

*Review Article*

## Markers Defining Pre Dialysis Chronic Kidney Disease Nutritional Status

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### ABSTRACT

Patients with Chronic kidney disease have poor nutritional status due to inadequate dietary intake, anorexia, hormonal disturbances, increase in resting energy expenditure, inflammation, metabolic acidosis, polypharmacy and co morbid conditions. Patients become malnourished which is progressive in nature and results in increased susceptibility to infection, impaired wound healing and loss of strength and vigour. Therefore it is essential to assess their nutritional status to improve their quality of life, decrease hospitalization and morbidity. Nutritional assessment, a complex, in depth process, confirms the presence, extent and degree of severity of malnutrition and determines the nutritional needs of the patient. There are two assessment methods i.e. Subjective which includes clinical history, nutritional physical examination and objective methods i.e. anthropometry, biochemistry and body composition. Metabolic and functional changes which occur in the initial stages of malnutrition are detected by clinical and biochemical markers whereas anthropometric markers can only be used for established malnutrition. As per studies, there is not even a single method to correctly assess nutritional status of chronic kidney disease patients because these techniques are affected by the hydration status of the patient, inflammation and disease state, body fat percent, cost factor, standardisation method and subjective nature of the tool. Thus more than one marker is needed which should be sensitive, easy to perform, valid, reliable and should accurately identify those with and without nutritional problem.

**Key Words:** Chronic kidney disease, nutritional status, malnutrition, nutritional assessment

### INTRODUCTION

Patients with chronic kidney disease (CKD) have poor nutritional status due to various factors such as anorexia, hormonal changes, polypharmacy and metabolic acidosis. Since patients' nutritional status predicts hospitalization rate, hospital days, morbidity and mortality, thus making nutritional assessment vital for improving patients' quality of life (QOL), clinical outcome, and help control cost of care.

There are two methods which identify those with nutritional risk. They are subjective and objective in nature with one or more limitations in each. For making assessment comprehensive and to increase sensitivity and specificity, combination of both methods becomes ideal.

#### **Malnutrition:**

Malnutrition is poor nutritional status, an ailment caused by an inadequate

or abnormal diet. <sup>(1)</sup> It is progressive and results in increased susceptibility to infection, impaired wound healing, decreased strength and vigor, poor rehabilitation and quality of life and increased hospitalization and morbidity.

Metabolic, functional and body composition alteration occur in the body as given in Figure 1, which adversely affects patient's prognosis, tolerance of treatment, outcome of disease, survival and health care cost.

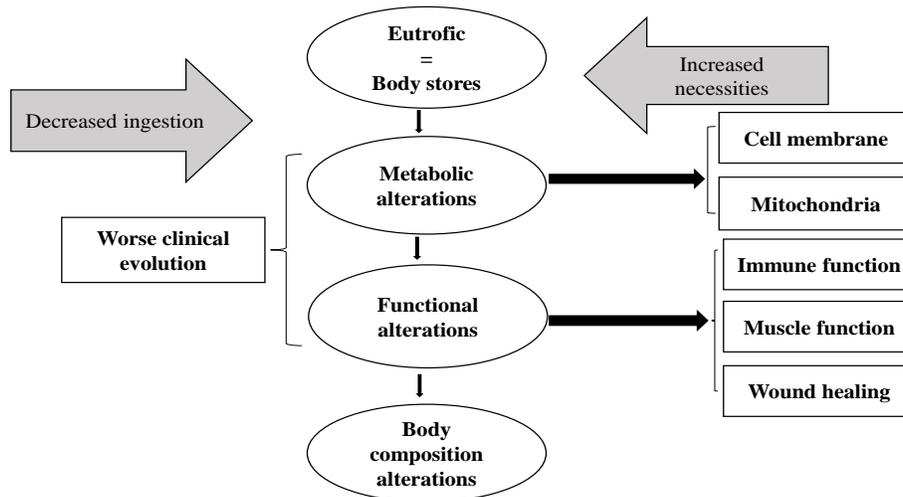


Figure 1: Malnutrition as a continuum: the several levels of its development.

