatric Surgery study, 67.5% of patients had remission of diabetes, 61.9% had resolution of dyslipidemia, and 38.2% had remission of hypertension after gastric bypass.<sup>12</sup>

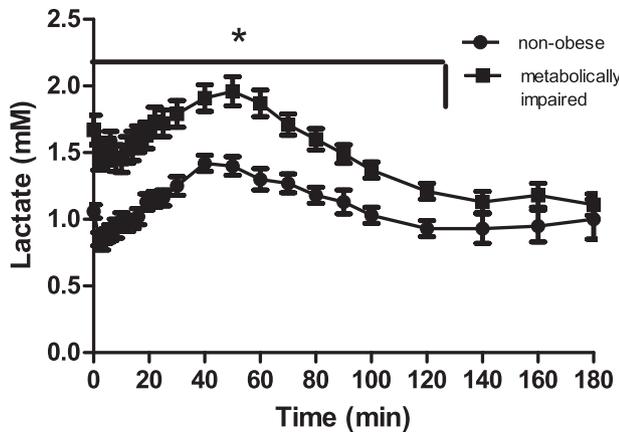
### Procedures

Blood was drawn from an antecubital vein in the morning after an overnight fast and immediately placed on ice. Blood cells were separated by centrifugation, and plasma was frozen at  $-80^{\circ}\text{C}$  until analyzed. Insulin was determined with an ultrasensitive immunoassay (Access I for samples from STRRIDE subjects and Access II for samples from POWER and recruited subjects, Beckman Coulter, Brea, CA). Lactate was determined with an oxidation assay (YSI Stat 2300, YSI Life Sciences, Yellow Springs, OH) for samples from STRRIDE and DxCG600 for samples from the POWER and community recruited subjects, Beckman Coulter, Brea CA).

Methods are described previously for exercise<sup>9</sup> and insulin-modified intravenous glucose tolerance test (IVGTT).<sup>10,14</sup> The following are brief descriptions of the exercise program and IVGTT. Chronic exercise comparable to  $\approx 12$  miles of walking per week at 65% to 80% peak oxygen consumption ( $\text{VO}_2$ ) or up to  $\approx 20$  miles of jogging per week at 65% to 80%  $\text{VO}_2$  max was done for 5 to 6 months by metabolically impaired subjects. With respect to IVGTT, initial blood samples were collected after an overnight fast. Immediately after, 50% glucose was administered, and at minute 20, insulin was administered. Frequent samples were collected for 3 hours.

### Statistics

Data are shown as mean  $\pm$  standard error of the mean except where noted. An unpaired  $t$  test was used to compare plasma lactate concentrations from an IVGTT between non-obese and metabolically impaired subjects and fasting plasma lactate concentrations before and after a 6-month exercise program in metabolically impaired subjects. Comparisons among the non-obese group, subjects with severe obesity group, and 1 to 3 months after gastric bypass (post-RYGB) group were made using a one-way ANOVA and a Tukey multiple comparison test for post hoc analysis. A paired sample  $t$  test was used to determine significance



**Fig 1.** Changes in plasma lactate during insulin-modified IVGTT (mean  $\pm$  standard error of the mean) in non-obese subjects and subjects with components of the metabolic syndrome (STRRIDE). Non-obese subjects: 15 women,  $42.3 \pm 3.4$  years of age,  $24.1 \pm 1.0$  kg/m<sup>2</sup> BMI. Metabolically impaired subjects: 27 women,  $54.2 \pm 1.2$  years of age,  $30.5 \pm 0.7$  kg/m<sup>2</sup> BMI. \*Significantly different from non-obese at  $P = .004$  to  $.0001$ .

between 1 week pre-RYGB and 1 week post-RYGB, and 1 to 3 months post-RYGB and 7 to 9 months post-RYGB fasting lactate. Pearson correlation coefficient was used to determine whether there was a relationship between fasting lactate and insulin sensitivity ( $S_i$ ) in the metabolically impaired and 1 to 3 months post-RYGB. Significance was set at a  $P < .05$ .

