Review

A Functional Biological Marker is Needed for Diagnosing Magnesium Deficiency

Kay B. Franz, RD, PhD, FACN

Department of Nutrition, Dietetics and Food Science, Brigham Young University, Provo, Utah

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Functional biological markers or biomarkers are now available for many nutrients which are used as nutritional status markers. Most sources of these biomarkers are products or precursors of enzymatic processes that can be measured in serum and plasma. At this time measurements of total or ionized magnesium (Mg) in serum, plasma, cellular components, urine or Mg retention from a load test are performed, but they may not always reflect Mg nutritional status. Biomarkers for Mg are needed which would reflect changes in biochemical processes where Mg is involved. Biomarkers for Mg need to be identified and evaluated in both animals and humans, with a determination of possible factors that may affect the reaction and biomarker concentrations. Some possible biomarkers for Mg include the following: Na/K ATPase, thromboxane B_2, C-reactive protein, and endothelin-1. Other possible biomarkers for Mg need to be identified.

INTRODUCTION

A hindrance in determining possible relationships between magnesium (Mg) status in the body and various health conditions is an inability to accurately measure Mg nutritional status. Many laboratory measures of Mg are now carried out where the results are considered to have a relationship to body stores of the macromineral, but these measures of Mg may not reflect cellular Mg status and may have no relationship to an individual's Mg status. New measures of Mg nutritional status need to be developed.

DISCUSSION

Functional biological markers or biomarkers are now available for many nutrients and are used as nutritional status markers [1,2]. A nutritional biomarker, ideally, is a substance that measures activity of a cellular enzyme or process. During a nutrient deficiency, a product or a precursor of an enzymatic reaction or process would be released from the cell and be able to be measured in both serum and plasma. As this substance increases or decreases, it would reflect the functional nutritional status of the nutrient.

Below are examples for two nutrients where biomarkers have been developed. These examples show how biomarkers measure specific processes in the body and are then a reflection of the metabolism of the nutrient and its nutritional adequacy.

Examples of Biomarkers for Iron and Vitamin B-12

Iron. There are several biomarkers for iron [2]. Three iron-related scenarios will be addressed:

- iron deficiency anemia,
- iron stores,
- development of iron deficiency before anemia occurs.

Hemoglobin and hematocrit are well-known markers of iron deficiency anaemia. An additional marker that measures mean corpuscular volume could also be used. Low hemoglobin, hematocrit, and mean corpuscular volume values help to quantify manifested iron deficiency.

Iron stores are best measured using plasma or serum levels of ferritin, the storage form for iron. The small amount of ferritin that occurs in plasma or serum is proportional to the iron stores of the body. In adults, 1 μg ferritin/L in plasma or serum is equivalent to 8 mg of stored iron. A high value for serum ferritin would indicate good iron stores, except that serum/plasma ferritin is increased in response to infection, alcohol intake and hyperglycaemia, and would give false high values for iron stores in these situations.

Address reprint requests to: Kay B. Franz, PhD, Dept. of Nutrition, Dietetics and Food Science, Brigham Young University, Provo, UT 84602. E-mail: kay_franz@byu.edu

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A relatively new marker for iron deficiency is the serum transferrin receptor (sTfR). This receptor begins to increase in plasma and serum before there are any declines in hemoglobin. When the cell content of iron begins to decrease, synthesis of the transferrin receptor is upregulated and increases in the plasma membrane. An extracellular part of this receptor is cleaved and released into the plasma, where it can be measured. As the sTfR increases, it demonstrates that a celluar iron deficiency is occurring and that more iron is needed.

Vitamin B-12. For vitamin B-12, there are only two recognized functions in higher animals [3]. One is involved with the remethylation of homocysteine to methionine and the second changes methylmalonyl-CoA to succinyl-CoA. If there is a vitamin B-12 deficiency, there is an increase in the both substrates: homocysteine and methylmalonyl-CoA, which subsequently becomes methylmalonic acid. Both homocysteine and methylmalonic acid increase in body fluids with a vitamin B-12 deficiency. An increase in homocysteine is not specific for vitamin B-12. Folate or vitamin B-6 deficiencies can also increase plasma homocysteine. An increase in methylmalonic acid is specific for a vitamin B-12 deficiency and is a valuable biomarker.

