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Relationship Between LDH and Mg in Monitoring of Hematologic and Non-Hematologic Malignant Diseases

Udristioiu A*

Doctorand in Molecular Biology, Titu Maiorescu University of Bucharest, Faculty of Medicine, Damboviciului Street No: 22, Postal Code 040051, District 4, Bucharest, Romania

***Corresponding author:**

Aurelian Udristioiu,
Doctorand in Molecular Biology, Titu Maiorescu University of Bucharest, Faculty of Medicine, Damboviciului Street No: 22, Postal Code 040051, District 4, Bucharest, Romania, Tel: 40723565637;
E-mail aurelianu2007@yahoo.com

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1. Abstract

1.1. Aim of this study was to evaluate the correlation between the serum levels of lactate dehydrogenase (LDH) and magnesium (Mg) in patients with diagnosed malignant diseases.

1.2. Method: Were analyzed LDH and Mg parameters on a cohort of patients (n = 75) comprising males (n= 36) and females (n=39) with a mean age of 57 years (SD= 12.5). The biochemical parameters were measured using a Vitros 250 dry chemistry analyzer (Johnson & Johnson, USA) using the slides for multi-layer spectrophotometry measurements.

1.3. Results; In the cohort study, 55 patients (73%) who received cancer therapy exhibited normal serum levels of Mg (normal value = 1.60-2.3 mg/dL; mean value = 2.2 mg/dL; SD = 0.2; p = 0.02). In contrast, 12 patients (16%), recently diagnosed with a malignant disease, who had not been treated, displayed high levels of serum Mg, (mean value = 2.89 mg/dL). Serum Mg levels were increased by the release of Mg^{2+} from malignant tissues in patients with malignant disease prior to treatment with cytostatic drugs. LDH levels remained elevated after initial cytostatic treatment until cancer remission. The number of copies of chromosomes in malignant tumors may be correlated with total serum LDH values.

1.4. Conclusion: Normal Mg levels with moderately elevated LDH levels were observed in all patients with regressive cancer after good responses to specific therapy. Low Mg levels with high serum LDH levels have also been observed in all patients with poor prognosis and metastases, meaning that Mg and LDH ion levels can be used as markers to monitor treatment responses in patients with or without metastasis.

2. Introduction

Magnesium, which is the second most abundant intracellular cation after potassium, plays a key role in regulating many cellular functions and enzymes, including ion channels, metabolic cycles, and signaling pathways. Magnesium ion (Mg^{2+}) is critical for maintaining the positional integrity of tightly grouped phosphate groups. These groups occur in many distinct parts of the cell nucleus and cytoplasm. Mg^{2+} maintains the integrity of nucleic acids, ribosomes and proteins. In addition, this ion acts as a trace element in the energy catalysis of cells.

Aim of this study was to evaluate the correlation between serum lactate dehydrogenase (LDH) and magnesium (Mg) levels in patients diagnosed with malignancy, admitted to the hospital department oncology.

3. Methods

Was analyzed a cohort of patients (n = 75) comprising males (n

= 36) and females (n =39) with a mean age of 57 years (SD = 12.5) who had cancer diseases and were admitted to the oncology department**.** The biochemical parameters were measured using a Vitros 250 dry Chemistry Analyzer (Johnson & Johnson, USA) using the slides for multi-layer spectrophotometry measurements.

In the study were excluded patients with non-neoplastic pathologies or diseases that can induce increased serum levels of Mg and LDH. These diseases included acute or chronic renal failure (CRF), ischemic heart disease, lung infarction, liver cirrhosis, acute or chronic hepatitis, massive muscle injury, megaloblastic anemia and severe syndromes that are associated with respiratory failure.

The CBC with the differential count, biochemistry samples, body radiography, ultrasound and computed tomography (CT) were used for the patient to establish the type of cancer diseases. In different types of leukemia, morphological cells were assessed in stage of differentiation between the pre-B and T cells, mature B cell stages and monocyte blast and myeloid cells. An initial panel of monoclonal antibodies was used to determine the immune phenotypes of the subgroups of differentiated T cells and B cells by flow cytometry. Activated B lymphocytes in CLL patients were defined as CD5+/CD19+, CD+_20cells that expressed CD23 and/or CD38 as surface markers.

