Published in final edited form as:

Surgery. 2019 November ; 166(5): 861–866. doi:10.1016/j.surg.2019.04.017.

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

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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, non-diabetic 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 exercise intervention.

Results—Metabolically impaired subjects had higher fasting lactate concentrations (P<.0001) and respond to a glucose/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 1–9 months post-surgery (0.95 ± 0.04 mM in non-obese, 1.26 ± 0.12 mM in subjects with severe obesity, and 0.68 ± 0.03mM 1–3 months post-gastric bypass). Six months of chronic exercise resulted in a 16% reduction (p = 0.028) in fasting lactate.

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Conclusions—Fasting plasma lactate was elevated in obese subjects with the metabolic syndrome compared to 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.

INTRODUCTION

Fasting lactate concentration has long been used to indicate the severity of acute illnesses and as a useful predictor of clinical outcomes.[1] In addition to the increase in lactate in tissue hypoxia/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 diabetics compared to lean controls subjects.[2] In the Atherosclerosis Risk in Communities (ARIC) Carotid MRI (CAR-MRI) trial, 1709 older adults (mean age 70.4 yr) were studied for an association between lactate and type 2 diabetes (T2D). The quartile with the lowest lactate concentrations had 12% incidence of T2D while 30 % of the highest quartile exhibited T2D. Lactate was still linked with T2D after adjustments for factors, such as age, gender, ethnicity, BMI and waist circumference.[3] 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.[4] Another data analysis from the ARIC study, (8045 subjects without diabetes at baseline and median follow-up of 12 years) showed that elevated lactate preceded T2D.[5] 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 non-diabetics.[3] 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.[6] Juraschek et al[4] 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 over 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[7] studied subjects after 5%, 11% and 16% weight loss and found that fasting plasma lactate was correlated with weight loss. Crawford et al[8] 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 12–20 week very low-calorie diet intervention which 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 as well as additional studies before and after gastric bypass surgery.

The ultimate purpose of the current study was to determine if fasting plasma lactate is related to metabolic status. If lactate is a valid marker of risk for development and/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 & 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[9] and POWER.[10] Additional non-obese subjects (n=39) and non-diabetic subjects with severe obesity (n=13) were recruited. Gender, 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, overweight with mild to moderate lipid abnormalities.[9,11] 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 one of two 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.[10] 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 (LABS), 33% of the subjects with severe obesity had diabetes at baseline, while 63% had dyslipidemia and 68% had hypertension.[12] Our group was the first to report remission of diabetes within a few days after gastric bypass.[13] Many other groups have confirmed and extended this finding; in the LABS 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.[12]

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°C until analyzed. Insulin was determined with an ultra-sensitive 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 DxC600 for samples from the POWER and community recruited subjects, Beckman Coulter, Brea CA).

Methods are described previously for exercise[9] and insulin-modified intravenous glucose tolerance test (IVGTT).[10,14] The following are brief descriptions of the exercise program and IVGTT. Chronic exercise comparable to ~12 miles of walking per week at 65–80% peak oxygen consumption (VO_2) up to ~20 miles of jogging per week at 65–80% VO_2 was done for 5–6 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 hr.

Statistics

Data are shown as mean ± SEM 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 months exercise program in metabolically impaired subjects. Comparisons between the non-obese, subjects with severe obesity, and 1–3 months after gastric bypass (post-RYGB) groups were made using a one-way ANOVA and a Tukey's Multiple Comparison Test for *post hoc* analysis. A paired sample t-test was used to determine significance between 1 week pre-RYGB and 1 week post-RYGM, as well as 1–3 months post-RYGB and 7–9 months post-RYGB fasting lactate. Pearson's Correlation Coefficient was used to determine if there was a relationship between fasting lactate and insulin sensitivity (S_i) in the metabolically impaired and 1–3 months post-RYGB. Significance was set at a $p<0.05$.