Functional Biomarkers for Magnesium

At this time we do not have a good biomarker for Mg. A list of possible biomarkers is needed, and then each biomarker needs to be evaluated in both animals and humans, with a determination about possible factors that may affect the reaction and the biomarkers concentration. The ideal biomarker would become changed in its concentration when bone Mg begins to decrease or when ionized Mg within cells begins to be compromised.

This ideal biomarker would be measured with a colorimetric test in both fresh or previously frozen serum or plasma. A colorimetric test would make it easy to incorporate into a clinical laboratory. Other types of tests may have to be used. A biomarker present in both serum and plasma would allow measurements in blood collected from major longitudinal health and nutrition studies and the calculation of risk of various chronic diseases. Blood cells, such as erythrocytes or monocytes, are difficult to isolate, and are not usually easily handled in clinical laboratories beyond those already established for hematology.

Possible Biomarkers for Magnesium

Magnesium deficiency or supplementation has been found to have effects on fundamental processes, such as pumps in the plasma membrane [4], platelet activity and thrombus formation [5], acute phase proteins [6], oxidative damage [7], and endothelial damage [8]. These processes may provide the right biomarker, but this biomarker must show evidence of change with Mg deficiency within the range usually seen in the human condition.

Na/K ATPase. Energy requiring pumps in plasma membranes require Mg [9,10]. Na/K ATPase is the most studied and its activity is decreased in a Mg deficiency [4]. Na/K ATPase activity is decreased in hypertension [11,12], obesity [13], insulin resistance [14,15], and complications of diabetes [16,17]. Na/K ATPase activity can be measured in erythrocyte plasma membranes. The procedure is long and complicated and must be carried out within a few hours or days. Samples cannot be frozen. These make Na/K ATPase a possible biomarker, but not an ideal one.

Platelet Activity and Thrombus Formation. Platelet activity and thrombi are increased in Mg [5] deficiency and decreased when Mg is given [18,19]. One measure of this activity is the stable degradation product of thromboxane A_2, thromboxane B_2 (TXB_2). In Mg deficient rats, TXB_2 was increased more than 10 times in comparison to control animals [20]. TXB_2 is increased in conditions often associated with possible Mg deficiency, such as cardiovascular disease [18], preeclampsia [21], and diabetes [22]. TXB_2 can be measured in serum, plasma, and urine. Studies of TXB_2 concentrations and graded intakes of Mg in animals are needed, along with studies of the effects of Mg supplementation in humans.

Acute Phase Proteins. C-reactive protein (CRP) is a marker for the acute phase reaction in humans. Because CRP is increased in cardiovascular disease [23], inflammation of unknown origin is theorized to be occurring. However, an increase in CRP has been identified in individuals with low serum Mg [6]. Increased CRP has been identified in cardiovascular disease [23,24], hypertension [23], stroke [25], diabetes [23,24], metabolic syndrome [24,26], and preeclampsia [27]. Because of CRP's relationship to inflammation, CRP as a Mg biomarker would not be exclusive for Mg alone. Further work is needed with both animals and humans to determine if there is a direct link with Mg.

Initiation of Oxidative Damage. Mg deficiency has been implicated in initiation of oxidative damage as evidenced by decreasing levels of glutathione and increasing levels of malondialdehyde [7,28]. Because of the large number of factors associated with modulating oxidative damage, such selenium, vitamin E, vitamin C, carotenes and others, it would be difficult to isolate one marker for Mg that is not affected by other factors. This process is unlikely to yield a good biomarker for Mg.

Endothelial Damage. Endothelin-1 is released from vascular endothelium and is a marker for endothelial damage. Its synthesis is upregulated in hypertension [29], cardiovascular disease [30], heart failure [31], diabetes [32], metabolic syndrome [33], and preeclampsia [8,34]. Mg decreases endothelin-1 in women with preeclampsia [8]. Endothelin-1 has be measured in both serum and plasma. The impact of Mg supplementation on elevated endothelin-1 levels in humans needs to studied. Animals studies are also needed.

CONCLUSION

A biomarker for Mg is needed that, ideally, can be determined in fresh or frozen serum or plasma, has few factors which would affect its concentration in serum or plasma, and its concentration should be a reflection of Mg nutritional status in cells and the total body. Both TXB_2 and endothelin-1 may be candidates for biomarkers for Mg. Both can be measured in plasma and serum. However, Na/K ATPase activity of membranes and CRP levels in serum are also possibilities. Both animal and human studies are needed to determine if these two candidates are feasible. Additional biomarkers for Mg need to be identified.

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