http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **23**(2):169-175
doi: 10.1515/rjdnmd-2016-0020

METABOLIC INTERPLAY OF HEPATIC ENZYMES – A CASE REPORT

Anca Ungurianu [1], ***Rucsandra Dănciulescu Miulescu*** [2,✉], ***Denisa Margină*** [1]

[1] "Carol Davila" University of Medicine and Pharmacy, Faculty of Pharmacy, Bucharest, Romania
[2] "Carol Davila" University of Medicine and Pharmacy, Faculty of Dentistry, N.C. Paulescu National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania

received: March 14, 2016 *accepted*: June 01, 2016
available online: June 15, 2016

Abstract

Introduction*: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are part of the routine blood tests and are usually used to assess liver or cardiac status. The most common disturbances are the mildly risen levels which are correlated with hepatic dysfunction and entail a wide variety of etiologies: viral, toxic, drug or are lifestyle related.* ***Case report****: Routine blood tests revealed high AST and ALT levels in an otherwise healthy 40-years-old male. After a series of supplementary tests the cause remained undetermined, so more attention was paid to the patient's daily routine. Recently he started an intense training program which led to extensive muscle damage causing an elevation of plasma transaminases' levels.* ***Discussion****: When dealing with a rise in AST and ALT levels in asymptomatic patients, physicians must carefully consider all aspects, from family and personal history, infectious diseases or toxins to medication and lifestyle, in order to avoid unnecessary tests and incorrect diagnoses or treatments.*

key words: *AST, ALT, exercise, cardiometabolic risk.*

Introduction

Alanine aminotransferase (ALT), also known as glutamate-pyruvate transaminase (GPT) and aspartate aminotransferase (AST), also known as glutamate-oxalacetate transaminase (GOT) are among routine liver tests, commonly used to assess liver function [1]. Elevated plasmatic levels of these enzymes can be associated with a wide range of illnesses, from serious ones such as cirrhosis or hepatitis to more benign ones (Figure 1). Frequently high aminotransferases levels are associated with alcohol intake, viral hepatitis, steatosis or medication use: acetaminophen, diclofenac and other non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX 2) selective inhibitors (celecoxib), amlodipine, flouxetine, imipramine or amiodarone [1-5].

Besides the most common hepatic causes of elevated transaminases, hemochromatosis, alpha1-antitripsin deficiency, autoimmune hepatitis can also be culpable. Some nonhepatic causes can be hemolysis, hyperthyroidism, celiac disease, myopathy or strenuous exercise as shown in Figure 2 [1,6].

Both aminotransferases have two isoforms, one present in the cytosol, the second in the

✉ 5-7 Ion Movila Street, Bucharest, District 2, Postal Code 11420; Tel: 0040748134500; Fax: 004021/2105575
corresponding author e-mail: rucsandra_m@yahoo.com

mitochondria [5]. ALT is located mainly in hepatocytes, while AST is found in the heart, skeletal muscle, kidney, brain and red blood cells [7].