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 intra-venous glucose tolerance test (IVGTT), where glucose was administered at time zero and insulin was administered at 20 minutes. Fasting plasma lactate was 58% higher in metabolically impaired subjects compared to non-obese subjects ($p < 0.0001$) and remain significantly higher ($p < 0.004$ to 0.0001) though 120 min of the IVGTT (figure 1).

Plasma lactate in subjects before and after RYGB, as well as before and after exercise

Severely obese subjects were studied with IVGTT 1 week before and 1 week after RYGB surgery (figure 2). Since 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. Prior to surgery, injection of glucose caused lactate to rise and injection of insulin accelerated the lactate rise (pre-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/insulin challenge.

As evident in figure 3, fasting plasma lactate in non-obese subjects, subjects with severe obesity, and 1–3 months post-RYGB differed significantly at $p < 0.05$. The 1–3 months post-RYGB and 7–9 months post-RYGB were not significantly different ($p = 0.51$).

The STRRIDE study also investigated the effect of exercise on metabolically impaired subjects. Six months of chronic exercise resulted in a 16% reduction ($p = 0.028$) in fasting lactate (figure 4).

Insulin sensitivity and lactate

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

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.[2–6] 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/insulin challenge. We also show that non-diabetic patients with severe obesity have elevated lactate at fasting. Furthermore, interventions such as gastric bypass surgery and exercise, that improve metabolic health, reduce fasting plasma lactate.

Insulin resistance is often cited as a cause of the metabolic syndrome. Lovejoy et al[15] 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 (post gastric bypass surgery) at comparable insulin sensitivities as the STRRIDE study. This is in agreement with the finding of Reed et al[14] who found that insulin sensitivity of non-diabetic patients did not improve a week after gastric bypass surgery, but we here report that plasma lactate was reduced. The present results (figure 5) demonstrate that the correlation reported by Lovejoy et al. is not evidence for a cause and effect relationship.

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.[16]

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 reduce in metabolically impaired individuals. In agreement, our published results[16–19] 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 figure 6. Complete oxidation of glucose and fatty acids were reduced by approximately 40% in muscle of obese individuals, compared to non-obese controls. To make up for this reduction in ATP 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.[19] Beta-oxidation of fatty acids generates acetyl-CoA, and incomplete oxidation products are acetyl-CoA and derivatives of acetyl-CoA.[20,21] Since acetyl-CoA is oxidized to CO_2 in the TCA cycle, an accumulation suggests impairment of the TCA cycle. These changes are shown in figure 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[14], 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 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.[7] 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.[22] 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.[22] 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_{2max}) was highly related to morbidity and mortality. Wei et al[23] 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[24] 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.[25–27] Together, these data suggest that an impairment in oxidative capacity in human skeletal muscle, as well as an increase in fasting plasma lactate, are linked with mortality and metabolic disease. Obtaining a simple and easy measure which reflects oxidative capacity may thus be important in treating/preventing metabolic disease.

Clinically, lactate levels are often used as a marker for illness and responsiveness to interventions.[1] Point-of-care fingertip lactate measurement is accurate in detecting normal or modestly elevated lactate values.[28] Measurements of lactate may be useful in prescribing preventative measures such as exercise and/or diet to be taken prior to the appearance of metabolic disease and to determine if 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.

FUNDING: This work was supported by grants from the National Institutes of Health, USA (HL-57354 to WK and DK078192 to BG)