## Results

### Plasma lactate in metabolically impaired subjects

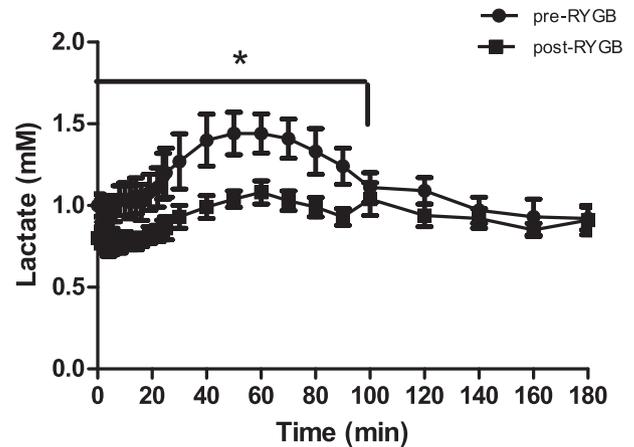
A group of healthy non-obese subjects was recruited for comparison with the metabolically impaired subjects (STRRIDE). Figure 1 shows plasma lactate during an IVGTT, whereas glucose was administered at time zero and insulin was administered at 20 minutes. Fasting plasma lactate was 58% higher in metabolically impaired subjects compared with non-obese subjects ( $P < .0001$ ) and remained significantly higher ( $P < .004$  to  $.0001$ ) through 120 minutes of the IVGTT (Fig 1).

### Plasma lactate in subjects before and after RYGB and before and after exercise

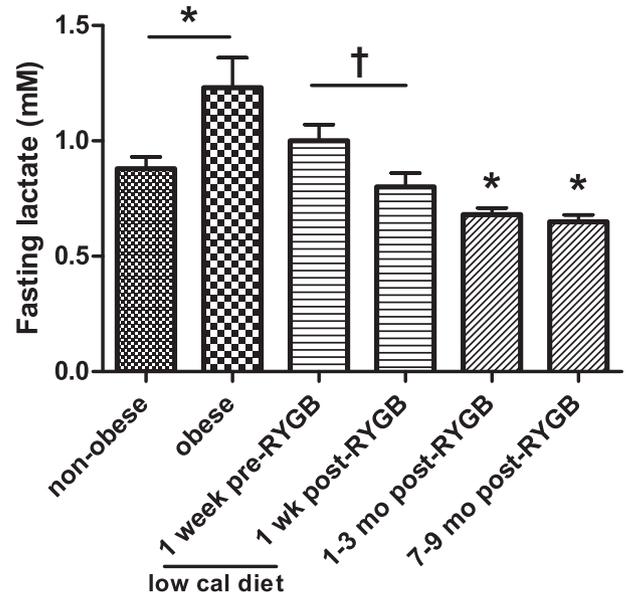
Severely obese subjects were studied with IVGTT 1 week before and 1 week after RYGB surgery (Fig 2). Because metabolism is altered by caloric intake, subjects were studied after 1 week on a diet (800 kcal/day) to roughly match caloric intake after RYGB surgery. Before surgery, injection of glucose caused lactate to rise and injection of insulin accelerated the lactate rise (before surgery). Remarkably, as early as a week after surgery, fasting lactate was reduced ( $P < .05$ ). More interesting was the minimal increase in lactate in response to the glucose or insulin challenge.

As evident in Fig 3, fasting plasma lactate in non-obese subjects, subjects with severe obesity, and 1 to 3 months post-RYGB subjects differed significantly at  $P < .05$ . The 1 to 3 months post-RYGB and 7 to 9 months post-RYGB were not significantly different ( $P = .51$ ).

The STRRIDE study also investigated the effect of exercise on metabolically impaired subjects. Six months of chronic exercise resulted in a 16% reduction ( $P = .028$ ) in fasting lactate (Fig 4).