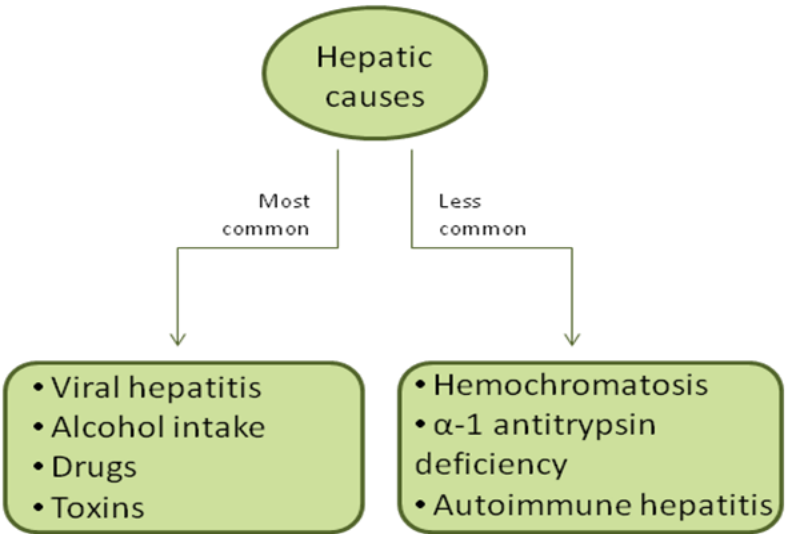

Figure 1. *Hepatic causes of high aminotransferases levels.*

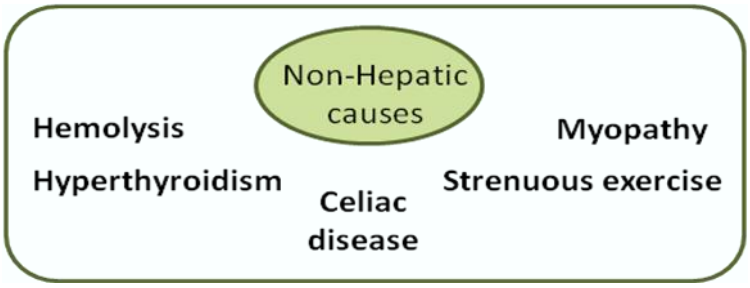

Figure 2. *Non-hepatic causes of risen transaminases.*

ALT is thought to be a marker for hepatic injury, being associated with fat accumulation and inflammation in liver and also with increased visceral adipose tissue, being an important marker for non-alcoholic fatty liver disease (NAFLD), in both obese and normal weight individuals [1,4,7,8]. AST is a myocardial infarction and an acute heart failure marker, although lately these high levels have been attributed to the acute central liver necrosis accompanying the circulatory alterations [1,5]. High AST levels have also been correlated with higher diastolic blood pressure and insulin resistance in both men and women and with a higher systolic blood pressure, BMI and waist circumference in men [7,9].

It has been shown that only four weeks of a fast-food diet combined with a sedentary lifestyle led to a pathological ALT plasmatic level [10]. Thus, a high level of ALT does not necessarily implicate liver damage; it has been hypothesized that the enzyme activity is adaptive to the liver's metabolic necessities. Intermittently high ALT levels can have a nutritional cause, especially when detected in the absence of steatosis, but can indicate a metabolic risk [5,9,10].

ALT and AST have more metabolic implications than gluconeogenesis and amino acid synthesis, being involved in the metabolism of fatty acids, glycerolipids and bile acids [5]. High levels of transaminases have lately been associated with cardiovascular diseases (CVD)

and metabolic syndrome (MS) or decreased liver insulin sensitivity, indicating the risk of developing type 2 diabetes mellitus (T2DM) or decreased liver insulin sensitivity and also the atherotrombotic risk [4,5,8,10]. Even higher values, still in the normal range but at the upper limit, can be indicators of an increased cardiometabolic risk (Figure 3) [7].

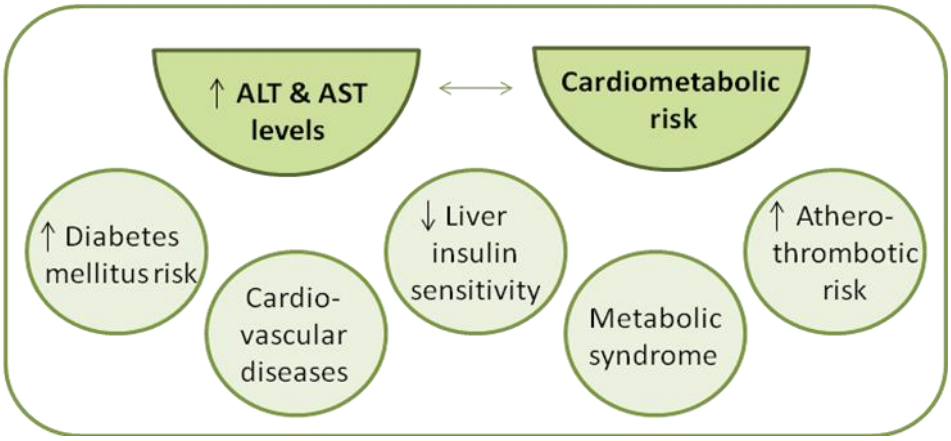

Figure 3. *Cardiometabolic implications of high AST/ALT levels.*

NAFLD was thought to be a disease with good prognosis, but recently it has been shown that patients who developed non alcoholic fatty liver disease and were found with increased levels of aminotransferases have a significant risk of developing serious liver disease and a low chance of survival due to CVD [10].

