

CHANGES IN THE REMOVAL OF BLOOD LACTATE INDUCED BY OBESITY

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Abstract: In the present study, it was found that lactate in obese individuals has a normal physiology in relation to non-obese individuals, but the time for this substrate to fall becomes slower in individuals who have a greater stock of lipids. This factor can be explained by the tendency to liver problems, as the liver is responsible for metabolizing 30% of the lactate produced in the body, suggesting that the inadequate functioning of this organ causes a slow process in the removal of this substrate from the circulation. As shown in the results of our study, although the obese were not sick, they presented serum parameters slightly above or close to the reference limits, so that they may have something abnormal in their health. Alkaline phosphatase concentrations (FAL ($p = 0,03$), and the enzymes AST (NO = 24 and O = 37,4 U/L), ALT (NO = 40,8 and O = 54,2 U/L) and γ -GT (NO = 5,0 and O = 10 U/L) showed a significant increase in obese individuals. Due to the observed increase in concentrations (NO = 125 and O = 198 U/L) in CK in obese individuals we can suggest that they have micro muscular injuries, with an increase in H^+ and lactate production. Adipose tissue is involved in other functions besides lactate production, such as the secretion of other substances that have an important metabolic role in the body. This work suggests the importance of adipose tissue as a producer of energy substrate for the organism as well as the importance of the liver in the metabolism of lactate in obese and non-obese individuals.

Keywords: Obesity, lactate, metabolism, adipose tissue, liver function.

INTRODUCTION

Obesity is considered a global health problem. In the last 20 years it has become a global pandemic, leading to various diseases such as type 2 diabetes, cardiovascular disease, depression, sleep-related illnesses and some

types of cancer. (NIGRO et al., 2014; SINGLA et al., 2010; YILMAZ; YOUNOSSI, 2014).

Unilocular adipose tissue (TAU) has cells with a single lipid droplet. Its size is variable. The larger the diameter, the lower the blood perfusion, causing the TAU to work anaerobically due to a low pressure of oxygen called anoxia, or even in the absence of oxygen giving rise to hypoxia. (ROONEY; TRAYHURN, 2011; TRAYHURN, 2013).

Lactate is formed through two glycolytic reaction products, pyruvate and the reduced coenzyme NADH. When the concentration of NADH accumulates in the cytosol, a sign of decreased mitochondrial activity, activation of the enzyme lactated dehydrogenase (LDH) occurs, which reoxidizes NADH in NAD⁺ and lactate form. In this way, the speed of the glycolytic pathway is maintained and even increased in the absence of O₂ (BENEKE et al., 2011; PRAKASH, 2008; SMEKAL et al., 2012; SVEDAHL, 2003). In skeletal muscle lactate is produced through strenuous exercise, extravasated to other cells, used as an energy substrate for energy production and metabolized by the liver, kidneys, skeletal muscle, heart and brain. (FAUDE et al., 2009; KRAUT; MADIAS, 2014; PRAKASH, 2008).

Studies suggest that WAT also produces lactate. Due to the hypoxia that occurs inside the fat cell, about 50 to 70% of the glucose is converted into lactate, increasing the release of this product into the blood stream by 5 to 8 times. (ROONEY; TRAYHURN, 2011; TRAYHURN, 2013). With the increase in lactate production, there is also the recruitment of monocarboxylate transporters (MCTs) that have the function of transporting lactate and ions. H⁺ (PEREZ DE HEREDIA et al., 2010), and, when lactatemia is high in adipose tissue, this compound activates a membrane enzyme called GPR-81 that acts to decrease free fatty acids in plasma, leading to anti-lipolytic action in the fat cell.

Thus, knowing that the literature data do not indicate a great difference in the concentration of lactate in the blood of obese and non-obese people despite clearly demonstrating the production of lactate by adipose tissue, in this work we evaluated whether there is a difference in the kinetics of lactate withdrawal from the blood obese and non-obese people when subjected to an exercise that causes an increase in lactatemia. To better characterize the subjects and also because the liver and heart are major recipients of the lactate produced, liver and heart function were monitored.

