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Accuracy and Limitations of the Diagnosis of Malnutrition in Dialysis Patients

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Abstract

Uremic malnutrition, also known as protein-energy wasting (PEW), is a common phenomenon in maintenance dialysis patients and a risk factor for poor clinical outcomes including worse quality of life and increased hospitalization and mortality. The paradoxical association between traditional cardiovascular risk factors and better outcomes in dialysis patients also referred to as “reverse epidemiology”, is a good example of the powerful effect-modifying impact of the nutritional status in this population. Measures of food intake, body composition tools, nutritional scoring systems, and laboratory values such as serum albumin are used to diagnose PEW and to assess the degree of severity of PEW without clearly validated diagnostic criteria. Some observational studies suggest that inflammation is a missing link between the PEW and poor clinical outcome in dialysis patients, although PEW per se may also predispose to illness and inflammation. Ongoing debate as to whether such surrogates as serum albumin or prealbumin concentrations are markers of nutritional status, inflammation, comorbidity or other conditions has led to confusion and diagnostic and therapeutic nihilism. Irrespective of the cause of hypoalbuminemia in dialysis patients, evidence suggests that nutritional interventions can increase serum albumin in dialysis patients. Hence, we should continue assessing serum albumin and other surrogates of nutritional status to risk-stratify patients and to allocate nutritional therapy, while well designed, large-scale, randomized, controlled trials of the effects of nutritional intake on clinical outcome are awaited.

Keywords

Dialysis; nutrition; inflammation; protein-energy malnutrition; food intake

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KKZ has received honoraria from Abbott Nutrition and BBraun, the manufacturers of oral nutritional supplements for CKD patients.

Introduction

Patients undergoing maintenance dialysis (MD) experience lower quality of life, significantly greater morbidity, higher hospitalization rates and higher mortality as compared to the general population.(1;2) Malnutrition, defined as a decline in protein and calorie intake followed by a decrease in the levels of various nutritional markers, develops once glomerular filtration rate (GFR) decreases to approximately <25–38 ml/min.(1) The prevalence of PEW is common even in patients with non-dialysis dependent CKD, as shown in a recent study of 1220 non-dialysis dependent CKD patients, of whom 45% had a serum albumin <3.6 g/dL and 22% <3.4 g/dL.(2) Numerous reports indicate that there is a similarly high rate of malnutrition ranging from 18% to 75% in MD patients.(3) In contrast to the general population where *over*-nutrition is associated with increased risk of cardiovascular disease, decreased nutritional measures such as a low body mass index or weight-for-height(4) or a reduced serum cholesterol concentration (<150 mg/dL)(5) appear to be strongly correlated with increased morbidity and mortality including higher risk of cardiovascular death in non-dialysis dependent chronic kidney disease (CKD) and in MD patients. This paradoxical observation can be referred to as “reverse epidemiology” in the CKD and MD population, and has been observed with regard to the impact of blood pressure on mortality in MD patients as well as in other conditions associated with chronic illnesses or debility.(6;7)

The strong predictive value of malnutrition in patients with all stages of CKD makes its accurate diagnosis important from a prognostic standpoint. Furthermore, its accurate diagnosis is imperative if therapeutic interventions against malnutrition are contemplated with a goal towards improving clinical outcomes. Diagnostic accuracy requires comparisons to gold standard tests. “Malnutrition” in CKD does not even have a uniformly agreed upon definition, let alone a gold standard test, which makes formal testing of clinically useful diagnostic tests difficult. We will first discuss the nomenclature of “malnutrition” arguing for the need for a more comprehensive terminology, and we will review the various diagnostic tests available to diagnose “malnutrition”, and their clinical utility as prognostic markers and as potential therapeutic targets.

Malnutrition: Nomenclatural clarification

The dictionary definition of malnutrition is “faulty nutrition due to inadequate or unbalanced intake of nutrients or faulty digestion or utilization of foods”.(8) The nomenclatural confusion related to malnutrition in CKD and MD is largely a result of a strict focus on low nutrient intake as the sole determinant of “malnutrition”, whereas in uremic patients one will most often detect a state of “wasting” as a result of more complex processes. MD patients have a high prevalence of comorbid conditions that are often associated with inflammatory processes.(9;10) There appears to be a strong association between malnutrition and inflammation in MD patients with both playing complementary roles in the development of wasting (11) and in these individuals both malnutrition and inflammation are associated with increased morbidity and mortality, including risk of cardiovascular death.(10;12) Since one of the effects of inflammation (and of other conditions such as metabolic acidosis or insulin resistance) can be the “faulty utilization of foods” in the form of hyper-catabolism, one can

indeed argue that the term “malnutrition” can and should be used broadly to encompass all pathologic states leading to an under-nourished state, not just the ones related to low food intake. Nevertheless, to better underscore the complex nature of uremic malnutrition a recent expert panel has recommended the use of the term protein-energy wasting (PEW) to describe states of under nutrition that could result from a complex interplay of decreased nutrient intake and/or increased catabolism.(13)