**Fig 2.** Changes in plasma lactate during insulin-modified IVGTT (mean  $\pm$  standard error of the mean) in patients 1 week before RYGB and 1 week after RYGB. Patients: 12 women,  $43.3 \pm 3.3$  years of age,  $44.6 \pm 1.4$  kg/m<sup>2</sup> BMI at baseline. \*Significantly different from pre-RYGB at minute 0, 8, 10, 14, 19, 30, 40, 50, 60, 70, 80, 90 at  $P < .05$  to  $.011$ .

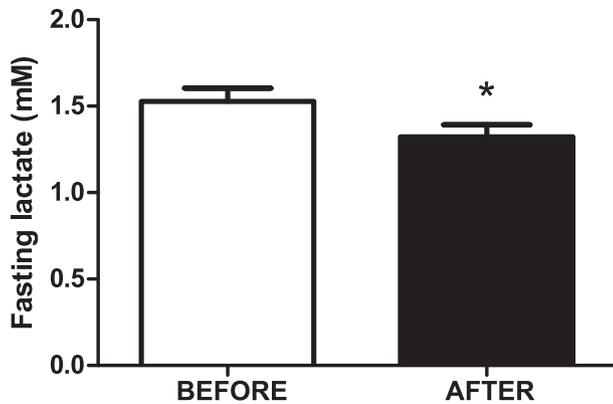


**Fig 3.** Fasting lactate (mean  $\pm$  standard error of the mean) in non-obese, obese, 1 week pre-RYGB, 1 week post-RYGB, 1- to 3-month post-RYGB, and 7- to 9-month post-RYGB patients. Non-obese patients: 39 women,  $33.5 \pm 2.0$  years of age,  $23.7 \pm 0.6$  kg/m<sup>2</sup> BMI. Nondiabetic obese patients: 13 women,  $43.2 \pm 2.9$  years of age,  $43.4 \pm 3.1$  kg/m<sup>2</sup> BMI. One week pre-RYGB patients: 12 women,  $43.3 \pm 3.3$  years of age,  $44.6 \pm 1.4$  kg/m<sup>2</sup> BMI. One- to 3-month post-RYGB patients: 22 women,  $42.5 \pm 1.9$  years of age,  $39.2 \pm 1.3$  kg/m<sup>2</sup> BMI. Repeated measure of lactate at 7 to 9 months post-RYGB is displayed to show that fasting lactate did not change in that timeline. \*Significantly different from non-obese at  $P = .032$ . †Significantly different from 1 week pre-RYGB at  $P = .02$ .

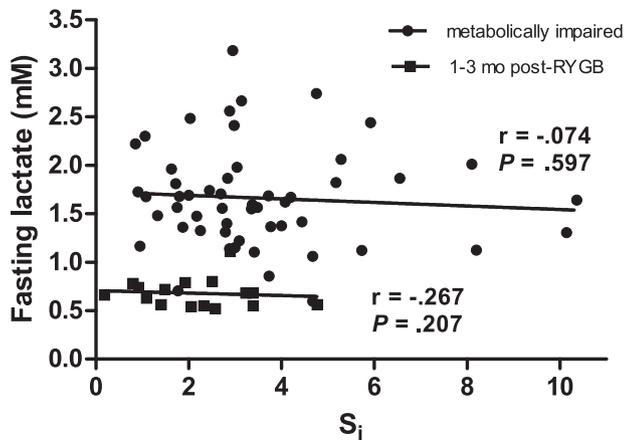
### Insulin sensitivity and lactate

Because insulin sensitivity was measured in both the STRRIDE and POWER studies, we were able to compare insulin sensitivity and fasting lactate (Fig 5). There was no relationship between insulin sensitivity ( $S_i$  from the IVGTT) and fasting plasma lactate concentration. In addition, lactate was lower after gastric bypass surgery at comparable insulin sensitivities to individuals with components of the metabolic syndrome.