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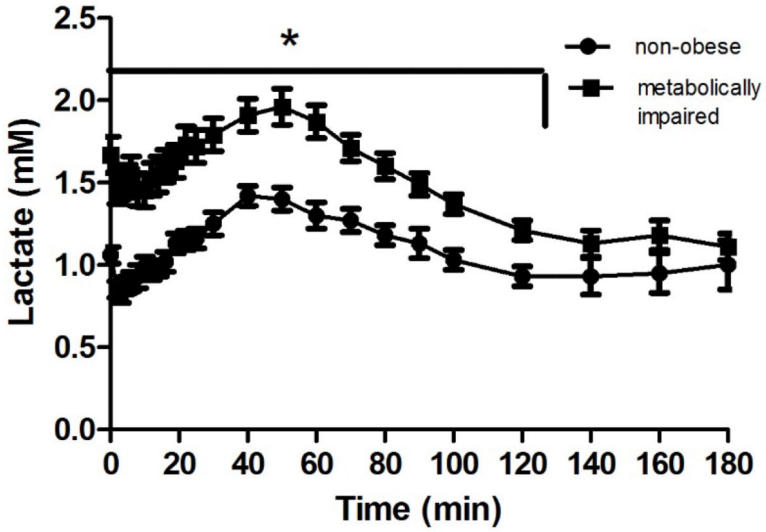

FIG. 1.

Changes in plasma lactate during insulin-modified IVGTT (mean ± SEM) in non-obese subjects and subjects with components of the metabolic syndrome (STRRIDE). Non-obese subjects; 15 females, 42.3 ± 3.4 years of age, 24.1 ± 1.0 kg/m^2 BMI. Metabolically impaired subjects; 27 females, 54.2 ± 1.2 years of age, 30.5 ± 0.7 kg/m^2 BMI. * Significantly different from non-obese at p = 0.004 to 0.0001.

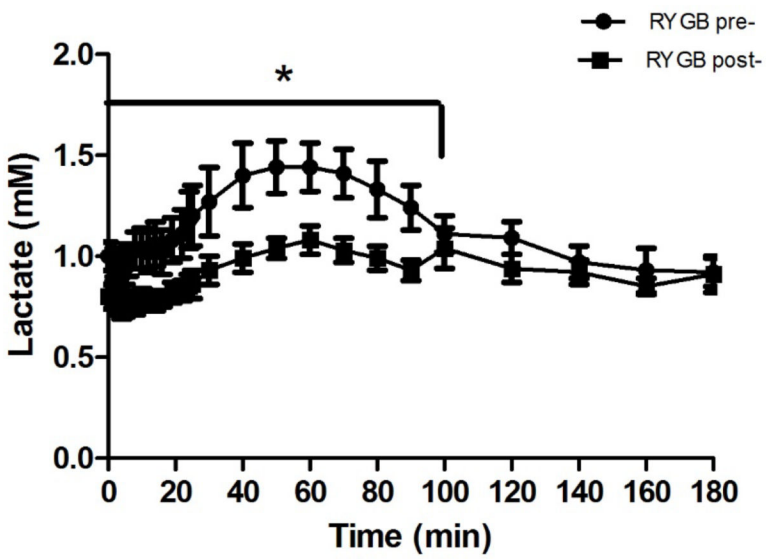

Fig. 2.

Changes in plasma lactate during insulin-modified IVGTT (mean ± SEM) in subjects 1 week pre-RYGB and 1 week post-RYGB Subjects; 12 females, 43.3 ± 3.3 years of age, 44.6 ± 1.4 kg/m^2 BMI at baseline. * Significantly different from pre-RYGB at minute 0, 8, 10, 14, 19, 30, 40, 50, 60, 70, 80, 90 at $p < 0.05$ to 0.011.

