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Opinion Paper

Undernutrition in childhood: Clinically based assessment tools and biological markers: Where are we and where should we go?

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SUMMARY

Despite its association with poor clinical outcomes and increased hospital costs, as of today undernutrition still goes undetected in paediatric hospitals. The reported prevalence of undernutrition in paediatric patients varies considerably. This disparity is partly due to the diversity of methods for its detection and assessment, as well as to the lack of consensus regarding its definition. Several methods, based on varied combinations of morphology characteristics, estimated nutritional intakes and medical conditions have been developed during the last 25 years. However, these tools suffer from poor sensitivity and selectivity particularly in acute conditions. Also while having their own merit, these tools mainly view malnutrition from the energy standpoint, disregarding assessment of specific micronutrients such as minerals and vitamins. In this position paper we make the point that in the era of personalized medicine, present technology offers the possibility of going beyond the traditional nutritional tools for assessing patients' status, and propose the measurement of selected micronutrients and allied metabolic markers in nutritional workup schemes adapted to each clinical condition.

What is known?

- Undernutrition still goes undetected in paediatric hospitals despite its association with poor clinical outcomes and increased hospital costs.
- Present simple nutritional assessment tools mainly consider malnutrition from the energy perspective.
- Micronutrient status is not covered in basic nutritional assessment tools.

What does this paper add?

- Proposal for including the measurement of selected micronutrients and allied metabolic markers in nutritional workups.

1. Introduction

Undernutrition in hospitalized children is associated with poor clinical outcomes and increased annual hospital costs, thus affecting both the patient safety and the health care system [1–3]. As of today, it however goes unnoticed in many hospital settings [4,5]. The variation in the prevalence estimates of this health status is multifactorial. First, malnutrition varies according to the socioeconomic environment. For example, protein-energy malnutrition accounts globally for 9.8/100.000 age-standardized deaths in the

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largest 50 countries for child and adolescent populations. More alarming, however, is the enormous gap witnessed between the developing and developed countries. It accounts for 11/100.000 age-standardized deaths in the former but only 0.1/100.000 in the latter [6]. It is also likely to vary with the clinical setting, the underlying disease and the subjective perception of the caregiver upon admission [7,8]. The different components and respective thresholds of nutrition assessment tools also contribute to the variation in reported prevalence [9].

Several malnutrition screening tools for hospitalized children have been developed: the Nutritional Risk Score (NRS) in 1995 [10], the Paediatric Nutritional Risk Score (PNRS) in 2000 [11], the Screening Tool for Risk On Nutritional status and Growth ($STRONG_{kids}$) and the Paediatric Yorkhill Malnutrition Screening (PYMS) in 2010 [12,13], the Screening Tool for the Assessment of Malnutrition in Paediatrics (STAMP) in 2012 [14]. Moreover, new tools were introduced to serve the general paediatric population: The Paediatric Digital Scaled Malnutrition Risk Screening Tool (PeDiSMART) in 2015 [15] and the Paediatric Nutrition Screening Tool (PNST) [16], as well as the modified STAMP: The Paediatric Malnutrition Screening Tool (PMST) [17] in 2016. While having their own merit, these tools aim at detecting patients with early signs of nutritional status alterations and classifying children based on their risk of developing nutritional and medical complications during hospitalization (low, moderate or high) through specific scoring systems based on patient characteristics and medical conditions. This might show to be insufficient in the context of assessing needs of critically ill patients whose survival increased in the recent years due to progress in paediatric critical care technology. For instance, Briassouli et al. [18] demonstrated, that prediction energy expenditure (PEE) equations inadequately predicted energy expenditure in malnourished critically ill children as defined by the weight-for-height Waterlow criteria [19].

The malnutrition status however extends beyond protein-energy tandem. Micronutrient deficiency has been described in toddlers, infants and children. This status could be exacerbated in a critical illness condition. Therefore, efforts should be made to improve nutrition assessment tools by including blood and urine biomarkers for specific micronutrients.