Malnutrition is a continuum, due to imbalance between nutrient intake and requirements, resulting in metabolic and functional changes in initial stages which progresses towards body composition and anthropometric changes later. <sup>(2)</sup>

### Pathway Of Malnutrition

In CKD, levels of circulating inflammatory cytokines increase. These cytokines are tumor necrosis factor (TNF)- $\alpha$ , which stimulates caspase 3 activity by decreasing the activity of phosphatidylinositol-3-kinase/Akt pathway. Caspase 3 cleaves the muscle protein and stimulates the ubiquitin– proteasome pathway (UPP) to break down muscle. <sup>(3)</sup> Muscle proteolysis is also stimulated by metabolic acidosis by an adenosine triphosphate– dependent pathway involving ubiquitin and proteasomes. It increases skeleton muscle breakdown, <sup>(4)</sup> reduces the

synthesis of albumin, induces negative nitrogen balance and degrades branched-chain amino acids and branched-chain ketoacids in CKD patients. <sup>(5)</sup> It also increases catabolic hormone secretion (cortisol), restricts the release of insulin-like growth factor-I, and promotes the synthesis of proteolytic enzymes.

### Causes Of Malnutrition

Causation of malnutrition in CKD is complicated. Various factors include:

- Poor food intake <sup>(4,6)</sup> due to depression, poor appetite <sup>(4)</sup> and anorexia. <sup>(5)</sup>
- Hormonal disturbances include insulin resistance, increased glucagon concentrations, and secondary hyperparathyroidism. <sup>(7)</sup> Hyperparathyroidism results in protein catabolic effect by enhancing amino acid release from muscle

tissue whereas insulin resistance accelerates muscle protein degradation. (8,9)

- Inflammation due to clinical and subclinical infections (10)
- Gastrointestinal disorders
- Metabolic acidosis (1) which leads to protein degradation in patients with CKD. (11)
- It damages the adaptive metabolic responses by stimulating the degradation of the essential, branched-chain amino acids and the degradation of protein in muscle (3)
- It suppresses albumin synthesis (12) and blocks the ability of patients to adjust to a low-protein diet.
- Polypharmacy causing gastrointestinal symptoms (13) and interference with food absorption.
- Intercurrent diseases (14)
- Comorbid diseases (diabetes mellitus, severe congestive heart failure, gastrointestinal disorders) interfere with indigestion and/ or assimilation of nutrients. CKD patients with diabetes are liable to protein deficit due to protein degradation and suppression of protein synthesis
- Psychosocial and socioeconomic factors
- Treatment modalities example, treatment interference with mealtime schedules, the ability to eat, and the types of foods patients willing to eat (15)
- Alcoholism
- Poor in utero conditions result in development of fewer nephrons predisposing to CKD and hypertension in adult life (16)

### **Methods To Assess Malnutrition**

As per Campbell et al. (2007) there is not even a single method to correctly assess nutritional status of CKD patients. (17) Thus for evaluating nutritional status, more than one marker is needed. The ideal nutrition marker should be easy to perform, but also identify those with high risk of morbidity and mortality with high specificity to identify changes in early stages and high sensitivity to bring modification only due to nutritional discrepancies. Methods of nutritional status assessment are objective and subjective. (18)

### **OBJECTIVE METHODS:**

#### **A) Biochemical Testing:**

Biochemical testing is a beneficial part in diagnosing the causes of protein deficiency in patients with CKD. It has the benefits of being objective, easily accessible and requires minimal patient cooperation. It has become the most practical way to identify CKD patients with malnutrition, inflammation or both.

#### **a) Albumin**

Albumin is abundant, easily available and has strong association with hospitalization and death risk, therefore it is the most extensively examined nutritional marker in almost all patient populations. (19) It is used to assess visceral protein stores (20) and is a commonly used marker to assess malnutrition. (21) In spite of its high specificity, its use for clinical purpose is questionable because of low sensitivity in identifying malnutrition because its level in blood is affected by various modifiable and non-modifiable factors such as smoking, older age, female sex, white race and several diseases. In addition it does not find out the nutritional diagnosis or nutritional treatment efficacy. (22,23) It has long half life (approx 14-20 days) and large distribution in the body therefore considered as a late marker of malnutrition. (24) It is thus, no more an indicator of nutritional status as it reflects

more on the severity of the disease than the nutritional status. <sup>(22,25,26)</sup> Though it is a good tool for assessing chronic changes but it is insensitive to acute changes.