Protein Energy Wasting: Diagnostic criteria

According to the International Society of Renal Nutrition and Metabolism (ISRNM) expert panel the diagnosis of PEW can be made using four main diagnostic criteria: (1) biochemical measures (serum albumin, prealbumin, transferrin and cholesterol); (2) measures of body mass (body mass index [BMI], unintentional weight loss and total body fat), (3) measures of muscle mass (total muscle mass, mid-arm muscle circumference and creatinine appearance) and (4) measures of dietary intake (dietary protein and energy intake) (Table 1). The expert panel also recognized additional measures such as appetite, food intake, energy expenditure, various measures of body composition, multiple laboratory markers (such as specific markers of inflammation) and also integrative nutritional scoring systems (subjective global assessment of nutrition and malnutrition-inflammation score). (13) The expert panel recommended that at least three out of the four diagnostic categories (and at least one test in each of the selected category) must be abnormal for the diagnosis of PEW. Optimally, each criterion should be documented on at least three occasions, preferably 2–4 weeks apart.(13) As none of the proposed tests are validated for PEW their use has to be applied with an understanding of their limitations.

Controversies surrounding the diagnostic tests of PEW

Biochemical measures

A low serum albumin is one of the strongest predictors of outcomes in CKD and MD patients,(2;14) but it remains unclear to what extent a low serum albumin, or its decline in time are a result of low nutrient intake, increased catabolism, protein losses, or a combination of these. Nevertheless, a broad definition such as PEW which encompasses a spectrum of abnormalities makes it possible to use serum albumin as a somewhat specific diagnostic criterion. Hypoalbuminemia secondary to decreased production due to liver disease may, however, not be representative of PEW. Low serum prealbumin (a.k.a. transthyretin) is also recommended as a biochemical marker of PEW, as they can develop either as a result of malnutrition, or inflammation.(15;16) However, serum prealbumin itself is also not a pure marker of PEW, as its levels can be increased in CKD as a result of retinol-binding protein degradation by the renal tubules and a consequent increase in the amount of transthyretin bound by it.(16) Nevertheless, low serum prealbumin, and especially a decrease in prealbumin over time has been shown to be a predictor of poor outcomes even in patients with normal serum albumin,(17) which suggests that it could be a bona fide diagnostic tool to be used in conjunction with other biomarkers. Low serum cholesterol levels represent one of the more controversial diagnostic criteria of PEW, due to the belief that such low levels are beneficial towards preventing cardiovascular events and cardiovascular mortality in the general population.(18) These beliefs persist in spite of the

consistent associations of low serum cholesterol with adverse clinical outcomes in MD(19–25) and in CKD patients,(26) and the failure of multiple large clinical trials of cholesterol lowering to show a lowering in mortality rates.(27–29) While decreased cholesterol levels that are the result of cholesterol-lowering therapy should obviously not be used to diagnose PEW, such diagnosis could be confounded by hypocholesterolemia induced by intentional dietary restrictions, although uncommon in the stage IV–V CKD population.

Measures of body mass

Body mass index is the most commonly applied measure representing the weight-for-height relationship, and a BMI level $<23 \text{ kg/m}^2$ can be used as a means to define PEW.(13) The accuracy of this threshold will, however, be influenced by race-ethnicity, especially in Southeast Asians, whereby similar levels may not indicate a pathologic state.(30) Indeed BMI may have differential associations with survival when African American, Hispanic and non-Hispanic Caucasian dialysis patients are compared,(31) Furthermore, the effect of BMI on outcome in ESRD patients may be to a great extent related to muscle mass than body fat. (32–34) Indeed higher muscle mass has been shown to be associated with greater survival in dialysis patients.(35;36) Furthermore, it is worth mentioning that the normal BMI in the general population according to the World Health Organization is $18.5\text{--}25 \text{ kg/m}^2$; hence, a significant proportion of CKD and MD patients with PEW based on a BMI $<23 \text{ kg/m}^2$ may be erroneously classified as having an ideal weight by practitioners not aware of the CKD-specific differences in this diagnostic criterion. Observational studies have suggested that a decline in BMI over time may be associated with increased mortality,(37;38) and unintentional weight loss in itself is considered a diagnostic criterion of PEW: it is recommended that a loss of 5% dry weight over 3 months should be considered diagnostic of PEW independent of the baseline weight.(13) Intentional weight loss is considered a beneficial (albeit regrettably infrequent) event in the general population, and hence it should probably not be regarded as a diagnostic criterion for PEW in CKD or MD. Whether or not intentional weight loss is beneficial or harmful, and whether the baseline body weight modifies the effect of intentional weight loss in these populations remains an open question that requires future testing in clinical trials. A third measure of body mass that can be considered to diagnose PEW is a low percentage of body fat, which has also been associated with adverse outcomes.(39–41) A percentage of body fat value of $<10\%$ was suggested as diagnostic of PEW,(13) but the specificity of this diagnostic criterion is also questionable in persons who are very muscular and athletic.