The metabolically impaired group identified in Figs 1, 4, and 5 are subjects from the STRRIDE study.<sup>9</sup> The 39 non-obese subjects



**Fig 4.** Fasting lactate (mean  $\pm$  standard error of the mean) in metabolically impaired subjects before and after 6 months of an exercise program (STRRIDE). Patients: 97 men and 76 women,  $52.4 \pm 0.5$  years of age,  $29.7 \pm 0.2$  kg/m<sup>2</sup> BMI at baseline. \*Significantly different from before at  $P < .0001$ .



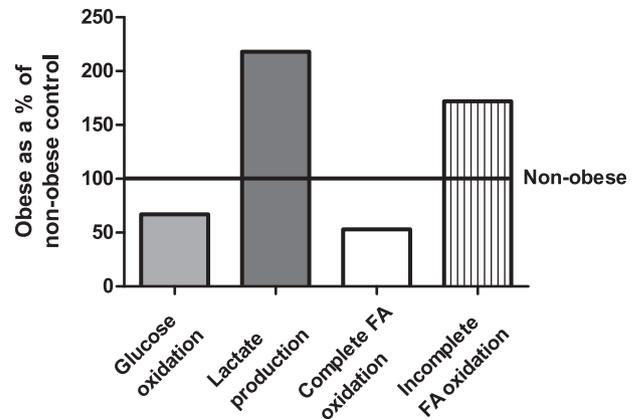
**Fig 5.** The relationships of fasting lactate and insulin sensitivity ( $S_i$ ) in metabolically impaired subjects (STRRIDE) and in 1- to 3-month post-RYGB subjects (POWER). Metabolically impaired subjects: 26 men and 27 women,  $51.6 \pm 1.0$  years of age,  $30.2 \pm 0.4$  kg/m<sup>2</sup> BMI. One- to 3-month post-RYGB subjects: 2 men and 22 women,  $42.8 \pm 1.9$  years of age,  $39.4 \pm 1.4$  kg/m<sup>2</sup> BMI.

and the 13 nondiabetic obese subjects in Fig 3 were from studies conducted at East Carolina University and did not include subjects from the STRRIDE or POWER studies.

## Discussion

Fasting lactate is elevated in metabolic diseases, such as diabetes, hypertension, dyslipidemia, etc., and may be a predictor of who is most at risk of developing metabolic diseases.<sup>2–6</sup> We have added to this growing base of evidence by showing that a group of patients recruited because they have components of the metabolic syndrome have elevated lactate at fasting and during a glucose or insulin challenge. We also show that nondiabetic patients with severe obesity have elevated lactate at fasting. Furthermore, interventions such as gastric bypass surgery and exercise, which improve metabolic health, reduce fasting plasma lactate.

Insulin resistance is often cited as a cause of the metabolic syndrome. Lovejoy et al<sup>15</sup> reported that basal (fasting) lactate was inversely related to insulin sensitivity. However, in neither the STRRIDE nor POWER studies were there correlations between insulin sensitivity and lactate. In addition, lactate was lower in the POWER study (after gastric bypass surgery) at comparable insulin

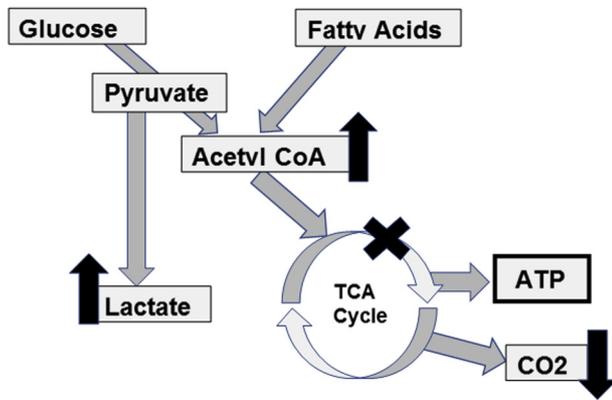


**Fig 6.** Fatty acid and glucose oxidation and lactate production in vitro incubated human muscle fiber strips from lean and severely obese subjects. Redrawn from data published in Friedman et al,<sup>16</sup> Hulver et al,<sup>18</sup> and Berggren et al.<sup>19</sup> FA, fatty acid.

