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Critical Appraisal of Biomarkers of Dietary Intake and Nutritional Status in Patients Undergoing Dialysis

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Characteristics of ideal nutritional biomarker(s) in patients undergoing dialysis

Diagnosis and management of protein-energy wasting (PEW) in patients undergoing dialysis is challenging, given the complexity of its pathophysiology and the many concurrent body compartments affected [1,2]. Clinical monitoring by routine laboratory biomarkers that assess PEW is necessary and must be part of a battery of complementary assessments such as body composition analysis.

Nutritional laboratory biomarkers are constituents in the blood or urine that can be used to estimate nutrient intake or nutritional status. Laboratory parameters of nutrient intake/status have the potential to be useful biomarkers in everyday basis, as they can be objectively measured and evaluated as indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic interventions. An ideal biochemical marker to use in the clinic should be inexpensive, directly linked to the pathophysiological process that it represents, closely correlated to symptom severity, sensitive and specific. It is therefore readily apparent that in dialysis patients, it will be highly difficult to reach such standards for any biomarker. Indeed, laboratory biomarkers are and can be influenced by uremic retention (and conversely residual renal function), fluid status, inflammation (as many nutritional markers also function as acute phase reactants) and renal replacement therapy (losses into dialysate). In this brief review we will provide a critical overview of available laboratory biomarkers in dialysis patients to estimate dietary intake and nutritional status, with special emphasis on the applicability for routine assessment in the clinical setting.

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Laboratory biomarkers of dietary intake

Biomarkers of dietary intake are useful to detect dietary habits, quality of diet and micro-/macro-nutrient deficiencies and excesses. This information is of importance in designing adequate nutrition therapy. The subjective nature of (self-reported) dietary intake assessment methods presents numerous challenges toward obtaining accurate estimates of nutrient intake [3]. This limitation can be partly solved with the use of dietary biomarkers, which more objectively assess dietary intake (or exposure) without the bias of self-reports. However, certain processes can impact on how accurately a nutritional biomarker can represent dietary intake. Physiologically, inter-individual differences in nutrient absorption by the intestine, and tissue turnover and excretion can occur, perhaps an issue of consideration given the functional alterations that commonly occur in the gastrointestinal tract of dialysis patients [4]. Additionally, and similar to any laboratory marker, errors can be introduced by the choice of specimen (plasma, serum, urine), time of sampling (fasting conditions, circadian variation, incorporation into tissue and specific cell tissue renewal), sample storage and degradation, and laboratory issues such as the method of detection employed and the performance of the technician [5].

Table 1 summarizes laboratory biomarkers of dietary intake of potential use in dialysis patients. Laboratory assessment should be performed under fasting conditions and preferably after the long interdialytic period. Very few of these biomarkers have been validated against dietary recalls in individuals with chronic kidney disease (CKD) and its use is extrapolated from non-CKD evidence. Evaluation of protein intake in dialysis patients could be evaluated by assessment of protein-derived nutrients such as creatinine, given that it originates from skeletal muscle-based creatine. However, one would need to assume that nitrogen balance is in steady state and correct for muscle mass measured by other techniques [6]. Specific essential amino acids, such as carninite, could also be considered reflections of protein intake provided that specific amino acid supplements are not ingested. Amino acid levels should be assessed before the dialysis session in order to avoid amino acid losses into dialysate [7].

In clinically stable patients, the protein equivalent of nitrogen appearance (PNA) can be used to estimate protein intake. In this way, the total nitrogen appearance of the body should be equal to or slightly smaller than the nitrogen intake. Because urea nitrogen appearance is highly correlated with total nitrogen appearance and because measurement of total nitrogen losses in urine, dialysate, and stool is inconvenient and laborious, regression equations to estimate PNA have been developed. In dialysis patients, PNA can be calculated by estimating the generation of urea nitrogen in blood (in hemodialysis) or in the dialysate (in peritoneal dialysis) [8], usually followed by normalization (nPNA) by body weight or body weight derived from the urea distribution space. nPNA assessment is recommended with a monthly frequency in HD patients and 4–5 times a year in PD patients [8]. nPNA would not be a valid indicator of protein intake in cases of catabolism, growth/anabolism (children, pregnant women, recovering from an intercurrent illness) or day-to-day changes in dietary protein intake. PNA should not be used to evaluate nutritional status in isolation, but rather as one of several independent measures when evaluating nutritional status.