MATERIALS AND METHODS

The sample consisted of 20 male individuals divided into 2 groups, non-obese (n = 10) and obese (n = 10), based on the percentage of body fat through the body mass index. (IMC) (DULLOO et al., 2010). All participants were without any type of physical activity for one year. This study was approved by the ethics committee of the Foundation Hermínio Ometto – Uniararas with opinion number 425,166, and all signed a consent form.

The body mass index (BMI) protocol was used to estimate the percentage of body fat, with a classification of 18.5 - 25 for non-obese and greater than 30 for obese according to the World Health Organization. (OMS) (DULLOO et al., 2010).

To induce an increase in lactatemia, the Ellestad protocol was used, with progressive loads by increasing the treadmill speed. In the first four stages, the slope was constant at 10% and from the fifth stage onwards, it increased to 15%, until the end of the test. Regarding speed, it started with 2.7 km/h, increasing to 4.8 km/h in the second stage and adding 1.6 km/h for each subsequent stage. The duration of each stage varied from three minutes in stages 1 and 5 and two minutes in the other stages until each participant was exhausted.

(NAUGHTON; SEVELIUS; BALKE, 1963).

Heart rate (HR) was determined using a heart rate monitor (Oxylane Rhythm 100, France) at rest and during exhaustion. Blood pressure (BP) was determined by an automatic digital blood pressure monitor (Tech Line Z-46, Taiwan) at rest and exhaustion.

Blood lactate was collected at rest and at exhaustion from each individual during exercise, through a puncture in the index finger. After exercise, blood was collected for lactate measurement at times 1, 5, 12, 20 and 60 min.

After the last blood collection, another 5 ml of blood were collected for biochemical analysis and centrifuged using the usual method. All analyzes were performed through the serum by the enzymatic method using the spectrophotometer (Bel Photonics UV-M51, Brasil), cada analise bioquímica used commercial kit (Labtest, Brasil), according to the manufacturer's instructions. The following parameters were evaluated: AST (Aspartate Amino Transferase); ALT (Alanine Amino Transferase); FAL (Alkaline Phosphatase); γ -GT (Gamma Glutamyl Transferase); BilirrT (Total Bilirubins); CK (Creatinokina); protection Tot (Total Proteins); Albumin (Albumin); AU (Uric Acid); Urea (Urea); Creat (Creatinine); COLT (Total Cholesterol); HDL (High Density Lipoprotein); Tri (Triglycerides).

Lactate was measured from whole blood using the method proposed by Maughan (1982). The device used was the Hitachi F4500 spectrofluorimeter, using $\lambda_{ex} = 460$ e $\lambda_{em} = 515$ nm.

Results are presented as means and standard deviation and medians and 95% confidence intervals, calculated using the Origin 6.0 program. ANOVA followed by Tukey's test was used to compare the means and values of $p < 0.05$ were considered different.

RESULTS

Table 1 presents the characterization data of the subjects. We can verify that both obese (O) and non-obese (NO) groups were homogeneous and did not present significant differences in terms of age and height. They show a significant difference in IMC ($p = 3e^{-7}$), which was the qualifying factor. The non-obese group (NO) presented $IMC = 23,5 \pm 1,2$ Kg/m² and the obese group (O) presented $ICM = 37 \pm 5,4$. The determining variable was weight, which showed a significant difference between the groups ($p = 1e^{-6}$). The groups showed no difference in resting heart rate or measured at the moment of maximum effort. The mean blood pressure (PAM) rest, calculated by the expression: $PAM = (PAS + PAD) / 3$ showed no difference between the groups, but when comparing the means of PAM at the moment of maximum effort, the results showed an increase in PAM of the individuals in the group O ($p = 4e^{-3}$).

Table 2 presents the biochemical data obtained in the serum analysis of the two groups. We can verify that the total cholesterol of both groups is above the reference range for adult men, established by the kit supplier. In the analysis of Triglycerides, although the statistical test used did not show a significant difference, the comparison of confidence intervals and medians (NO = 184 e O = 242 mg/dL) indicates a tendency to increase in the obese group (O). There was also a positive correlation between the variation in the subjects' triglyceride concentration and their IMC ($R = 0,4$).