sensitivities as the STRRIDE study. This is in agreement with the finding of Reed et al<sup>14</sup> who found that insulin sensitivity of nondiabetic patients did not improve a week after gastric bypass surgery, but we here report that plasma lactate was reduced. The present results (Fig 5) demonstrate that the correlation reported by Lovejoy et al is not evidence for a cause and effect relationship.<sup>15</sup>

The results of this study raise an important question: What causes lactate to be elevated in metabolically impaired individuals and how is lactate reduced after gastric bypass surgery? Steady state blood lactate is determined by the rate of production and utilization. An increase in lactate concentration, as seen with metabolic diseases, could be a result of increased production or decreased utilization. Reduced utilization by conversion of lactate to glucose through gluconeogenesis is an unlikely cause of increased lactate because that would be accompanied by a reduction in blood glucose. In most, if not all, metabolic diseases, lactate and glucose are concurrently elevated, and hypoglycemia has not been reported. Thus, we conclude that elevated steady state lactate is likely the result of increased production, primarily in muscle. This conclusion is supported by our published observation that lactate production was elevated in muscle of subjects with severe obesity.<sup>16</sup>

Lactate production is a reflection of the gap between energy requirements of the tissue and the ability to produce energy through aerobic mitochondrial oxidation. In the skeletal muscle of healthy individuals under resting conditions, mitochondrial substrate oxidation supplies the majority of energy that is required and lactate production through anaerobic glycolysis is minimal. Lactate production is increased by either increasing energy expenditure, as in sprint exercise, or through a reduction in aerobic energy production. Elevated lactate production in muscle of obese individuals leads to the conclusion that aerobic substrate oxidation must be reduced in metabolically impaired individuals. In agreement, our published results<sup>16–19</sup> demonstrate that the oxidation of glucose and free fatty acids are reduced in the muscle of severely obese individuals. The results of our studies with muscle from severely obese and non-obese control subjects are summarized in Fig 6. Complete oxidation of glucose and fatty acids were reduced by approximately 40% in muscle of obese individuals compared with non-obese controls. To make up for this reduction in adenosine triphosphate production from aerobic substrate oxidation, there was a compensatory increase of lactate production by approximately 2-fold. There was also a remarkable increase in the incomplete oxidation of fatty acids.<sup>19</sup>  $\beta$ -Oxidation of fatty acids generates acetyl-coenzyme A (CoA), and incomplete oxidation



**Fig 7.** Pathways of glucose and fatty acid oxidation. Data supporting this figure are summarized in Fig 6. Oxidation of glucose and fatty acids was depressed in the muscle from obese subjects (decreased CO<sub>2</sub>). To compensate for the depressed aerobic ATP production, anaerobic glycolysis was increased in obese muscle (increased lactate). Incomplete oxidation of fatty acids (increased acetyl CoA) suggests there is impaired function of the TCA cycle in muscle of obese subjects. ATP, adenosine triphosphate; CoA, coenzyme A; TCA, tricarboxylic acid.

products are acetyl-CoA and derivatives of acetyl-CoA.<sup>20,21</sup> Because acetyl-CoA is oxidized to CO<sub>2</sub> in the tricarboxylic acid cycle, an accumulation suggests impairment of the tricarboxylic acid cycle. These changes are shown in Fig 7.

Muscle lactate production was elevated in the obese subjects before surgery and dramatically reduced after RYGB. We found no change in insulin sensitivity in these early periods after RYGB,<sup>14</sup> showing that uptake of glucose into the muscle was the same before and after surgery. As lactate production represents the gap between aerobic substrate oxidation and energy utilization, our interpretation of these data is that aerobic glucose oxidation, particularly in skeletal muscle, increased after RYGB.