There is no perfect biomarker to measure total fat intake, but plasma and adipose tissue fatty acid composition in dialysis patients can be taken as a measure of dietary fat quality, as recently demonstrated by Huang *et al.* [9]. The authors observed that essential fatty acid composition (eicosapentanoic [EPA] and docosahexanoic [DHA] acids from fish oil and linoleic acid from vegetable oils) can appropriately reflect the quality of long-term fat intake and the specific intake of foods containing those types of fat [9]. Given the laborious nature of these analyses, however, they may be relegated to research studies at this time.

Assessment of circulating vitamin levels can be useful for the diagnosis of dietary deficiencies. Of particular relevance is the light-sensitive nature of some vitamins (vitamins D and B) or the rapid degradation after extraction of others (vitamins A, E, C) [10]. This should be taken into consideration when preparing the samples and it may have introduced error in *a posteriori* measurements from large dialysis cohort studies. Assessment of micronutrients as a reflection of dietary intake is hampered by the intake of common medication in dialysis patients that interferes with these (such as potassium, iron, calcium and phosphate). Selenium is a common deficiency in these patients that can be assessed reliably.

Laboratory biomarkers of nutritional status

A significant hurdle in preventing and treating malnutrition is accurate clinical detection, particularly at early stages when interventions may be more effective. A crucial feature of clinical patient monitoring is the importance of following trends over time. Without previous values, isolated laboratory values can be deceiving. In addition, biochemical markers and other nutritional estimations should be studied in the entire clinical context and, if a particular value does not make sense in the clinical picture, it should be investigated in more detail. A number of biochemical assessments can be obtained routinely in dialysis patients and be of help for screening and assessment of nutritional status. Albumin and prealbumin are the most classical examples in this category, and their advantages and disadvantages are reviewed in another article in this issue of the journal. Additional laboratory biomarkers of use to monitor nutritional status are detailed in Table 2.

Several biomarkers (in pre-dialysis conditions and stabilized serum) can be indicative of PEW and justify a more thorough assessment of nutritional status. Of those, serum ***creatinine*** may be an appropriate surrogate of muscle mass in ESRD patients when residual renal function is lost or minimal [6]. Although reference values are difficult to ascertain given its dependency on muscle stores for each individual, creatinine may be useful for the detection of short term changes which would denote muscle mass losses. Serum creatinine seems less affected by inflammation [11]. Normalizing creatinine to body surface area allows comparison between individuals with differing creatinine intake and metabolism (e.g. racial differences) [6]. Low serum ***urea*** levels may indicate a low intake of protein or amino acids. Low serum ***cholesterol*** values (below 150 mg/dL) can be a good marker for detecting chronic lower food intake, but this should be evaluated in the context of potential lipid-lowering medication and other additional nutritional assessment methods, particularly those related to appetite, energy and protein intake [12]. ***Bicarbonate/BUN*** may be useful to corroborate other findings but it has limited value as a single measure.

Transferrin is a protein whose main function is to transport iron in plasma. Transferrin can be determined directly or estimated from total iron binding capacity (TIBC) by the equation: Transferrin = (TIBC x 0.8) − 43. As a carrier protein of iron, changes in iron status lead to variations hepatic transferrin synthesis, which represents an important limiting factor in its use as a nutritional marker. This limitation is particularly valid for dialysis patients in frequent need of iron supplementation. Like other visceral proteins, transferrin may also be affected by a patient's inflammatory status.

Inflammatory biomarkers, such as CRP, have mainly been interpreted in the context of the accuracy of nutritional biomarkers. It is undeniable that the condition of PEW present in many dialysis patients is the result of both under-nutrition and excess protein catabolism associated with inflammation [1,2]. Inflammation also leads to under-nutrition by inducing appetite loss [13]. Thus, for a proper interpretation of laboratory biomarkers of nutritional status, it is critical to investigate inflammatory status as well. This can be assessed by directly measurements of inflammatory biomarkers in serum and supplemented by clinical evaluation [14]. Inflammation and malnutrition operate together and for that reason, persistently low levels of inflammatory biomarkers such as C-reactive protein, fibrinogen or related may be indicative of poor nutritional status especially when associated with low levels of nutritional biomarkers.