Analyzing the result of the activity of enzymes that are markers of liver function (Table 2), we can verify an increase in the activity of the alkaline phosphatase enzyme (FAL) of obese subjects ($p = 0.03$). Considerable changes are also observed when the confidence intervals and medians of the enzymes are compared. AST (NO = 24 e O =

Parameter	NO	O	p
Age (years)	43,4±4,1	43,9±4,9	0,8
Height (m)	1,72±0,1	1,73±0,1	0,9
Weight (Kg)	69,7±5,9	111±17	1e ^{-6*}
IMC (Kg/m ²)	23,5±1,2	37,3±5,4	3e ^{-7*}
FC Rep. (bat/min)	79,3±6,1	78,7±5,7	0,8
FC Max (bat/min)	181±10	179±11	0,8
PAM Rep (mmHg)	93,7±7,4	93,3±9,8	0,9
PAM Max (mmHg)	120±8,9	133±9,3	4e ^{-3*}

* significant difference

NO – not obese; O - Obese; IMC – Body mass index; FC Rep – Resting heart rate; FC Max - Maximum heart rate; PAM Rep - Mean Resting Blood Pressure; PAM Max – Pressão Arterial Média Máxima. PAM= (PAS+2PAD) /3

Table 1 - Characterization of subjects

Análise	Int. Ref.	NO	O	p	NO95%	MNO	O95%	MO	R
AU (a)	1,5-5,9	4,9±2,0	6,4±1,4	0,07	3,6-5,1	4,0	4,7-7,7	7,3	0,4
Uréia (a)	15-40	34±6	39±7	0,08	29-35	32	34-47	37	0,3
Creat (a)	0,7-1,2	0,7±0,3	0,6±0,3	0,32	0,6-0,9	0,8	0,5-0,8	0,6	-0,3
COLT (a)	<200	246±51	229±23	0,39	225-267	244	225-267	244	-0,3
HDL (a)	>40	35±20	48±26	0,24	25-33	28	28-79	42	0,1
TRI (a)	<150	172±75	114±36	0,10	106-220	184	188-324	242	0,4
AST (b)	11,7-36,8	24,0±5,4	33,3±13	0,06	22,5-25,0	24,0	25,2-42,6	37,4	0,5
FAL (b)	26-100	49,6±25	69,6±11	0,03*	32,1-63,8	48,2	56,3-79,9	71,9	0,3
ALT (b)	12-45	36,4±20	44,9±22	0,38	23,8-47,6	40,8	23,8-67,6	54,2	0,2
g-GT (b)	5,0-38	7,2±6,5	8,4±3,1	0,62	4,1-5,5	5,0	5,0-10	10	0,1
BilirrT. (a)	<0,20	0,11±0,1	0,20±0,2	0,24	1e ⁻³ -0,25	0,05	0,05-0,30	0,20	0,2
CK (b)	24,0-188	129±94	192±62	0,09	72,9-125	125	135-219	198	0,3
Prot.tot (c)	5,8-8,0	6,2±8	6,6±4	0,14	5,5-67	6,5	6,3-6,8	6,6	0,3
Album (a)	2,9-4,7	32±0,5	32±0,4	0,77	2,8-3,6	3,2	3,0-3,3	3,1	0,0

a) mg/dL; b) U/L; c) g/dL

Int. Ref. – Reference interval established for the methodology used; NO – Mean and standard deviation of the values obtained for non-obese subjects (n=10); O - Mean and standard deviation of the values obtained for obese subjects (n=10); p-p Value obtained by ANOVA followed by Tukey's test comparing the means of NO and O; NO95%- 95% confidence interval of data obtained for non-obese subjects; **MNO** – Median of the non-obese range; **O95%** - confidence interval of 95% data obtained for obese subjects; **MNO** – Median of the obese range; **R** – linear correlation parameter of the data obtained versus the ICM.

Table 2 - Biochemical Analysis

37,4 U/L), ALT (NO = 40,8 e O = 54,2 U/L) e g-GT (NO = 5,0 e O = 10 U/L). It should also be noted that there is a positive correlation (R=0.5) between enzyme activity AST e o IMC of the subjects.