Lactate production, most likely in the muscle, is elevated in metabolically impaired subjects, and this leads to substrate driven glucose production in the liver. Elevated plasma lactate concentration being the cause of increased glucose production is supported by the results of Chondronikola et al.<sup>7</sup> They found that lactate concentration and glucose production were correlated in obese subjects before and after weight loss. We have termed this scenario of elevated lactate and glucose production the vicious Cori Cycle.<sup>22</sup> A few days after RYGB surgery, both plasma lactate and glucose return to normal levels in diabetic patients. We have proposed that this is a result of increased pyruvate oxidation, less lactate production, and decreased substrate driven gluconeogenesis.<sup>22</sup> These changes in muscle metabolism may provide an explanation for the remission of diabetes in response to RYGB.

The capacity of the aerobic system and health are closely related. A remarkable and relevant discovery was the epidemiological observation that the maximal ability to use oxygen during exercise (VO<sub>2max</sub>) was highly related to morbidity and mortality. Wei et al<sup>23</sup> followed 25,714 men and reported that “low cardiorespiratory fitness was a strong and independent predictor of cardiovascular disease and all-cause mortality.” Myers et al<sup>24</sup> followed 6,213 men for 6.2 years and reported, “Exercise capacity is a more powerful predictor of mortality among men than other established risk factors for cardiovascular disease.” There is also a substantial body of evidence that mitochondrial function is impaired in the muscle of obese and diabetic patients.<sup>25–27</sup> Together, these data suggest that an impairment in oxidative capacity in human skeletal muscle, and an increase in fasting plasma lactate, are linked with mortality and metabolic disease. Obtaining a simple and easy measure that reflects oxidative capacity may thus be important in treating and preventing metabolic disease.

Clinically, lactate levels are often used as a marker for illness and responsiveness to interventions.<sup>1</sup> Point-of-care fingertip lactate measurement is accurate in detecting normal or modestly elevated lactate values.<sup>28</sup> Measurements of lactate may be useful in prescribing preventative measures such as exercise and diet to be taken before the appearance of metabolic disease and to determine whether such measures are having a positive impact in improving metabolic health. We propose that lactate should be more thoroughly investigated as a biomarker for metabolic health before the appearance of disease and as a biomarker for improved metabolic health.

## Acknowledgments

The authors would like to thank our participants in these studies and Jordan Sturgill for her assistance.

## Disclosure

No authors have any personal conflicts of interest.