The sample stability was maximal at one hour at 15-25°, in conformity with the conditions of the delivery of samples for the primary sample collection, following the instructions of the manufacturer and respecting the Procedures of Collection of Diagnostic Blood Specimens by Venipuncture, NCCLS Document H4-A3 Wayne, PA: NCCLS; 1991. We excluded samples from the study based on the following criteria: an icteric index > 65 for conjugated bilirubin and an icteric index > 37 for un-conjugated bilirubin, hemolysis with an H index > 400, turbidity for triglycerides > 300 mg/dl and serum containing para-proteins (multiple myeloma).

The diagnosis of LAM-3 was made based on blood smears, the examination of bone marrow (BM) aspirates, the evaluation of promyeloblasts (greater than 30% in BM), and the presence of a specific immune phenotype. Immunocytochemical detection was performed to confirm the diagnosis of LAM-3 using FAR Leukemia kits and there were positive results for the peroxidase reaction for promyelocytes, myelocytes, granulocytes, and peripheral blood cells (POX+) and negative results for the peroxidase reaction for the blast cells. For evaluation of the neutrophil alkaline phosphatase (NAP) levels in granulocytes (negative or low values in LAM-3) using the in vitro NAP test protocol (Code SP 910, Chemical Company), with positive results, on the smear of peripheral blood smear, granulocytic lysosomes that appear as dark blue or black grains in the cell cytoplasm.

4. Results

Among the patients, 8 patients were diagnosed with lung cancer, 18 patients were diagnosed with breast cancer, 19 patients were diagnosed with genital cancer, 23 patients were diagnosed with colorectal cancer, 5 patients were diagnosed with chronic lymphocytic leukemia (CLL), one patient was diagnosed with acute promyelocytic leukemia (LAM-3) and one patient was diagnosed with chronic monocytic leukemia (CML).

The results were interpreted for each patient based on medical history, clinical and para-clinical examinations and other signs of malignant diseases. Among the patients in this study, 55 patients (73%) exhibited normal serum levels of Mg (normal range value = 1.60-2.3 mg/dL; mean value = 2.2 mg/dL; SD = 0.2; p = 0.02) following cancer therapy. Six patients (8%) exhibited low levels of Mg (range = 0.60-1.50 mg/dL; mean value = 1.05 mg/dL). However, 12 patients (16%) displayed high levels of serum Mg (range =2.6-3.27 mg/dL; mean value = 2.89 mg/dL). The levels of serum lactic dehydrogenase (LDH) were also evaluated in patients newly diagnosed with cancer and in patients with unfavorable responses to the cancer therapy (range = 240-1330 U/L; mean value = 787 U/L; SD =1.33; p = 0.002; normal values 135-225 U/L), (Table 1).

Table 1: Serum LDH and Mg levels of patients with malignant diseases< (Normal value in healthy patients: LDH = 135-225 U/L, Mg = 1.6-2.3 mg/Dl).

Serum LDH and Mg levels of patients with newly diagnosed malignant diseases	**Serum LDH and Mg levels of patients in the remission stage of malignant disease following cancer therapy**	**Serum LDH and Mg levels of patients with unfavorable responses to cancer therapy**
Lung	**Lung**	**Lung**
Cancer	**Cancer**	**Cancer**
Mean value:	Mean value:	Mean value:
LDH =1270	LDH = 254	LDH = 1330
Mg =2.85	Mg =1.60	Mg =1.26
Breast	**Breast**	**Breast**
Cancer	**Cancer**	**Cancer**
Mean value:	Mean value:	Mean value:
LDH = 1250	LDH =250	LDH = 1260
Mg =2.55	Mg =1.80	Mg =0.87

Colorectal Cancer	**Colorectal Cancer**	**Colorectal Cancer**
Mean value:	Mean value:	Mean value:
LDH = 1250	LDH =250	LDH =1260
Mg =2.70	Mg =1.7	Mg =0.63
Acute and Chronic Leukemia	**Acute and Chronic Leukemia**	**Acute and Chronic Leukemia**
Mean value:	Mean value:	Mean value:
LDH = 1290	LDH = 255	LDH =1330
Mg =3.75	Mg = 2.05	Mg =1.6

