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Biomarker Concept for Mineral Requirement

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DEFINITION OF NUTRITIONAL BIOMARKERS

Potischman and Freudenheim in the year 2003 defined nutritional biomarker as "any biological specimen that is an indicator of nutritional status with respect to intake or metabolism of dietary constituents. It can be biochemical, functional or clinical index of status of an essential nutrient or another dietary constituent.

CATEGORIES OF NUTRITIONAL BIOMARKERS

There is more than one scheme used to categorise nutritional biomarkers. Biomarkers can be grouped according to what they assess. A single biomarker may be included in one or more of the following categories:

1. **Biomarkers of dietary exposure** assess dietary intake of different nutrients, non-nutritive components, foods, food groups, or dietary patterns.
2. **Biomarkers of nutritional status** assess not only intake but also metabolism of the nutrient(s) and possibly effects from disease processes. Potentially these may not reflect the nutritional status of a single nutrient, but may indicate the interactions of several nutrients.

Another classification scheme distinguishes recovery, concentration, predictive and replacement biomarkers as the followings.

1. **Recovery biomarkers** are based on the concept of metabolic balance between intake and excretion during a fixed period of time. Recovery biomarkers are directly associated with dietary intake and can be used to assess absolute intake (not only to

rank intake). There are relatively few recovery biomarkers, including doubly labelled water, urinary nitrogen, and urinary potassium.

2. **Concentration biomarkers** are correlated with dietary intake and used for ranking of individuals. They are not used to determine absolute intake because they are related to metabolism, personal characteristics (Eg. age, sex), and lifestyle factors (Eg. smoking, physical activity). Examples of concentration biomarkers include plasma vitamin C or plasma carotenoids.
3. **Predictive biomarkers**, which do not completely reflect dietary intake, but can predict it to some extent, such as urinary sucrose and fructose. Similar to recovery biomarkers, these are sensitive, time dependent and demonstrate a dose-response with intake; the key distinction is that their overall recovery is lower.
4. **Replacement biomarkers**, which serve as a proxy for intake when it is not possible to capture because information in nutrient databases is unsatisfactory or unavailable. Examples include sodium, phytoestrogens, polyphenols or aflatoxin.

MINERAL BIOMARKERS

Nine trace minerals are available or considered nutritionally important. vz. Iron, Zinc, Copper, Selenium, Iodide, Manganese, Molybdenum, chromium and Cobalt. The availability of bio marker would differ between these trace minerals and its source.

CATEGORIES OF BIOMARKERS

Plasma / serum

For clinical investigations it is easy working with these types of samples. However, sensitivity and specificity vary among different trace minerals. Plasma or serum is used with accuracy for selenium. For zinc these types of samples have low sensitivity and Copper, zinc, Iron lack specificity.

Cellular components of blood

These samples are not regularly used in clinical cases but for research works the samplings are carried out. Eg. whole blood selenium can be used as a long term biomarker. Erythrocyte membrane Zinc is sensitive to dietary restriction of zinc. Neutrophil Zinc and other total leukocyte and or lymphocyte zinc may be used as samples for zinc analysis. But these types of samples require further analysis and validation.

Hair and others

Hair could be a potential biomarker. There is considerable disrepute for this sample due to commercial issues.

Urine

Mineral homeostasis is maintained by the excretory system especially kidney Eg. Iodine, Selenium, chromium, Molybdenum.

Faeces

Iron, Copper, Manganese and Zinc can be estimated using faeces. Hepatic storage and biliary excretion are important for copper and Manganese metabolism.

Iron

Plasma or serum ferritin (iron that is not needed for the body is stored with in the cells as ferritin). Small quantity of ferritin is available in the plasma or serum that is proportional to the quantity stored intracellularly. Each 1µg ferritin/L plasma is proportional to approx. 8 mg of storage iron. Levels ≤ 12 µg ferritin/L plasma are indicative of iron store absence. However, high plasma ferritin is also associated with cardiovascular diseases and neoplasm, especially adenoma of the colon. Ferritin is an acute phase protein and is increased in the infections and inflammation.

Plasma transferrin or total iron-binding capacity is increased with storage - iron depletion before there is evidence of iron deficiency. But it is less sensitive biomarker than ferritin. However, one advantage is that plasma transferrin level is reduced during infection and inflammation.

In the functional iron deficit, there is increase in plasma soluble serum transferrin receptor concentration (sTfR). This sTfR is the biomarker which is sensitive and specific for early iron deficiency. Because it increases, when the supply of iron is reduced to bone marrow, even though there is no reduction in haemoglobin concentration.

Serum transferrin saturation is measured to 30-35%. when there is inadequate supply of iron to the bone marrow The levels will be Is than 15%. This saturation is affected also due to chronic diseases.

Zinc protoporphyrin/heme ratio or erythrocyte protoporphyrin concentration is increased when there is reduced supply of iron to the developing red blood cell. This occurs because of the synthesized protoporphyrin is retained rather than incorporating into the hemoglobulin.