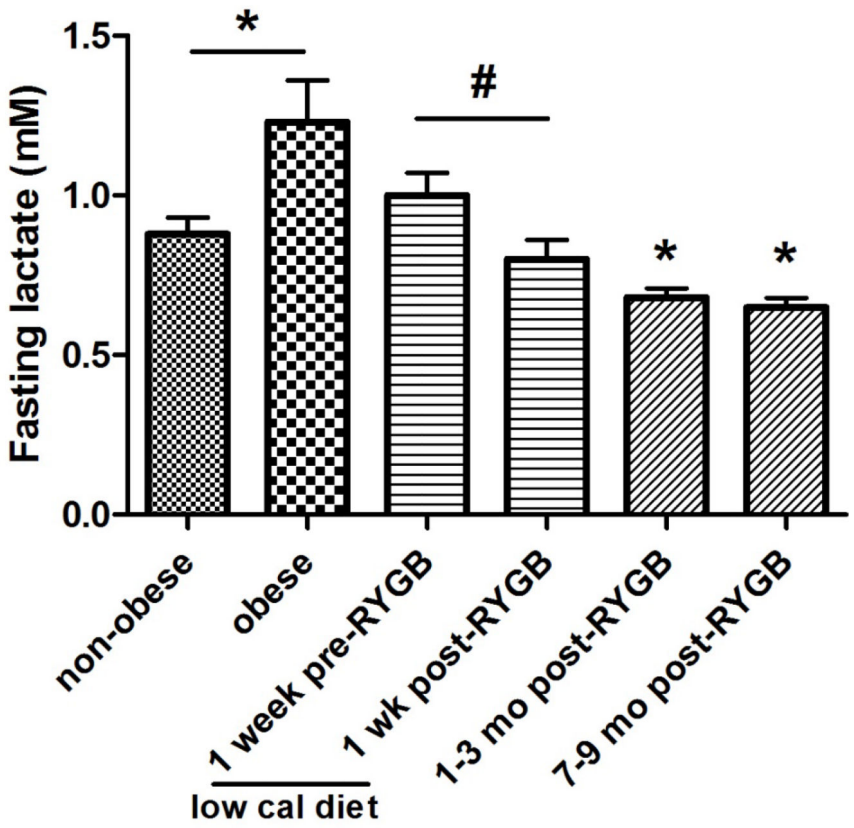

Fig 3.

Fasting lactate (mean ± SEM) in non-obese, obese, 1 week pre-RYGB, 1 week post-RYGB, 1–3 month post RYGB, and 7–9 month post RYGB. Non-obese subjects; 39 females, 33.5 ± 2.0 years of age, 23.7 ± 0.6 kg/m^2 BMI. Non-diabetic obese subjects; 13 females, 43.2 ± 2.9 years of age, 43.4 ± 3.1 kg/m^2 BMI. 1 week pre RYGB; 12 females, 43.3 ± 3.3 years of age, 44.6 ± 1.4 kg/m^2 BMI. 1–3 month post-RYGB subjects; 22 females, 42.5 ± 1.9 years of age, 39.2 ± 1.3 kg/m^2 BMI. Repeated measure of lactate at 7–9 months post-RYGB is displayed to show that fasting lactate did not change in that timeline. * Significantly different from non-obese at p = 0.032. # Significantly different from 1 week pre-RYGB at p = 0.02

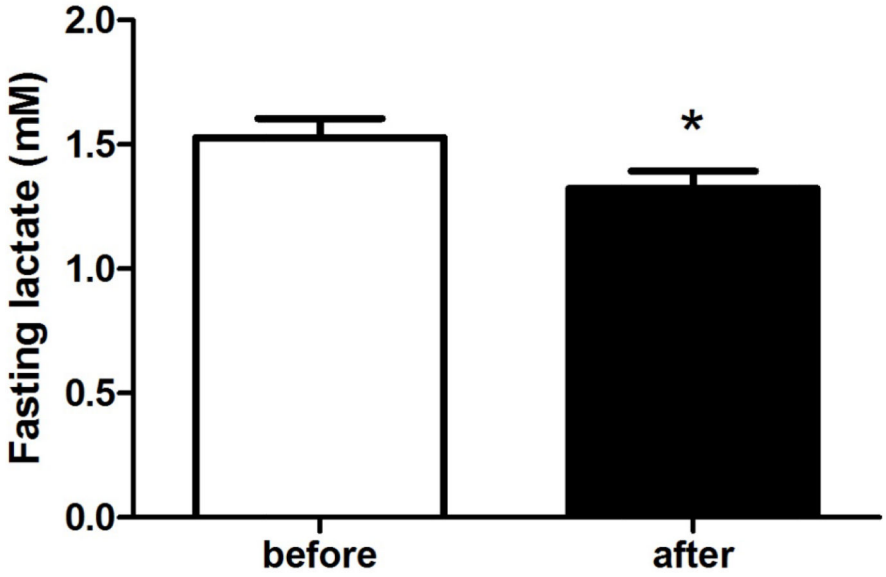

Fig. 4.