5. Discussions

5.1. Comments of Results

The serum Mg level is increased via Mg^{2+} release from malignant tissues in patients with malignant disease prior to treatment with cytostatic drugs. In the different malignant diseases, the serum Mg values were high, normal or low, independent of the serum LDH values. The LDH levels remained elevated after initial cytostatic treatment until cancer remission. The number of copies of chromosomes in malignant tumors may be correlated with total serum LDH values. LDH levels in cancer patients are elevated due to high levels of LDH-3 isoenzyme in patients with malignancies and high levels of LDH-4 and LDH-5 isoenzymes, elevated patients with cancer of liver, muscle, lung and tissue tissues. conjunctive. High concentrations of serum LDH damage the cell membrane. Thereafter, malignant cells become invasive and metastasizes.

5.2. Cellular Physiopathology of Mg^{2+}

The magnesium serum levels are kept constant within very narrow limits (0.65-1.05 mmol/dL; 1.58-2.25 mg/dL), by flow regulation**,** via ascending loop of Henle o kidney [*Walter F and al. 2005,*] *Popescu MP, 2011, Stefano A, 1993*]. Malignant cells use Mg^{2} + ions in metabolic pathways more frequently than normal cells do and absorb magnesium from normal tissues, including bones and muscles.

In cells, the immediate energy sources involve glucose oxidation. In anaerobic metabolism, the donor of the phosphate group is adenosine triphosphate (ATP), and the reaction is catalyzed via the hexokinase or glucokinase: Glucose +ATP-Mg^{2+} = Glucose-6-phosphate (Δ Go = - 3.4 kcal/mol with hexokinase as the co-enzyme for the reaction [*Udristioiu A ,2002]*. Mg^{2+} helps fix ATP in the active centers of co-enzymes and other kinases that are ATP dependent. The enzyme Glucose-6-phosphate, accumulating in the cell follows the path of degradation of anaerobic glycolysis. The process of converting glucose-6-phosphate into fructose-6-phosphate is catalyzed via the enzyme phosphoglucomutase with the co-factor ATP-Mg^{2+}.

The conversion of glucose-6-phosphate into fructose-6-phosphate is a reversible reaction because of small energy difference (Δ Go = (- 4 kcal/mol). In the following step, the conversion of G-6-phosphate into F-1-6-bisphosphate is mediated by the enzyme phosphofructokinase with the co-factor ATP-Mg^{2+}. This reaction has a large negative free energy difference and is irreversible under normal cellular conditions. Mg^{2} + is essential for maintaining the integrity of tightly grouped and positioned phosphate groups. These clusters appear in numerous distinct parts of the cell nucleus and cytoplasm. The Mg^{2+} maintains the integrity of nucleic acids, ribosomes and proteins. In addition, this ion acts as an oligo-element with role in energy catalysis [*Black B, 1995*].

Membranes and cell walls have poly-anionic charges on the surface. This has implications for ion transport, especially since different membranes preferentially bind different ions. Both Mg^{2} + and Ca^{2} + regularly stabilize membranes by cross-linking phosphorylated lipid groups. Biological membranes are impermeable to Mg^{2} (and other ions). Therefore, transporter proteins must facilitate the flow of Mg^{2+} into and out of cells or intracellular compartments. Intracellular calcium induces mitochondrial swelling and aging. The proliferation of osteoclast cells occurs when the intracellular Ca/Mg ratio is 3/2. Mg2+ generally interacts with substrates via the inner coordination sphere, stabilizing anions or reactive intermediates, binding ATP and activating molecules for nucleophilic attack.