Some of its limitations are, its levels is affected by synthesis, degradation, losses, volume of distribution and exchanges between intra- and extravascular spaces. <sup>(23)</sup>

Its synthesis is reduced in liver disease and there is marked decrease in levels due to increased transcapillary loss, losses through gastrointestinal tract and kidneys, due to burns, and peritonitis and volume overload in CKD patients. Inflammation, infection, trauma, <sup>(27)</sup> malignancy or tissue necrosis, increase synthesis of positive acute phase reactants (APR), as C-reactive protein (CRP), metabolic acidosis <sup>(28)</sup> also leads to substantial losses in serum albumin. <sup>(23)</sup>

Serum albumin still is a reliable marker of general clinical status because it is highly predictive of poor clinical outcomes in all stages of CKD. <sup>(29,30)</sup>

#### **b) Prealbumin**

Prealbumin is a negative acute phase protein, having shorter half life (2.5 days), thus has become an alternative marker to assess nutritional status, <sup>(31)</sup> or combined with C-Reactive Protein, it seems to be the most sensitive parameter to monitor nutritional intervention. <sup>(32)</sup> Because of its shorter half life and lower body pool, it is more sensitive than serum albumin in finding out changes in visceral protein stores <sup>(33,34)</sup> and is thus responsive to recent changes, especially calorie and protein inadequacy. With reduced renal catabolism, serum prealbumin concentration tends to increase in CKD patients making it an ideal marker.

#### **c) Amino Acids**

Concentration of plasma amino acids is used as a sensitive indicator to reflect recent protein intake and thus measure nutritional status in uremic patients. Plasma total essential amino acids, ratio of essential

to non essential amino acids, and certain essential amino acids such as branched chain amino acids, valine, leucine, isoleucine and lysine tend to decline in disease condition. Thus, the use of plasma amino acid concentrations for evaluation of body nutrition is beneficial.

#### **d) Creatinine**

Creatinine is formed in body through diet and endogenously by skeletal muscle tissue. It is formed at a very constant rate. It can predict mortality independent of inflammation. Low concentration (> 10mg/dL) of creatinine is associated with poor clinical outcome and should be evaluated for muscle wasting. <sup>(35)</sup> Low serum creatinine depicts low intake of creatinine and creatine in diet as well as reduced lean body mass. Limitation of using creatinine as an indicator is that the women, children and males with low muscle mass will have lower rates of creatinine generation, thus the serum creatinine will be less. Regardless of the limitation, its precision in estimating protein intake and ease of measurement of SUN/ creatinine ratio, makes it a useful tool in non dialyzed CKD patients.

#### **e) Cholesterol**

Low dietary energy intake (below 150-180mg/dL) can be indicated through low serum cholesterol concentration. A study by Koppel et al., 2000 showed correlation of low serum cholesterol with serum albumin, prealbumin and creatinine and with mortality. <sup>(5)</sup> Inflammatory stress is also be responsive of low cholesterol levels and high CRP.

#### **f) Blood urea nitrogen (BUN)**

BUN should be used to evaluate nutritional status along with other tools of protein intake since its concentration increases in protein catabolic conditions, even with reduced protein intake and decrease gradually with established uremic malnutrition in CKD patients. <sup>(36)</sup>

### **g) Bicarbonate**

As kidney function deteriorates, total bicarbonate concentrations generally decrease in CKD patients. <sup>(37)</sup> A small alteration of serum bicarbonate concentrations correct nutritional status reduces muscle proteolysis via the ubiquitin-proteasome system and slows the rate of CKD progression. <sup>(38)</sup>

### **B) Anthropometry:**

Anthropometry is the simplest technique with methodology quickly available and can be used to confirm uremic malnutrition and to detect long term changes in nutritional status. <sup>(39)</sup> It is practical, inexpensive, describes body size, identify levels of fatness and leanness in adults with CKD but less reliable and is subjected to intraobserver and interobserver variability. Also there may be assessment errors due to the alteration in the hydration status of tissues. <sup>(18)</sup> Some anthropometric techniques are given below which can be used for CKD patients.