Fasting lactate (mean ± SEM) in metabolically impaired subjects before and after 6 months of an exercise program (STRRIDE). Subjects; 97 males and 76 females, 52.4 ± 0.5 years of age, 29.7 ± 0.2 kg/m^2 BMI at baseline. * Significantly different from before at $p < 0.0001$.

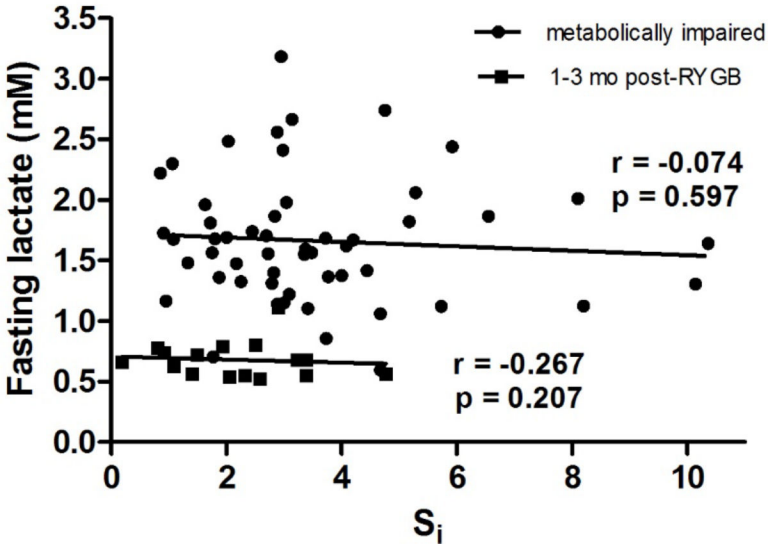

Fig. 5.

The relationships of fasting lactate and insulin sensitivity (S_i) in metabolically impaired subjects (STRRIDE) and in 1–3 mo post-RYGB subjects (POWER). Metabolically impaired subjects; 26 males and 27 females, 51.6 ± 1.0 years of age, 30.2 ± 0.4 kg/m^2 BMI. 1–3 month post-RYGB subjects; 2 males and 22 females, 42.8 ± 1.9 years of age, 39.4 ± 1.4 kg/m2 BMI.

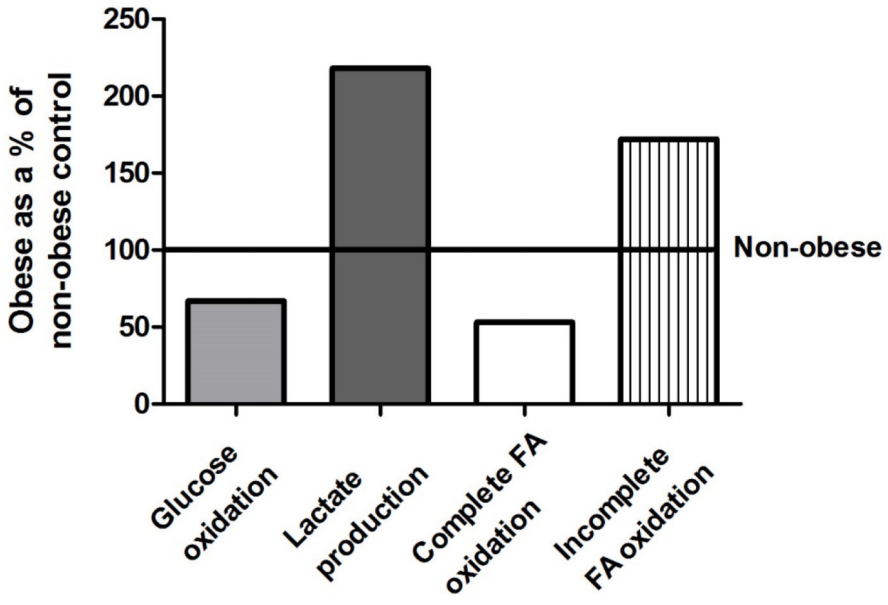

FIG. 6.