A magnesium ion progressively removes nearly all of the water via a selective pore before the magnesium ion is released on the far side of the membrane. The changes occur in low percentages of ligand exchange in the coordination complex comprising water and the Mg2 + ion [*Lunin VV, 2006, Dalmas O, 2017*]. The transport mechanism depends on the 3-D structure of the complex that arises by hydrating the Mg2 + ion in the aqueous medium. The inner shell of the complex comprises 6 water molecules, relatively closely related, and the outer shell comprises 12-14 water molecules [*Kehres DG, 2002]*. The pore is a funnel-shaped pentamer with two transmembrane spirals on each monomer composed of chains of atoms chained in carbohydrates and lipids. The ion channel consists of an inner group of 5 spirals and closes through the voluminous hydrophobic residues**,** (Figure 1).

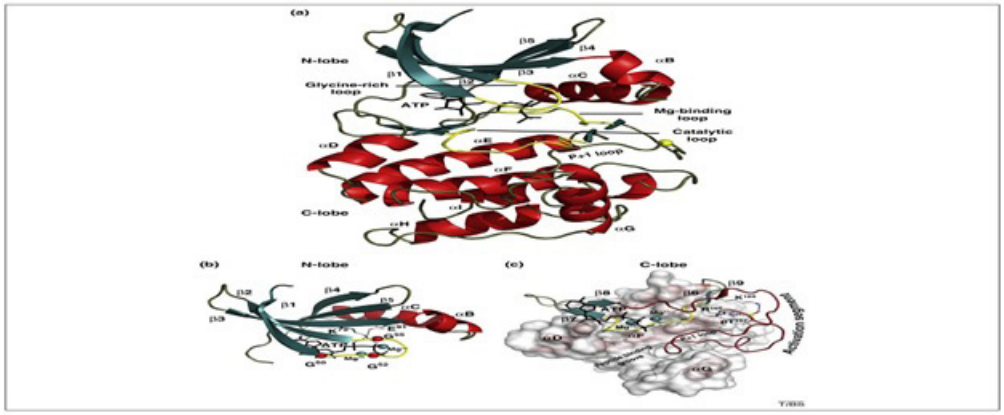

Figure 1: The structure of the conserved protein kinase core: alpha Protein kinases have a characteristic bi-lobal fold. *[The N Terminal lobe contains five beta wires and a conserved universal aC helix he C-lobe is mostly helical (colored red). (a), An ATP molecule is bound to a deep cleft between the lobes. The catalytically important loops are colored yellow. (b) N-lobe structure. The Gly-rich loop coordinates the phosphates within ATP. Three conserved glycine residues are shown as red spheres. Lys72 from the beta 3 strand couples the phosphates and the alpha C-helix. Catalytic and regulatory machinery binds the rigid helical core of the C-lobe. The extended activation segment (colored dark red) contains a phosphorylation site that is bound to b9 (K189) and the HRD-arginine (R165), [Dalmas O, 2010].*

5.3. Cellular Physiopathology of Isoforms LDH

The LDH enzyme, presented in serum as a tetramer, is composed of two monomers, LDH-A and LDH-B, which can be grouped into 5 isoenzymes: LDH-1 (B4), LDH-2 (B3-A1), LDH- 3 (B2-A2), LDH-4 (B1-A3) and LDH-5 (A4) and convert anaerobic to lactate in different cells. Total LDH, which is derived from processes. The LDH-A gene is located on chromosome 11, while the LDH-B gene is located on chromosome 12. LDH is used as a marker to monitor the response to chemotherapy in patients with neoplasm with or without metastases. [Harrison, 2018].

The LDH levels remained elevated after initial cytostatic treatment until cancer remission. In the malignant cells the transformation of pyruvic acid into lactic acid altered the process of glycolysis from the aerobic to the anaerobic pathway. The LDH enzyme catalyzes the reversible reduction of pyruvate in lactate by using the cofactor NADH as a co-enzyme. Neoplastic conditions promote high intracellular LDH production and increased use of Mg^{2} + during multiple molecular syntheses with the reaction, Pyruvate acid > LDH/NADH > Lactate acid + NAD.

In aerobic glucose metabolism, the oxidation of citric acid requires ADP and Mg^{2+}, which will increase the speed of the reaction: Iso-citric acid + NADP (NAD) --- isocitrate dehydrogenase (IDH) = alpha-ketoglutaric acid. In the Krebs cycle, the IDH1 and IDH2 isoenzymes are dependent on the NADP + cofactor which catalyzes the inter-conversion of the amino acid D-isocitrate to alpha-ketoglutarate.