Cardiovascular disease, metabolic syndrome and diabetes mellitus are associated with brain impairment and dysfunction. Interestingly, high ALT and AST levels have been linked to an increased external-cause mortality: suicide, due to depression encountered in alcoholics and patients using antiviral treatment or trauma injury explained by cognitive decline due to hepatic encephalopathy or alcohol intake [4]. Brain function impairment can also be caused by a fluctuation of plasma glutamate due to its leakage from the skeletal muscle which acts as a glutamate deposit. It seems that the blood increase of transaminases could be an adaptive mechanism involved in maintaining glutamate homeostasis [11].

As discussed above, high plasmatic values of ALT and AST can have a wide range of etiologies, many clinical implications and can even be used as predictors for the future development of certain diseases.

There is a high prevalence of asymptomatic patients with increased AST and ALT values, with rises lower than five times the normal upper limits being the most common [1] and the accidental discovery of these levels usually leads to expensive, ample and even invasive diagnostic techniques [10].

Therefore, physicians must take into consideration all aspects when coming across a patient with elevated transaminases: family history, personal anamnesis, over the counter (OTC) and prescription drugs used, diet and lifestyle [1], because taking into consideration only liver damage when encountering risen levels of aminotransferases could lead to a misdiagnosis, an incorrect treatment and an unfavorable prognosis [5].

Case report

A routine blood test revealed high levels of AST and ALT in a 40-years-old male, with no prior significant medical conditions. The patient showed no sign of the most common risk factors when considering liver damage such as alcohol

abuse, a high fat diet or a sedentary lifestyle. Personal and family medical history was taken into consideration revealing a predisposition to dyslipidemia, thus NAFLD was the temporary diagnosis, until further tests were carried out.

The supplementary tests included an abdominal ultrasound and hepatitis virological tests. The ultrasound revealed a normal, homogeneous structure of the liver, with no nodules or fatty infiltration, thus ruling out steatosis as a diagnosis. When screening for hepatitis B or C, the tests came back negative (Table 1), concluding that the unusual transaminases' levels were not of a viral etiology.

Table 1. Hepatitis B/C screening.

Test	Results	Reference Values
HBs Antigen	0.423	(<0.9)
Anti HBs Antibodies (quantitative assay)	<2	(<10)
Anti HCV Antibodies	0.031	(<0.9)

Table 2. Pre-/Post-Intensive training AST and ALT levels.

Exercise / Biochemical parameter	Medium (Pre-TRX)	High	Medium (Post-TRX)	Reference Values
AST (IU/L)	15.82 ± 2.38	130.5	17.3	<38 IU/L
ALT (IU/L)	15.78 ± 0.32	81.7	21.2	<41 IU/L

Finally, reviewing the results presented above and finding no cause for the unusual plasmatic transaminases' levels, a closer look was taken into the patient's lifestyle. It was found that he currently started a new type of physical training: Total Resistance eXercise (TRX), a highly demanding training program, which led to prolonged muscle soreness and fatigue.

In the table above (Table 2) are presented the transaminases' levels before TRX training (a mean of the values from 2 previous years), the values found during the routine tests in the period of intense training and the values recorded two weeks later, after ceasing the strenuous exercise program.

TRX training is useful in developing core strength, flexibility and balance. Also, it was found to be more effective than classic core stability exercises in alleviating low back pain, a common cause of work-related ailments, which is experienced by 80% of people at least once in their lifetime, 5% developing chronic low back pain [12].

Instability training methods are very common resistance training techniques, TRX being a suspension training method that uses straps to suspend certain body segments and work against their weight [13]. However, being a highly demanding program, it can put a strain on the body, determining a change in normal blood parameters due to muscular tissue destruction, AST and ALT being among them.

Discussion

Liver, muscle and heart stress increases during physical exercises [14]. Strenuous exercise can cause muscle damage which entails local inflammation and oxidative stress, leading to the degeneration and reconstruction of the tissue [15-17].

