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Metabolic Homeostasis, Biomarkers and Medical Education Assessment

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The maintenance of metabolic homeostasis is of paramount importance for critically ill patients and electrolyte disorders, which are common homeostatic disbalances in adult patients in Intensive Care Units (ICU), have been increasingly associated with a rise in morbidity and mortality, as has been improper treatment of electrolyte disorders.[1,2] Given the disorders (e.g. severe burns, trauma, sepsis, brain damage, malignancies and heart failure) are associated with the disturbances in electrolyte homeostasis, it is of critical importance to institute a proficient management in a hospital intensive care setting/environment. Hyponatremia (the most common electrolyte disorder) generally alludes to a condition where sodium level in the blood is abnormally low. It interesting that the release of anti-diuretic hormone and hence the impairment of water excretion are so frequent in hospitalized patients, that virtually all patients are at risk of hyponatremia. Many cases of dysnatremia are acquired after a patient is admitted to the ICU, and the presence of dysnatremia is associated with poor prognosis. Interestingly, limited number of prospective, randomized, controlled studies have been conducted to evaluate the optimal treatment of electrolyte disorders. Magnesium, calcium and phosphorus are important electrolytes involved in the regulation of homeostasis. Intituting a robust strategy for the treatment of “hyponatremia and hypernatremia”, “hypokalemia and hyperkalemia”, “hypophosphatemia and hyperphosphatemia”, “hypocalcemia and hypercalcemia”, and “hypomagnesemia and hypermagnesemia” is therefore of critical importance. The actual electrolyte correction requires individual adjustment based on the patient's clinical condition and response to therapy. However the utility in monitoring them in critically ill patients is still unclear.

This issue of *Archives of Medical and Biomedical Research* reports the outcome of a prospective, non-interventional, single center study in the intensive care unit of a tertiary care hospital to determine the incidence and clinical presentation of magnesium, phosphorus, and calcium abnormalities in patients admitted to the ICU. Calcium and phosphorus are recognized to be responsible for much of the structural integrity of the bony skeleton and also to participate in several diverse processes, such as enzyme activation, cell division, blood coagulation, and membrane stability. Hypocalcemia caused by critical illness is usually

multifactorial (e.g. hypoalbuminemia, metabolic or respiratory acidosis, hypomagnesemia, renal failure, massive blood transfusions) although calcium loss due to increased tissue sequestration of calcium may be the predominant cause in patients with pancreatitis, septicemia, burns, or toxic shock. Tetany is the commonest symptom associated with an acute reduction in plasma ionized calcium. The characteristic clinical features of these electrolyte disorders present as neurological and cardiac manifestations.

Ionized calcium, serum calcium, magnesium, and phosphorus along with arterial blood gases (ABG) were measured on admission with clinical features recorded in an approved format in 300 consecutive patients admitted to the ICU over a period of two years. Thereafter, ionized calcium, serum phosphorus, serum magnesium, and ABG were monitored every alternate day. Hypocalcemia was the commonest electrolyte abnormality seen in 165 (55%) patients followed by hyperphosphatemia seen in 74 (24.67%) and hypophosphatemia seen in 72 (24%) patients. Hypocalcemia with renal failure was seen in 52 (31%) patients ($p = 0.009$). Hypophosphatemia and hypomagnesemia were commoner with respiratory failure i.e. 23 (31.95%) and 13 (27.66%) patients, respectively. An association of liver disease with hypomagnesemia was noted in the study ($p < 0.05$). Arrhythmias associated with electrolyte abnormalities were the most common clinical observation, seen in 69 (41.81%) patients with hypocalcemia, 20 (42.55%) with hypomagnesemia, and 29 (40.27%) with hypophosphatemia. The abnormalities reported may be associated with arrhythmias, blood transfusions, and diuretic use and may have a bearing on the clinical outcome. The comments from Balci *et al*[3] is noteworthy – "Hypomagnesemia is known to have a high prevalence rate, but its diagnosis may be intrigued by some factors: it has nonspecific manifestations that are frequently overlooked; magnesium level is not examined "routinely" in blood test and patients may be hypomagnesemic, even with a normal serum magnesium level. Thus magnesium deficiencies are generally masked by other electrolyte deficiencies. Clearly a multi-centered study with stringent patient selection and longer follow up will possibly serve in understanding the role of these electrolytes and this has global health implications. Further, while the kidney is a principally responsible organ for retention and excretion of electrolytes and fluid in healthy individuals, pathophysiologic mechanisms and hormonal interactions of anti-diuretic hormone, aldosterone, and parathyroid hormone, and other factors such as physiological stress also play important roles in regulating fluid and electrolyte balance in the organism[1-4].