## References

- Andersen LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW. Etiology and therapeutic approach to elevated lactate levels. *Mayo Clin Proc.* 2013;88:1127–1140.
- Chen YD, Varasteh BB, Reaven GM. Plasma lactate concentration in obesity and type 2 diabetes. *Diabetes Metab.* 1993;19:348–354.
- Crawford SO, Hoogeveen RC, Brancati FL, et al. Association of blood lactate with type 2 diabetes: The atherosclerosis risk in communities carotid MRI study. *Int J Epidemiol.* 2010;39:1647–1655.
- Juraschek SP, Shantha GPS, Chu AY, et al. Lactate and risk of incident diabetes in a case-cohort of the atherosclerosis risk in communities (ARIC) study. *PLoS ONE.* 2013;8:e55113.
- Juraschek SP, Selvin E, Miller ER, Brancati FL, Young JH. Plasma lactate and diabetes risk in 8045 participants of the atherosclerosis risk in communities study. *Ann Epidemiol.* 2013;23:791–796.
- Yin X, Subramanian S, Willinger CM, et al. Metabolite signatures of metabolic risk factors and their longitudinal changes. *J Clin Endocrinol Metab.* 2016;101:1779–1789.
- Chondronikola M, Magkos F, Yoshino J, et al. Effect of progressive weight loss on lactate metabolism: A randomized controlled trial. *Obesity (Silver Spring).* 2018;26:683–688.
- Crawford SO, Ambrose MS, Hoogeveen RC, Brancati FL, Ballantyne CM, Young JH. Association of lactate with blood pressure before and after rapid weight loss. *Am J Hypertens.* 2008;21:1337–1342.
- Kraus WE, Torgan CE, Duscha BD, et al. Studies of a targeted risk reduction intervention through defined exercise (STRRIDE). *Med Sci Sports Exerc.* 2001;33:1774–1784.
- Coen PM, Tanner CJ, Helbling NL, et al. Clinical trial demonstrates exercise following bariatric surgery improves insulin sensitivity. *J Clin Invest.* 2015;125:248–257.
- Bateman LA, Slentz CA, Willis LH, et al. Comparison of aerobic versus resistance exercise training effects on metabolic syndrome (from the studies of a targeted risk reduction intervention through defined exercise—STRRIDE-AT/RT). *Am J Cardiol.* 2011;108:838–844.
- Courcoulas AP, Christian NJ, Belle SH, et al. Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. *JAMA.* 2013;310:2416–2425.
- Pories WJ, MacDonald KG, Morgan EJ, et al. Surgical treatment of obesity and its effect on diabetes: 10-y follow-up. *Am J Clin Nutr.* 1992;55(2 Suppl):582S–585S.
- Reed MA, Pories WJ, Chapman W, et al. Roux-en-Y gastric bypass corrects hyperinsulinemia: implications for the remission of type 2 diabetes. *J Clin Endocrinol Metab.* 2011;96:2525–2531.
- Lovejoy J, Newby FD, Gebhart SS, DiGirolamo M. Insulin resistance in obesity is associated with elevated basal lactate levels and diminished lactate appearance following intravenous glucose and insulin. *Metab Clin Exp.* 1992;41:22–27.
- Friedman JE, Caro JF, Pories WJ, Azevedo JL, Dohm GL. Glucose metabolism in incubated human muscle: Effect of obesity and non-insulin-dependent diabetes mellitus. *Metab Clin Exp.* 1994;43:1047–1054.
- Houmard JA, Pories WJ, Dohm GL. Is there a metabolic program in the skeletal muscle of obese individuals? *J Obes.* 2011;2011:250496.
- Hulver MW, Berggren JR, Cortright RN, et al. Skeletal muscle lipid metabolism with obesity. *Am J Physiol Endocrinol Metab.* 2003;284:E741–E747.
- Berggren JR, Boyle KE, Chapman WH, Houmard JA. Skeletal muscle lipid oxidation and obesity: Influence of weight loss and exercise. *Am J Physiol Endocrinol Metab.* 2008;294:726.
- Thyfault JP, Cree MG, Tapscott EB, et al. Metabolic profiling of muscle contraction in lean compared with obese rodents. *Am J Physiol Regul Integr Comp Physiol.* 2010;299:R926–R934.

21. Baker PR, Boyle KE, Koves TR, et al. Metabolomic analysis reveals altered skeletal muscle amino acid and fatty acid handling in obese humans. *Obesity (Silver Spring)*. 2015;23:981–988.
22. Pories WJ, Dohm GL. Diabetes: Have we got it all wrong? Hyperinsulinism as the culprit: Surgery provides the evidence. *Diabetes Care*. 2012;35:2438–2442.
23. Wei M, Kampert JB, Barlow CE, et al. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA*. 1999;282:1547–1553.
24. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346:793–801.
25. Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med*. 2004;350:664–671.
26. Ritov VB, Menshikova EV, He J, Ferrell RE, Goodpaster BH, Kelley DE. Deficiency of subsarcolemmal mitochondria in obesity and type 2 diabetes. *Diabetes*. 2005;54:8–14.
27. Hesselink MKC, Schrauwen-Hinderling V, Schrauwen P. Skeletal muscle mitochondria as a target to prevent or treat type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2016;12:633–645.
28. Gaieski DF, Drumheller BC, Goyal M, Fuchs BD, Shofer FS, Zogby K. Accuracy of handheld point-of-care fingertip lactate measurement in the emergency department. *West J Emerg Med*. 2013;14:58–62.