The inflammatory response caused by intensive training involves neutrophils' migration within 24 hours to the damaged tissue, which are replaced by macrophages that remain in the muscle up to 14 days. Both neutrophils and macrophages help degrade the tissue by reactive oxygen species (ROS) formation and may enhance the production of pro-inflammatory cytokines, but the inflammatory mechanisms are not completely elucidated [15].

The formation of ROS is usually regarded as an unwanted process, but physiological quantities are necessary to the well-functioning of a cell, including the skeletal muscle one. Extensive production of ROS is associated with contractile dysfunction of the muscle cell [16], being directly linked to the intensity and duration of training [11,18,19].

Both regular physical activity and intensive training are linked to the increase of ROS and reactive nitrogen species (RNS) production, but it was found that this mechanism is vital to the muscle's adaptation to intense physical activity [17,20]. It must be taken into consideration that improving the organism's antioxidant capacity is one of the benefits of exercise and that ROS production is presumed to activate pathways involved in regulating the endogenous antioxidant systems [17,19,21]. A rise in the activity of antioxidant enzymes has been reported, enzymes such as glutathione peroxidase, superoxide dismutase, nitric oxide synthase or catalase [17].

An increase of antioxidant capacity post-exercise has been reported in both in healthy individuals and in heavy drinkers [21,22]. However, acute strenuous exercise leads to an increase of oxidative stress and could possibly be damaging, while regular training has protective effects, stimulating the endogenous antioxidant systems [17,19,21].

Along with inflammatory processes and an increase in ROS/RNS formation, a rise of AST and ALT levels was found following intensive physical exercise. The aminotransferases' elevation was maintained for at least a week post-exercise, the effects of training depending on the type and intensity of the exercise, the fitness level and gender of the subject [22,23]. It was reported that the increase is higher and more rapid for AST than ALT and AST/ALT ratio higher than 1 for one week post exercise, then returns to normal [23]. The patient in our case report also showed a higher AST level, with an AST to ALT ratio of 1.59 following strenuous exercise.

The AST/AST ratio is used in clinical practice with some limitations. It has been found that in many acute and chronic liver diseases like steatosis or hepatitis C the ratio is close to 1. When it comes to alcoholic liver disease the ratio is greater than 2 and in the case of patients with Wilson's disease is more than 4 [1].

Elevation in ALT and AST levels have also been reported after stress and anaerobic metabolism in athletes and soldiers due to a rise of catecholamines' level and muscle cells destruction, recently being linked to glutamate homeostasis. A glutamate balance is crucial for the correct brain functioning and is maintained through a redistribution to peripheral tissues which act as deposit, the most significant being the skeletal muscle. Strenuous physical exercise determines a temporary rise of plasma glutamate, due to muscle damage, along with an elevation of AST, ALT and 2-ketoglurate levels, indicating the importance of hepatic transaminases' adaptive response in maintaining the glutamate homeostasis [24].

Of course, asymptomatic elevation of transaminases could be of infectious or toxic nature, drug or lifestyle related [1,23]. Sport associated increase of aminotransferases is a

result of more than one process: myocyte destruction accompanied by inflammation, oxidative stress and glutamate leakage, a certain level of dehydration and liver's adaptive mechanisms to the overload of catabolites [24].

Although there have been many findings confirming the increase of aminotransferases due to high intensity muscle training [22-24], some studies of moderate physical exercise found no significant difference in transaminase plasmatic levels post-exercise [15].

Conclusion

The task of a physician when coming across a patient with mildly elevated values of AST and ALT is not an easy one, due to the large variety of etiologies involved, rises lower than five times the normal limits being the most common. Diurnal/monthly variations and family/personal history should be revised due to the fact that transaminases can be predictors for the future development of certain metabolic maladies. Lifestyle choices such as diet, especially fast food or alcohol abuse, and physical activity, in particular recent changes in routine or exercise type/intensity should be analyzed. OTC and prescription drugs must be taken into consideration, but usually they are the most seeked after culprit along alcohol and rarely overlooked. Therefore, taking into consideration only liver damage when encountering a risen AST or ALT level could lead to further extensive and expensive tests, an inaccurate diagnosis and an incorrect treatment.

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