The median values of the total bilirubin concentration results also show an increasing tendency in the obese groups. (NO = 0,05 e O = 0,20 mg/dL), enzyme activity CK (NO = 125 e O = 198 U/L) and uric acid concentration (NO = 4,0 e O = 7,3 mg/dL). There was a positive correlation between variations in uric acid concentration and IMC of the subjects (R = 0,4).

The subjects' resting lactatemia showed no difference (p = 0.4) between the groups. (NO = 2,0 ± 1,1 mmol/L e O = 1,6 ± 0,8 mmol/L). After exertion, there was an increase in lactatemia, as expected and the curves of lactate removal from the blood of individuals belonging to the two groups are represented in Figure 1. We can see that lactatemia decreased rapidly and at 60 minutes had the same fasting levels for the two groups.

In order to better understand whether there was a difference in the rate of lactademic fall in the first 20 minutes between the groups, the area under the curve was calculated and the two groups were compared. In Figure 2, we can see a small increase in the median area in the O group, when compared to the NO group, indicating a lower lactate removal rate.

DISCUSSION

It is well known that in obesity, fat cells increase in size. (CINTI, 2012; MCGOWN et al., 2014; PROENCA et al., 2014; TRAYHURN, 2013). After a certain size, it becomes impossible to O₂ reach the mitochondria of these cells in a convenient way, due to its diffusion coefficient in the water and also due to the weak irrigation of this tissue, causing a condition of hypoxia. (CINTI, 2005;2012; ROMACHO et al., 2014;

SINGLA et al., 2010; TRAYHURN, 2013; WALDEN et al., 2012). Although adipose tissue is a tissue with low metabolic activity, there is a need to produce ATP and these cells, for that, carry out anaerobic glycolysis, which has lactate as its final product. Adipocytes present, in their membranes, specific transporters for lactate, the monocarboxylate transporters (MCTs) (PEREZ DE HEREDIA et al., 2010). They also have receptors for this protein (GPR-81) through which lactate intervenes in the control of lipólise (CAI et al., 2008; GE et al., 2008; KUEI et al., 2011; ROONEY; TRAYHURN, 2011; TRAYHURN, 2013; WANDERS; GRAFF; JUDD, 2012).

In a resting state, the human organism has a basal concentration of lactate in the blood (lactatemia), mainly originated from the anaerobic metabolism of red blood cells. The literature does not show much difference in resting lactatemia between lean and obese people. (BAKKER et al., 1996; JAMES et al., 1999), although there is agreement in the production of lactate by adipocytes, especially in obesity (BENEKE et al., 2011; ROONEY; TRAYHURN, 2011; TRAYHURN, 2013).

The classic way to increase lactatemia is physical exercise above the individual's aerobic capacity. In this condition, muscle fibers enter anaerobic conditions and export lactate to the blood, and lactatemia rises considerably. After exercise, blood lactate quickly returns to the resting value due to the removal of this compound mainly by aerobic muscle fibers, by the heart and liver. (BENEKE et al., 2011; FAUDE et al., 2009; SMEKAL et al., 2012; SVEDAHL, 2003).

Another known case in which lactate production occurs in the presence of O₂ is the metabolism of cancer cells, the so-called Warburg effect (VANDER HEIDEN; CANTLEY; THOMPSON, 2009). It is known that cancer cells have an anaerobic phase and the lactate produced is consumed by cells from