Metabolites are obvious candidates for biomarker screening because they represent the downstream effect of enzyme catalysis and other biotransformations and are smaller in number than the proteome. Metabolism, which is mainly an anabolic process in the growing stage, may sometimes change due to either over-nutrition or starving conditions, leading to many abnormalities and giving rise to metabolic disorder based diseases. Many simple intermediate compounds are generated during the process of metabolism leading to the production of ATP. Thus metabolomics (the systems biology of small molecules) is a new approach for the untargeted identification of potential biomarkers. A particular advantage of metabolomics over targeted metabolite measurement is in hypothesis generation: the discovery of changes in molecules that were not already associated with a biological phenomenon. The ability of metabolomics to determine high-throughput system-wide physiological phenotypes gives it immense power in the

field of tumor biology and the cancer macro-environment/micro-environment for further understanding of factors responsible for the incidence of various types of diseases including cancer, diabetes and diseases of overt inflammation[5-7].

Interestingly, normal cells use a controlled mechanism during their whole life span and consume different metabolites in a guarded way according to their requirement from the available pool of metabolites surrounding the cell microenvironment. However, cancerous cells do not follow the normal controlled mechanisms due to their metabolic disorders, leading to the genesis of metabolic markers. Cancer cells use metabolites in an uncontrolled and inappropriate manner from the surroundings. For example, receptors used for the transport of metabolites such as glucose (which is transported by glucose transporter, GLUT) do not work in cancerous cells the way they do in normal cells. This mechanism supports the survival of cancerous cells while impacting adversely on the survival of neighboring normal cells. The myokines (cytokines changing the environment both inside and outside the cells and tissues leading to the genesis of metabolic based diseases) are the same proteins as cytokines, which are of low molecular weight and are responsible for metabolic disorders related to obesity and type 2 diabetes. As cytokines are known to influence immunological changes, similarly myokines are considered key molecules that cause changes in the local environment to initiate the development of metabolic disorders e.g. type-2-diabetes and cancer.

There continues to be worldwide growth in the numbers of medical, pharmacy and biomedical sciences schools and programs. The modality for assessing the academic programs has an impact on their success[8,9]. Innovative methods of teaching are a goal of many educators to deliver innovative curriculum. Teaching students in ways that keep them engaged and interested in the content is a challenge to any educator. Learning is a lifelong process and in order to achieve this goal, students should always be competitive and focused in their learning. Students actively learn by observing and performing activities, the process of learning is far more accelerated when a practical implementation is associated and the learner is benefited with the applied knowledge and skills and it also involves trial and error at times during self-exploration. Studies have shown that medical quizzes improve students' comprehension and enhance interest levels in the subject. These however have been mostly based on single subject quizzes, delimited by the curriculum and traditional assessment. Studies comparing traditional test scores before and after a quiz-exercise show irregular improvement in scores. Quiz competitions as teaching learning methodology has a statistically significant improvement in their performance. In a study that explored which aspects of the mediquiz students find "the most useful" and which is the "the most interesting", and what would be the ideal balance between the two, not presuming that they are mutually exclusive, there appears to be a moderate preference for 'interesting' questions provided that the answers linked back meaningfully with the subject. The rationale conclusion is that a fast-paced interactive and stimulating quiz game can be utilized to provide a formative assessment and feedback to both learners and teachers. There is a potential to engage in a collaborative skills and academic performance development to enhance students learning in medical schools and schools of biomedical sciences embracing pharmacology, pathophysiology and integrative pharmacotherapy.

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