Clearly identifying early deficient states is the imperative first step in planning effective nutrition intervention programs. However, present nutrition assessment tools based on medical characteristics suffer from only being relevant once a deficient state has reached an advanced stage. Using vitamin K as an example, global coagulation tests such as the prothrombin time (PT) or activated partial thromboplastin time (APTT) are insufficiently sensitive or selective to detect early vitamin K insufficiency, yet they are routinely used. Despite well preserved coagulation function, evidence of suboptimal hepatic vitamin K status was present in 65 of 93 children (70%) with cystic fibrosis, on the basis of low serum phylloquinone concentration, increased under-carboxylated prothrombin (factor II), also known as Protein Induced by Vitamin K Absence-II (PIVKA-II), or both abnormalities [20]. Evidence of extra hepatic vitamin K insufficiency was also demonstrated in these children through a negative correlation between serum phylloquinone concentration and undercarboxylated osteocalcin, the presumed inactive form of the protein. Vitamin K insufficiency may also be associated with an uncoupling of the normal balance between bone formation and resorption in children with cystic fibrosis [20]. Evidence suggests that extrahepatic vitamin K dependent proteins may be more sensitive to suboptimal vitamin K status than the seven hepatic-synthesized vitamin K-dependent clotting factors that PT and APTT laboratory tests reflect [21]. They thus could be better indicators and used in nutritional assessment schemes particularly adapted to the clinical conditions and to the population investigated.

One caveat of classical nutritional assessment tools and of evaluation of nutritional intakes is that they are based on the assumption of uniform manifestation of deficient states and of nutrients bioavailability in different patients. To attest to this erroneous postulate, whereas megaloblastic anaemia is frequent in vitamin B_{12}-deficient patients, only ~25% of them will present with peripheral neuropathy [22]. Moreover, patients who have developed peripheral neuropathy or subacute combined degeneration of the cord may have no discernible haematological diathesis [23].

As for nutrients bioavailability, any condition impeding the absorption of lipids modifies the disposal of fat-soluble vitamins since their absorption takes place predominately in the proximal intestine and is dependent on bile and pancreatic secretion, ensuring an adequate lipid digestion process. Hence inherent to their physiopathology, celiac disease, chronic pancreatitis, Crohn's disease and cystic fibrosis all impede fat-soluble vitamin absorption. In a similar manner, Crohn's disease also modifies the bioavailability of the water-soluble vitamin B_{12} because of the frequent involvement of the terminal ileum – the predominant site of absorption for vitamin B_{12}. The prevalence of this deficiency has previously been underestimated in this patient cohort through the use of serum vitamin B_{12} assays that are unable to identify the minor portion of vitamin B_{12} that is bound to transcobalamin and hence available to meet metabolic need [24].

While the direct measurement of the abundance of some vitamins reflects status, there is a growing appreciation that using metabolic markers in tandem to reflect utilisation by target tissues can be beneficial. For example, the disadvantage of using serum phylloquinone concentration in isolation to evaluate vitamin K status only represents the abundance of a single vitamer, rather than all K vitamins. The putative health roles of the vitamin K_2 series, the prokaryotic origins and sources of which are distinct from that of the plant-synthesized phylloquinone, are beginning to be better understood [25]. Further, phylloquinone measurement alone as a biomarker also suffers from its association with serum lipids and does not reflect the metabolic conversion of phylloquinone to menaquinone-4 in humans [26]. For instance, using PIVKA-II as a functional marker of vitamin K status, Santorino et al. [27] reported that 20% of Ugandan neonates were bordering overt deficiency. High rates of vitamin K-deficiency are not limited to Uganda and have been reported in South East Asia (e.g., Japan, Thailand, Malaysia, Vietnam and China) with incidence rates for bleeding ranging from 11 to 116 cases per 10^5 births [28].