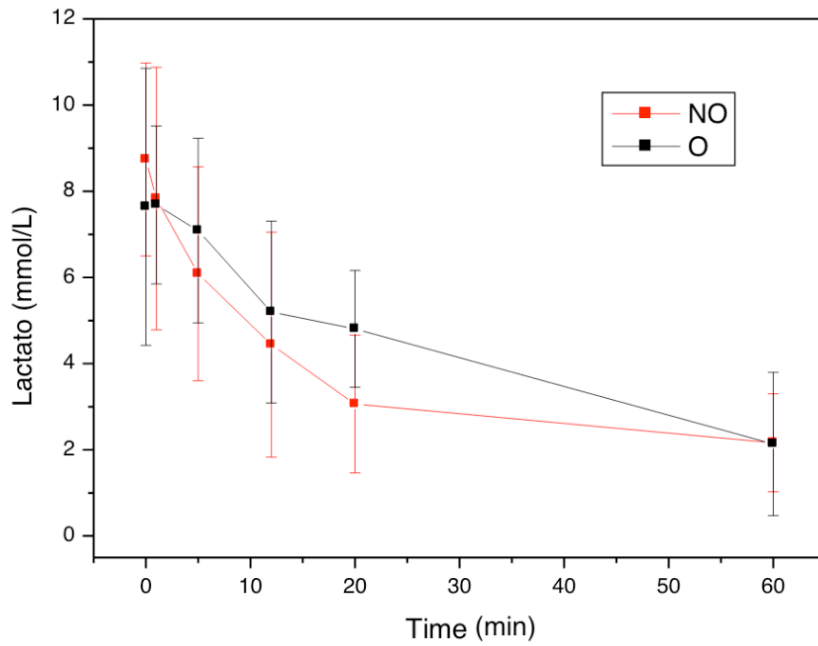


Figure 1 – Variation in blood lactate concentration (mmol/L) collected at times 1, 5, 12, 20 and 60 minutes after exhaustive exercise. At rest, blood lactate concentration values were: NO = $2,0 \pm 1,1$ e O = $1,6 \pm 0,8$ mmol/L.

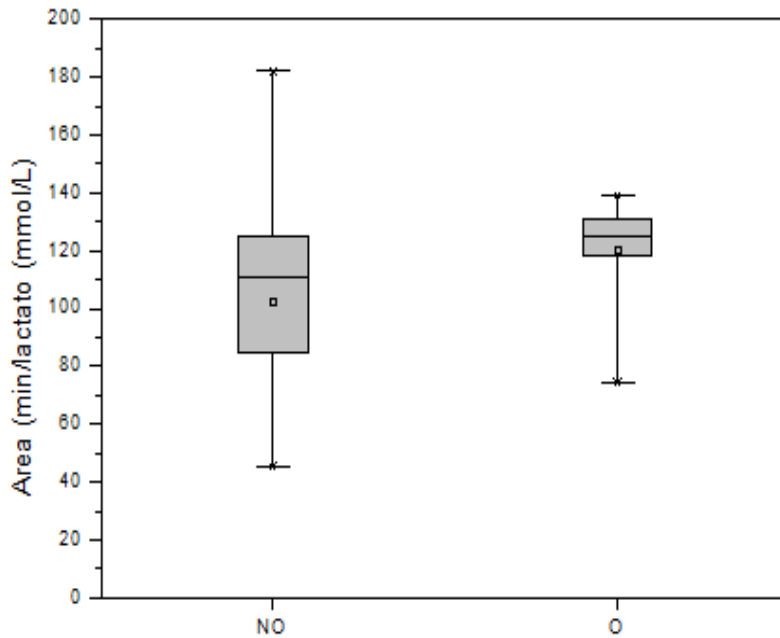


Figure 2 – Area under the curve of the first 20 minutes of the curves shown in Fig. 1

other regions of the tumor, which are more irrigated and in aerobiosis, so the presence of tumors does not substantially alter lactatemia. (DOHERTY; CLEVELAND, 2013).

The data presented in this work show that obesity did not alter the subjects' resting lactatemia or blood lactate concentration measured 60 minutes after exercise. However, the rate of decrease in lactatemia during the first 20 minutes was slightly different, being slower in the obese group, indicating that obesity or its effects altered the rate of withdrawal of lactate from the blood.

This behavior can be explained by the data obtained in the other analyzes that were carried out. Obese subjects had maximum mean arterial pressure (PAM Max) higher than the control group (non-obese), and this result may be due to three essential physiological effects for the circulatory system to supply blood flow to the musculature, which are massive sympathetic discharge, increased cardiac output and increased blood pressure. blood pressure. The greater the obesity, the greater the resistance to blood flow through the vessels and the greater the cardiac effort performed during physical activities, suggesting this difference in PAM Max between obese and non-obese (JURASCHEK et al., 2014; TRACHTA et al., 2014).