Fatty acid and glucose oxidation and lactate production in *in vitro* incubated human muscle fiber strips from lean and severely obese subjects. Redrawn from data published in Friedman et al[16], Hulver et al[18] and Berggren et al[19].

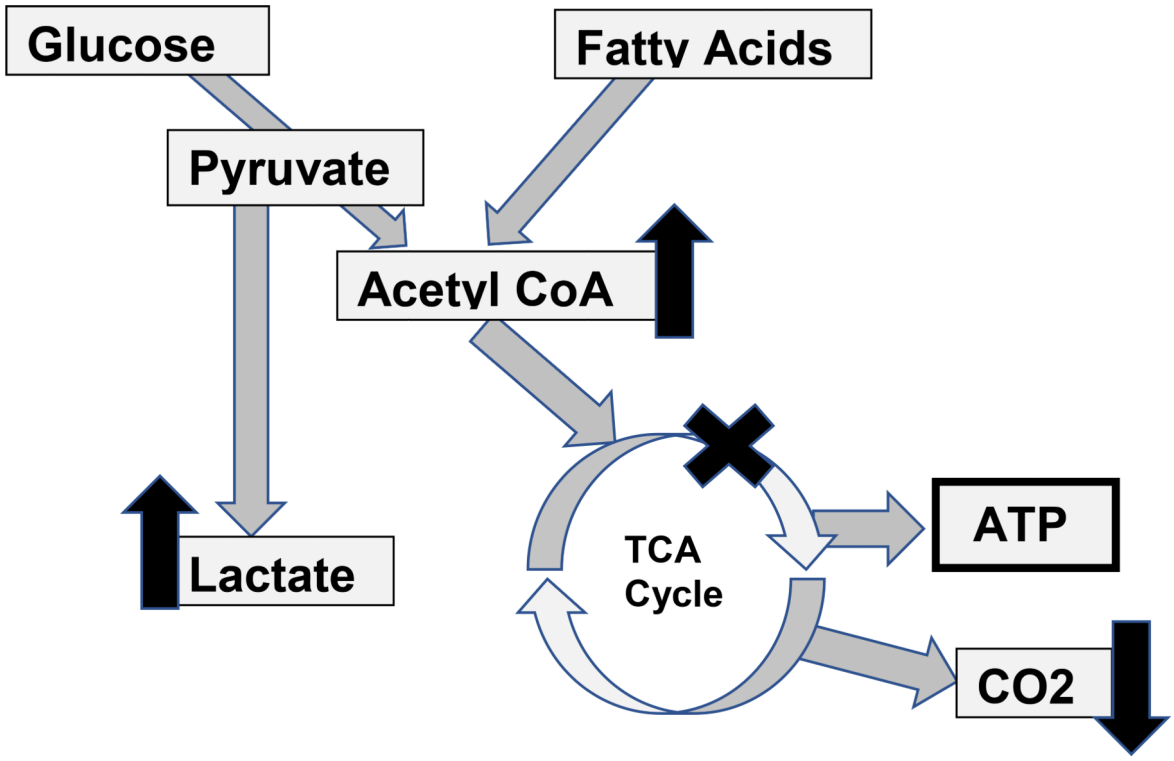

Fig. 7.

Pathways of glucose and fatty acid oxidation. Data supporting this figure are summarized in figure 6. Oxidation of glucose and fatty acids was depressed in muscle from obese subjects (decreased CO_2). 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.