Although blood and urine biomarkers are invaluable companions for the assessment of micronutrient status, we have to be alert to the numerous biological factors that may contribute to the effective nutritional status. Polymorphic genes involved in vitamin absorption and metabolism have to be considered, as false assurance may be provided through inappropriately interpreting laboratory tests. For example, Delvin et al. [29] demonstrated an interaction between age and MTHFR genotype on plasma folate and homocysteine concentrations. More recently, Zinck et al. [30] reported, in a large epidemiological study, the association between the cubilin (intrinsic factor–cobalamin receptor) (*CUBN*) gene single nucleotide polymorphism (SNP) rs78035, located in the 3′-untranslated region and decreased red blood cell folate, highlighting the interaction between vitamin B_{12} and folate metabolism. Moreover, a genetic epidemiological study in British adults and older adults shows the variability in cB_{12} (a combined indicator of B_{12} status) and its constituents to be highly heritable ($h2 = 55\%$–64%) [31]. As a further example, Szili et al. [32] also reported that the cumulative genetic variation of 4 SNPs explained 13.1% of the

variance in serum $25OHD_3$ concentrations, and that when comparing the favourable to the adverse haplotypes of nicotinamide adenine dinucleotide synthase (*NADSYN*) and of vitamin D 25-hydroxyalse (*CYP24RA1*), mean serum $25OHD_3$ concentrations almost doubled. (38.4 vs 20.2 nmol/l). Moreover it must be borne in mind that critical illness causes micronutrient deficiencies by itself as illustrated in the case of alleged vitamin D deficiency and lack of response to supplementation in sepsis, opening the question whether in this condition vitamin D supplements are really efficacious [33].

2. Conclusion

As we approach the beginning of the third decade of the 21st century, we are better placed than ever to develop and apply biomarkers of micronutrient status having clinical utility in childhood. Contemporary analytical methods have lower sample requirements when compared with techniques commonly used at the end of the 20th century that made the evaluation of paediatric reference ranges challenging in some cases. Furthermore, point-of-care devices for the evaluation of micronutrient status are increasingly available which will reduce the dependency on expensive laboratory hardware and aid micronutrient status assessment in developing countries [34,35].

Our understanding of confounding factors that have previously impeded the interpretation of biomarkers has also greatly improved. Despite these advances, some institutions still extrapolate adult reference ranges to childhood and employ a single clinical decision cut-off when interpreting biomarkers of micronutrient status - which we now know is inappropriate for several of the vitamins. For instance, plasma retinol and RBP concentrations, increasing with maturity, are lower in childhood than in adults [36]. Vitamin D is another example as there is much debate with regards to optimal serum $25OHD_3$ concentrations [37,38]. However, there is some evidence that children with deficient states may benefit from replacement regimes titrated to higher serum $25OHD_3$ concentrations but this is yet to be firmly established [39]. From the above discussion, it becomes clear that in the era of personalized medicine, we have the opportunity to go beyond the traditional nutritional tools for assessing patients' status. We thus propose the measurement of selected micronutrients and allied metabolic markers be added to nutritional workup. This requires, as demonstrated by Zhang et al. [40] in older adults, that reference ranges and cut-offs be carefully adapted to the target groups to avoid over- or under-diagnosis of malnutrition.

We are conscious that adding micronutrient assessment leads to additional burden to the healthcare systems, and that local contexts should be taken into account and so strategies adapted accordingly. Hence cost benefit studies with a knowledge transfer approach are warranted. Acknowledging that micronutrient deficiency may also be present in the absence of protein-energy malnutrition, it is important to develop and include micronutrient malnutrition clinical screening tools to the present arsenal to obtain a comprehensive nutritional assessment.

Ending on a philosophical note, quoting Briassoulis et al. [41] “The focus on excellence should be disseminated in “excellence reports” for emulation and propagation across world's clinicians and nurses, together with those relating to error and harm. Departures from Nutrition Support guidelines should be linked to outcomes encouraging the transition from a reactive to a proactive approach to best practise.”

Conflicts of interest

None declared.

CRediT authorship contribution statement

E. Delvin: Conceptualization, Writing - original draft, Writing - review & editing. **D.J. Harrington:** Conceptualization, Writing - original draft, Writing - review & editing. **E. Levy:** Conceptualization, Writing - original draft, Writing - review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.06.008.

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