#### **a) Body Mass Index (BMI):**

BMI is an index of overweight or obesity and leanness. It has direct relationship with levels of body fatness. <sup>(40,41)</sup> It analyzes the total body mass without making a distinction between components like muscle, visceral fat, subcutaneous fat, bone, and fluid. BMI is calculated by two simplest measures i.e. height and weight, which will give indications of nutritional status. BMI can be calculated as body weight divided by squared height (kg/m<sup>2</sup>) and compared with the standard cut off points; it categorizes patients as severely underweight, underweight, normal, overweight, obese and morbidly obese. <sup>(42)</sup> BMI is not considered as ideal method because its value is affected by fluid balance. Therefore it underestimates malnutrition in CKD patient population. Although BMI still remains a useful clinical

tool since it is easier and more reliable to measure in primary care than other anthropometric variables which have significant operator variability. <sup>(43)</sup>

#### **b) Waist Hip Ratio (WHR):**

WHR is calculated taking ratio of two measurements, waist circumference (WC) and hip circumference (HC). WC is a useful, simple and an inexpensive method which was developed to assess intra-abdominal fat <sup>(44)</sup> and is measured at the umbilicus level using smallest circumference, midpoint between the lower ribs and iliac crests after expiration by using a flexible plastic tape measure while subjects are standing straight and the head facing straight forward. <sup>(45)</sup> Hip circumference is determined at the level of maximal protrusion of the gluteal muscles i.e. using the greatest circumference between iliac crest and thighs. <sup>(46)</sup> In a US based study by Elsayed et al. (2008), it was reported that WHR results may be confounded by the variation in muscle and peripheral mass of the hip, thereby affecting its reliability. <sup>(41)</sup> Also, WHR increases in women with age depicting reduction in fat deposits in the hips making it a variable marker and thus more difficult to interpret across a wider age range.

For CKD risk assessment, as per recent clinical guidelines, WC (independently or combined with BMI) is preferred over WHR. It measures central adiposity which has been shown to correlate significantly with higher mortality, cardiovascular disease (CVD), <sup>(47)</sup> hypertension, dyslipidaemia and metabolic syndrome. <sup>(48)</sup> CKD patients have metabolic derangements affecting adversely the nutritional status, making WC a good alternate marker of visceral adipose tissue (VAT). WC alone is correlated with both visceral and subcutaneous fat, thus making it a superior tool and can be used as clinical

marker for CKD risk at primary care setting.<sup>(49)</sup>

**c) Mid Upper Arm Circumference (MUAC) and Mid Arm Muscle Circumference (MAMC):**

MUAC and MAMC are the measurements used to measure fat free mass and total body protein,<sup>(50)</sup> and thus become useful markers of nutritional status. To estimate muscle mass, mid point is determined between the acromion and the olecranon process and mid upper arm circumference is measured to the nearest 0.1 cm with a flexible tape which is placed gently around the arm to avoid compression of soft tissues. Since there is variation in subcutaneous fat, mid-arm circumference is adjusted for subcutaneous tissue in order to estimate mid arm muscle circumference (MAMC):

$MAMC (cm) = \text{mid arm circumference (cm)} - 0.314 \times \text{triceps skinfold thickness (mm)}$ <sup>(51)</sup>

**d) Skinfold Thickness**

Skinfold thickness measures subcutaneous fat thickness which indicates internal adipose tissue.<sup>(52)</sup> It is an inexpensive, reproducible, non-invasive, and easy to perform method to assess body fat. When there is weight gain or weight loss it affects the thickness of subcutaneous tissue,<sup>(51)</sup> hence is a good marker. It provides an account of the percent of body fat by summation of all skinfold thicknesses, and by subtraction from total body weight, gives value for fat-free mass. Skinfold thickness is measured at one site but should be done at three or more locations: triceps, subscapular and either lateral thoracic or suprailiac. It is recommended to do measurements on left side of the body for consistency. Standardised technique, same observer and same point of measurement with three readings ensure correct measurement.<sup>(51)</sup> It has some limitations such as, its estimation depends on the accuracy of the calliper,<sup>(53)</sup> it is less accurate method to assess total body

fat and there is large inter-observer variations.<sup>(54)</sup>

**C) Body Composition:**

Determination of body composition is an important tool for the assessment of nutritional status in uremic patients. Body cell mass (BCM) is formed by visceral and somatic protein deposits. It is lean body mass without bone mineral mass or extracellular water, and is the body's metabolically active tissue, which decreases in malnutrition as well as in inflammatory state.<sup>(55)</sup> Monitoring BCM becomes an important criterion for adequate nutritional therapy and preventing protein-energy malnutrition.<sup>(56)</sup>