Measures of muscle mass

Due to potential confounding by body water or fat mass BMI is not a reliable measure of body composition, and hence of PEW; a more reliable measure is low muscle mass, albeit the sarcopenia that develops as a result of ageing could again be considered a physiologic phenomenon and hence could decrease the specificity of this diagnostic criterion of PEW. (13) This criterion is in addition also not very practically feasible, since there are currently no universally accepted easily applicable and accurate tools to measure muscle mass or its changes over time in clinical practice.(42) Methods such as bioelectrical impedance analysis and near-infrared interactance have been shown to reliably correlate with other measures of nutritional status and to predict outcomes,(43–47) but they require specialized equipment

and are still not available for mainstream clinical use. An alternative method is to indirectly assess muscle mass based on pre-dialysis serum creatinine or on urinary creatinine appearance.(48–50) The accuracy of this is, however, affected by intestinal creatinine degradation and by the dialysis dose (in MD patients).(51)

Measures of dietary intake

Assessment of dietary intake in dialysis patients is somewhat challenging.(52) Moreover, there are racial and ethnic differences in the amount of protein and fat intake in that African American dialysis patient appear to have higher fat intake.(53) Unintentional decrease of dietary protein intake of <0.80 g/kg/day for at least 2 months for dialysis patients or <0.6 g/kg/day for patients with CKD stages 2–5, and unintentional decrease in dietary energy intake of <25 kcal/kg/day for at least 2 months are also recognized as indicative of PEW. (13) The precise measurement of these indicators is, however, problematic.(54;55) Furthermore, the above thresholds are considered rather conservative as the daily protein and energy needs of most dialysis patients are thought to be significantly higher,(56) hence it is likely that their specificity would be high, but their sensitivity would be low.

Conclusions

Determining the accuracy of the diagnosis of PEW would require a formal assessment of a certain diagnostic test against a gold standard. The lack of either a well-defined formal test or a gold standard test for PEW makes formal assessment of diagnostic accuracy impossible. Furthermore, the multitude of potential diagnostic criteria that can be employed to define PEW and the many flaws of these criteria could even make the very diagnosis of PEW difficult. Using a combination of criteria that encompass various different aspects of PEW makes an accurate diagnosis of this condition more likely, but one has to be cognizant of the pitfalls and exceptions that could render the applied diagnostic criteria invalid.

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Table 1
Diagnostic criteria of protein-energy wasting in chronic kidney disease, and their potential drawbacks

	Diagnostic criteria	Advantages	Drawbacks
Biochemical Markers	Serum albumin <3.8 g/dL	Widely available. Robust association with adverse outcomes.	Decreased production may not represent PEW.
	Serum prealbumin (transferrin) <30 mg/dL	Robust association with adverse outcomes.	Level affected by kidney function.
	Serum cholesterol <100 mg/dl	Widely available. Robust association with adverse outcomes.	Low level as a result of diet and exercise may not reflect PEW.
Body Mass and Composition	BMI <22 kg/m ² (under 65 years) <23 kg/m ² (>65 years)	Widely available. Robust association with adverse outcomes.	Low level as a result of diet and exercise may not reflect PEW.
	Unintentional weight loss over time: 5% over 3 months or 10% over 6 months	Specificity may be high.*	May be masked by fluid gain in MD patients.
	Total body fat percentage <10%	Sensitivity may be high.*	Low level as a result of diet and exercise may not reflect PEW.
Muscle Mass	Muscle wasting: Reduced muscle mass of 5% over 3 months or 10% over 6 months	Sensitivity may be high.*	Decrease in muscle mass could be a result of normal ageing. Measurement tools not widely available.
	Urinary creatinine appearance	Practically feasible method.	Can be affected by intestinal creatinine degradation and by the dialysis dose.
Dietary Intake	Unintentional low dietary protein intake: <0.80 g/kg/day for at least 2 months for dialysis patients or <0.6 g/kg/day for patients on CKD stages 2 to 5	Specificity may be high.*	Conservative cutoffs may result in low sensitivity.*

* No formal assessment of sensitivity and specificity available.