Plasma lipoprotein concentration shows that subjects in both groups had total cholesterol and triglyceride levels above the reference range. The reference interval assumes a 12-hour fasting prior to analysis and this was not met in this experiment. Due to eating habits, chronic use of alcohol and sedentary lifestyle, part of the population has dyslipidemia. (LIU; LI, 2015), and in this work there was no diet control and all subjects were sedentary.

Total cholesterol is the sum of the following fractions, HDL (high-density lipoprotein), LDL (low-intensity lipoprotein) and VLDL

(very low-density lipoprotein). The role of these lipoproteins is to transport lipids through the body, and their altered fractions suggest an increase or decrease to assess the risk of diseases such as atherosclerosis, coronary and brain diseases, showing a great risk in both groups studied.. AGUILAR; FERNANDEZ (2014) in their work suggest that high total cholesterol lowers the secretion of hormones visfatin, leptin, and adiponectins by adipose tissue that play an important role in several metabolic pathways, such as in some basic physiological responses, such as appetite and satiety.

In the obese group there is a tendency of higher triglycerides in relation to the non-obese. Triglycerides are formed by three fatty acids esterified with glycerol, their metabolism takes place in the liver and intestine and their transport is carried out by VLDL and chylomicrons. Fatty acids are highly energetic and are deposited in muscle and adipose tissue. BELLIS et al. (2014), YANG, L. et al. (2014) e JU LEE; YEOL KIM (2015) suggest in their studies that the increase in triglycerides is the first indication of dyslipidemia, a cardiac risk factor, type 2 diabetes, hypertension, liver disease and gout. These factors show that, in our study, the obese group has a great tendency to have some disease associated with increased triglycerides..

The alkaline phosphatase (FAL) observed between the groups showed a significant increase ($p < 0.05$), showing an increase in the obese group. THE FAL its function is to catalyze the hydrolysis of several phosphomonoesters at alkaline pH, it is found in various tissues, including intestinal, liver and bone. In plasma, the hepatic and bone form is the most common and its increase is related to liver, biliary, hepatitis and cirrhosis problems. ALI et al. (2015) suggests that the FAL increases lipid accumulation in human preadipocytes. BUCHET; MILLAN; MAGNE

(2013), in their studies say that a diet rich in fat and with the FAL alteration induces a great propensity of individuals to develop hyperlipidemia and hepatic steatosis.

Following the liver functions, the great tendency in the obese group of alteration of alanine amino transferase (ALT), this enzyme is found in large amounts in the liver, but is also present in skeletal muscle, kidneys and brain in small amounts, its increase is linked to the evaluation of liver lesions, and its reference values depending on the case are markers for hepatitis, cirrhosis and Hepatic steatosis. The obese group also showed a tendency to increase the activity of the enzymes AST (aspartate aminotransferase) e γ -GT (gamma glutamyltransferase) in serum, compared with non-obese. As well as the increase in enzyme activity ALT and FAL, indicate changes in liver and biliary activity (BURTIS, 1994).

The trend of increased activity of the CK enzyme (creatine kinase) in the serum of obese subjects should also be highlighted. The total serum CK enzyme represents the sum of the

activity of the three main isoenzymes: MM, from the muscles; MB, from the heart muscle and BB, from the brain (BRANCACCIO; MAFFULLI; LIMONGELLI, 2007; KOCH; PEREIRA; MACHADO, 2014). The increase in the activity of this enzyme in people who have not suffered a heart attack or central nervous system disease is usually related to micro injuries induced in muscle fibers by physical exercise. (BALTUSNIKAS et al., 2015; BRANCACCIO et al., 2007; KOCH et al., 2014; POKORA et al., 2014). Our results suggest that the obese group had more micro lesions than the non-obese.

In the present study, we concluded that lactate in obese individuals has a normal physiology in relation to non-obese individuals, but in its reconversion kinetics from the first minute to the twelfth minute, its decay rate is slower in obese individuals. Such slowness can be explained by the tendency of obese people to have liver problems, and this organ delays the lactate withdrawal process.

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