Methods to estimate BC are:

**a) Dual-energy absorptiometry (DEXA)**

DEXA is a reliable and convenient method for patients with kidney failure.<sup>(57,58)</sup> This method quantifies bone mineral content (BMC) and bone mineral density of the hip and spine. It assesses three main body components (fat mass, fat-free mass and bone mineral mass) with high precision and with minimal exposure to radiation. It is appropriate with wide range of BMI's. Patient is moved on the instrument, two low radiation energy levels are passed through the body and consecutive computer calculations are made which allows quantification and total and regional analysis of adipose and soft tissues and estimation of fat mass (FM) and non-skeletal fat-free mass (FFM).<sup>(59)</sup> But it is an expensive method and requires trained personnel for its proper usage. Also its use is restricted due to body weight, length, thickness, and width of the available table scan area. In addition it requires regular maintenance and calibration for accuracy. One major limitation is that it includes body water in the fat-free mass compartment.<sup>(60,61)</sup> DEXA is not a gold standard, it is still recommended by the Kidney Disease Outcomes Quality Initiative

(K-DOQI) as a reference method to assess body composition in CKD patients. <sup>(62)</sup>

#### **b) Bioelectric Impedance Analysis (BIA)**

BIA is an accurate and reproducible measure to assess body composition in different patient populations, including CKD patients. <sup>(63)</sup> It is simple, practical, fast, noninvasive, painless, inexpensive method which can be easily used at bed side and can be used for many purposes with kidney disease. <sup>(64, 65)</sup> It estimates Total Body Water (TBW), Fat Free Mass (FFM) and Total Body Fat (TBF). <sup>(66)</sup> This method differentiates the proportions of intra- and extra-cellular fluid volumes under multiple frequencies. Because of its features like providing information on hydration status and identifying edema in predialysis patients, it has been preferred by many nephrologists. <sup>(67)</sup>

#### **D) Handgrip Strength (Hgs):**

Reduction in skeletal muscle mass and its function are good indicators of malnutrition; therefore handgrip strength is used as a marker of the body lean muscle and is not affected by inflammation or the hydration status of patients. It is a simple, inexpensive and easy to perform tool and can be used for bedside test. <sup>(68)</sup> It is measured by Harpenden dynamometer on both arms. Its estimation shows marked difference in well nourished and malnourished patients. Factors like muscle mass, motivation, muscular weakness due to uremia, age, body position and elbow position and disease such as arthritis affect HGS results. <sup>(69)</sup>

### **SUBJECTIVE METHODS**

#### **A) Subjective Global Assessment (Sga):**

Subjective methods are based on the characteristics of individual and are not affected by the nature of CKD i.e. fluid shift, hypoalbuminemia and other non nutritional factors which certainly affect

objective methods. <sup>(70)</sup> SGA was developed in 1980, which is validated for several patient populations. <sup>(71,72)</sup> For CKD nutritional management, SGA is recommended because it is not affected by any metabolic anomalies. <sup>(73, 74)</sup>

SGA is a nutritional assessment universal tool, first introduced in 1987 for CKD patients for routine monitoring, predicting uremic malnutrition and mortality risk. <sup>(4)</sup> It is a simple, accurate, low cost and easy performance tool which remains superior over other complex methods. It identifies established malnutrition and can detect early malnutrition before any changes occur in body composition. <sup>(75)</sup> It is considered as reference method to validate other assessment methods <sup>(75)</sup> such as bioelectrical impedance analysis <sup>(17)</sup> and mid-upper arm anthropometry. <sup>(76)</sup> It is based on subjective and objective aspects of clinical history and physical examination, including details on weight loss, gastrointestinal symptoms, dietary intake, functional capacity, comorbidities, subcutaneous fat and muscle mass losses. It has certain limitations such as lack of sensitivity to detect acute changes in nutritional status. <sup>(77)</sup> It is not as good in detecting degree of malnutrition; <sup>(78)</sup> it can only detect presence of malnutrition and in addition it is based on subjective assessment, which reduces the reproducibility. <sup>(79)</sup>