The IDH1 and IDH2 genes are mutated in > 75% of different malignant diseases. Two distinct alterations are caused by tumor-derived mutations in IDH1 or IDH2: the loss of normal catalytic activity in the production of α-ketoglutarate (α-KG) and the gain of catalytic activity to produce 2-hydroxyglutarate (2-HG) [*Hartmann C, 2009*].

The last product of the reaction is a competitive inhibitor of multiple α-KG-dependent dioxygenase enzymes, including demethylases, prolyl-4-hydroxylase, and TET enzymes (Ten-Eleven-2 Translocation), and causes genome-wide alternations in histone proteins and methylation. DNA [*Raymakers RA, et al., 2009*]. IDH1 and IDH2 mutations are found in primary and secondary leukemias and in malignancies of the pre-leukemic clone, including myelodysplastic syndrome and myeloproliferative neoplasm, [*Wagner K, 2010.*].

The energetic sum of anaerobic glycolysis is Δ Go = -34.64 kcal/mol**.** However, a glucose molecule contains 686 kcal/mol, and the energy difference (654.51 kcal) allows the potential for un-controlled reactions during carcinogenesis. The reaction ADP^{3}+ P^{2-} + H^{2}- ATP + H_2O is reversible. The terminal oxygen from ADP binds the P^{2-} by forming an intermediate penta-covalent complex, resulting in the formation of ATP and H_2O. This reaction requires Mg^{2+} and an ATP-synthetase, which is known as the H+-ATPase or the Fo-F1-ATPase complex. Intracellular calcium induces mitochondrial swelling and aging. The proliferation of osteoclast cells occurs when the intracellular Ca/Mg ratio is 3/2. Mg^{2+} generally interacts with substrates via the inner coordination sphere, stabilizing anions or reactive intermediates, binding ATP and activating molecules for nucleophilic attack [*Kehres, DG, et al, 2012*].

The LDH enzyme, presented in serum as a tetramer, is composed of two monomers, LDH-A and LDH-B, which can be grouped into 5 isoenzymes: LDH-1 (B4), LDH-2 (B3-A1), LDH- 3 (B2-A2), LDH-4 (B1-A3) and LDH-5 (A4) and convert anaerobic to lactate in different cells. Total LDH, which is derived from processes. The LDH-A gene is located on chromosome 11, while the LDH-B gene is located on chromosome 12. LDH is used as a marker to monitor

the response to chemotherapy in patients with neoplasm with or without metastases [8].

The number of chromosome copies in malignant tumors can be correlated with the total serum LDH values. LDH levels in cancer patients are elevated due to high levels of LDH-3 isoenzyme in patients with malignancies and high levels of LDH-4 and LDH-5 isoenzymes, elevated patients with cancer of liver, muscle, lung and tissue tissues. conjunctive. High concentrations of serum LDH damage the cell membrane.

Normally, cells in the body communicate via intra-cytoplasmic channels and maintain the energetic potential across cell membranes, which is 1-2.5 µmol of ATP in the form of ATP-ADP/ATP-ADP-IMP. If the intra-cellular and extra-cellular levels of Mg^{2+} are high, the extra-cellular charges of the cells will not be uniformly distributed. This change in distribution induces a high net positive charge for the cell and induces a loss of contact inhibition via the electromagnetic induction of oscillation, [*Kehres DG*, et al ., 2010] *Chien MM* et al. 1999, Milionis H J, 1999].Thereafter, malignant cells become invasive and metastasize.

6. Conclusions

Normal levels of Mg with moderately increased LDH levels were observed in all patients who had cancer that was in the regression phase following good responses to a specific cancer therapy. Low levels of Mg with high levels of serum LDH were observed in all patients with poor prognosis and metastases. The total serum level of LDH, which is released by cytolytic cells during the progression of malignant diseases, and the serum Mg level can be used as markers for monitoring treatment responses in patients with neoplasm with or without metastasis.

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