Conclusions

The regular screening of nutritional intake and nutritional status in the clinical setting should be based on simple available tools. Laboratory biomarkers such as those discussed above can be considered, but keeping in mind their limitations and interactions. Optimal monitoring of PEW in dialysis patients requires the concurrent evaluation of multiple parameters, particularly using measures that assess different aspects/compartments of the PEW etiology. No single measure provides a complete overview of PEW status. Combining information based on laboratory parameters, body composition and dietary intake seems to be an ideal way to assess nutritional status. For instance, taking into consideration concurrent estimates of body weight and creatinine trimestral variation (as an estimate of muscle mass compartment) could provide additional diagnostic information: Both muscle gain (increase in creatinine) and fat gain (concurrent increase in dry weight) are associated with a survival benefit. However, the biggest survival benefit was observed for patients gaining both dry weight and creatinine [15]. Regardless of the method, it is important to keep in mind that none is perfect and definitive, and the results should always be analyzed in the clinical context of each individual patient.

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Table 1

Laboratory biomarkers of dietary intake; Considerations regarding its use in dialysis patients.

Dietary Intake	Laboratory biomarker	Considerations
Energy	Doubly labelled water	Complex and sophisticated; Unavailable for routine testing; Not validated in dialysis patients. Difficult to evaluate the disappearance of the isotope in the dialysate
Protein	nPNA	In blood or peritoneal dialysate; Fasting; Inaccurate in conditions of anabolism or hypercatabolism; Recommended ranges are: Non-dialyzed CKD: ~0.6–0.8 g/kg/day Hemodialysis: ~1.2 g/kg/day Peritoneal dialysis: ~1.3 g/kg/day
	Creatinine/creatine	Can represent animal protein intake if corrected for creatinine-muscle mass. Inaccurate in conditions of anabolism or hypercatabolism. Because of all this, poor marker.
	Carnitine	Can represent vegetable protein under the assumption of no supplement consumption
	Essential Amino acids	Consider losses into dialysate. Under the assumption of not consuming supplements.
Fat	Fatty acid composition	In serum or adipose tissue (preferred). Provides a measure of dietary fat quality, not fat amount. Reliable estimators of essential fatty acid intake (n-3 polyunsaturated fatty acids, linoleic acid, among others).
Vitamins		
	Fat-soluble vitamins (A, D, E and K)	Degradation by light exposure (D). Degraded quickly after extraction (A, E).
	Water soluble vitamins (C and B)	Degradation by light exposure (B). Degraded quickly after extraction (C).
Micronutrients		
	Selenium	Valid to detect deficient intake.
	Potassium	Unreliable dietary intake marker in dialysis. High levels can signify underdialysis or alterations in the GI tract (site of potassium elimination). Steroids, ACEIs and potassium-sparing diuretics may raise potassium levels. Acidosis and hyperglycemia promote loss of intracellular potassium and raise potassium levels.
	Iron	Unreliable marker of dietary intake in dialysis patients due to anemia medications.
	Calcium/Phosphate	Unreliable markers of dietary intake in dialysis patients due to CKD-MBD alterations, concurrent medications, and Ca^{++} in the dialysate.

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Table 2

Laboratory biomarkers of nutritional status (except for albumin and prealbumin) and considerations regarding their use in dialysis patients

Biomarker	Reference values	Recommended range in CKD patients	Considerations
Creatinine	Not established.	Not established. Time trends may denote muscle mass losses	Screening measure that justifies further assessment of nutritional status
Urea Nitrogen	<20 mg/dL	varies	Screening measure that justifies further assessment of nutritional status
Cholesterol	< 200 mg/dL <5 mmol/L	Within reference range Values < 100–150 mg/dL can be indicative of PEW	*Advantages:* Readily available; Inexpensive. *Disadvantages*: Reduced by inflammatory response, statins. Screening measure that justifies further assessment of nutritional status
Bicarbonate	21–25 mEq/L	Varies	Marker of acidogenesis per amount of protein intake
Transferrin	250–450 mcg/dL	Within reference range	*Advantages:* Short half-life; Low influence of extracellular volume *Disadvantages*: Influenced by iron stores; Reduced by inflammatory response; Not recommended
CRP	<3 mg/dL	Within reference range in non-dialyzed CKD; In dialyzed CKD median levels are around 5 mg/dL	Not a nutritional indicator, but it is important to take into consideration when evaluating PEW and the rest of biomarkers