For iron deficiency haemoglobin and haematocrit can be used as a nonspecific biomarker. Levels less than 12-13 g Hb/dL is indicative of anaemia. Mean corpuscular volume (MCV) and mean corpuscular hemoglobulin (MCH), when both are low may be attributed to nonspecific markers for iron deficiency anaemia.

Hence, for identification or diagnosis of an iron deficiency, combination of markers needs to be used. Ferritin or MCV together with erythrocyte protoporphyrin and transferring saturation all can be used in the diagnosis.

Iodine

Urine iodine is the standard method of diagnosis because almost 90-95% of the iodine is excreted in urine. Serum thyroid stimulating hormone (TSH) is increased in the cases of iodine deficiency, but does not cross the upper limit. Thyroglobulin

concentration in the serum can be correlated with urine iodine. Blood spot filter paper could be used for sampling in the above said assays. Increase in triiodothyronine (T_3) and decrease in thyroxine (T_4) may be observed with iodine deficiency. Hence thyroid function tests, provides highly useful biomarkers for iodine deficiency and long-term iodine status in the body.

In recent times ultrasonography of thyroid gland is used as a biomarker. Size increase may be attributed to the iodine deficiency. Iodine turnover studies using radioactive iodine (^{131}I) administered intravenously could be used as a research tool to diagnose daily iodine requirement and accumulated concentration in the thyroid gland.

Zinc

Zinc is an important mineral; the deficiency of this mineral leads to growth retardation and also zinc involved in immunity development and is found in the surface of erythrocyte (Red cell membrane). Also found in the membrane of platelet, neutrophil and monocytes.

Plasma zinc at present most widely accepted biomarker. However, zinc intake and absorption values were not correlating in some of the studies. It is observed that there is a prompt homeostatic mechanism available in which variations in the plasma may not occur. In children it is estimated that plasma concentration less than 70µg/dL appears to be useful predictor of growth response after zinc supplementation.

Plasma zinc alone may not be a biomarker for zinc status or deficiency. On the other hand, studies are focused on hypozincemia and acute phase response, these studies may result in some biomarkers in future. Carbonic anhydrases (zinc incorporated) but this zinc is not getting depleted. But erythrocyte cell membrane zinc, is sensitive to zinc depletion or deficiency. But the sample preparation of individual cell types from the blood is difficult. Such complexity may be eased for using it as a biomarker.

Zinc in the hair were measured low when there is an impaired growth. Hence hair zinc could be used as a biomarker. Excretion values in the urine and faeces could be analyzed. Excretion of zinc is reduced in severe dietary zinc restriction; this may reflect dietary zinc intake. Metallothionein monocyte messenger RNA is the potential biomarker for zinc. Reverse transcriptase polymerase chain reaction reveal that levels reduce in zinc diet restriction and increase during the supplementation of zinc.

Zinc dependent enzymes alkaline phosphatase, copper-zinc superoxide dismutase and lymphocyte 5' – nucleotidase. Even though these enzymes lack sensitivity and specificity in future these enzymes may be useful biomarkers.

Selenium

Selenium is important for antioxidant function. Plasma selenium of approx. 8µg/dL is accounted for by the physiological requirement of the selenoproteins GPX_3 (Gultathione peroxidase) and selenoprotein P.

Plasma selenium level below 8µg/dL indicate impaired selenium status. Hence plasma selenium could be effectively used as a biomarker for short term selenium status. Whole blood selenium can be used as a long-term biomarker. But for studying whole blood in the atomic absorption spectrophotometry acid digestion is required which is not required for plasma sample.

Selenium can be estimated from the hair and nail sample also. In keshan disease (congestive cardiomyopathy) in China the above samples were used to estimate selenium deficiency. Plasma glutathione peroxidase (GPX_3) provides functional marker for selenium. But samples get easily contaminated while collection and storage, so, this may not be clinically useful.

Copper

Plasma copper and ceruloplasmin are the most useful biomarkers of copper status. These are measured as the protein or as oxidase enzyme activity. In copper deficiency the levels are low. These biomarkers may not be useful in copper intake after certain level.

Ceruloplasmin is synthesized from copper in liver. This is the bound form of copper. So, circulating copper level dependent on ceruloplasmin. Ceruloplasmin also an acute phase reactant and is increased in infection and inflammation. But ceruloplasmin level may get reduced when the protein deficiency and increased level of estrogen for prolonged period. Cytochrome c oxidase activity in platelet and leukocytes (copper dependent enzyme) may be of future candidate of research in copper biomarker.

Activity of peptidylglycine α - amidating monooxygenase (PAM) could be another potential candidate of copper biomarker. Plasma diamine oxidase is another copper dependent enzyme which increases in level after copper supplementation. Activity of copper in signal meditated activity in immune cells may be useful in identifying novel biomarkers of copper status.

Manganese - Plasma manganese is the biomarker for this trace mineral.

Molybdenum – urine molybdenum

Chromium – plasma chromium and urine. But both these markers are not reliable.

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