As per Detsky et al. (1994), when combined with albumin, SGA remains the best clinical tool to identify patients with or suspected of having malnutrition. <sup>(80)</sup> It identifies the etiology of malnutrition, whether due to decreased nutrient intake, malabsorption, maldigestion, increased demand, or excessive nutrient loss, <sup>(72)</sup> but should be used in combination of anthropometric, laboratory, and dietary intake measures to make a comprehensive nutritional assessment. <sup>(81)</sup>

### **B) Patient Generated Subjective Global Assessment (Pgsga)**

PGSGA is a continuous measure, is a scored version of SGA. It detects acute changes in the nutritional status and thus can be used in response to interventions. <sup>(82,83)</sup> It prioritizes patients requiring more urgent treatment. As compared to SGA, PG-SGA score has a high reliability, sensitivity (98%), and specificity (82%) for both oncology and hemodialysis patients. <sup>(84-86)</sup> It classifies patients in three subgroups: well nourished (SGA-A); moderately or suspected of being malnourished (SGA-B); and severely malnourished (SGA-C) and gives numerical scoring to assess nutritional status. In this, patient completes the first part of assessment; scores are assigned by the professional which makes this tool less subjective. <sup>(87)</sup> Higher the scores, greater is the risk of malnutrition, <sup>(85)</sup> which is further used to determine how intensive nutritional intervention is required. But PGSGA is dependent on information given by the patient <sup>(86)</sup> and therefore may increase patient burden. In addition it requires well trained personnel to carry out the assessment.

### **C) Dietary Intake:**

Quality and Quantity of food intake examination is important in the management of patients with chronic kidney disease (CKD). <sup>(88)</sup> For CKD patients, option of dietary assessment methods relies on the stage of kidney disease and the specific nutrients with increased attention.

#### **a) 24 hour recall:**

24 hour recall of foods quantifies and reminds patient of his/her food intake on the previous day. <sup>(89,90)</sup> Interviewer takes food recall by providing food models and standardized utensils. To reduce the underestimation of food intake on the weekend and for better understanding of compliance, 7 day recall is considered as better method than 3 day recall with

coefficient of variation 20%. 24 hour recall is useful for illiterate people. Though its use is limited to know usual dietary pattern in a short time. There is also a need to have proper quantification of portion sizes consumed by the patient and requires trained staff to take interview. Moreover this method relies on memory of the patient and hence underreporting of food items is common.

#### **b) Food Records:**

Food record gives information on qualitative and quantitative data on food intake. It is generally collected for 3 days (2 week days and 1 weekend). To make this record precise, time of eating, food types, beverages, their portion sizes, any in between snacks and preparation method should be included. Advantages of using this tool is that it does not depend on individual's memory and therefore it makes intake more reliable because recording is easy as it is done at the same time of eating. Under-reporting, error in conversion of weight and volume, change of eating habits during recording, burden on patients and literacy of patients are some of its limitations. <sup>(91,92)</sup>

#### **c) Dietary diary and dietary history:**

Dietary diaries and dietary history are simple and direct methods but they lack accuracy in estimating actual intake. <sup>(93)</sup> Their validity is questioned when short duration dietary reports are taken. It also consumes a lot of time and underestimates intake. <sup>(94)</sup> In this method, patients recall intake with the additional information on food allergies, aversions and food preferences for longer duration of time. This method can be used to bring intervention and improve patient's intake.

#### **d) Nutrition Quality of Life (NQOL):**

Once person is diagnosed with CKD, physical and functional status is affected which further affects patients' food preferences and intake, thereby affecting

quality of life (QOL) and possibly their nutritional status. <sup>(95, 96)</sup> New approach in assessing dietary intake and its quality is by assessing nutrition related quality of life survey. It can be determined by knowing physical enjoyment of food and social and nurturing aspects. It completely gives attention to problems associated with food, eating, and nutrition and how these factors affect the patient's overall QOL.

### **Summary**

To identify malnourished patients or those at risk of malnutrition, detailed nutritional assessment is indicated by using multiple markers since individual marker alone cannot assess nutritional status. Biochemical testing can be used to understand adequacy of intake but it is difficult to interpret and sometimes leads to false conclusion. Albumin is considered as a reliable marker, though its level is affected by various factors. Prealbumin, because of its shorter half life and small pool in the body is taken as an ideal marker for CKD patients. Other biochemical markers such as serum amino acid, creatinine, C Reactive Protein, cholesterol, BUN and bicarbonate can also be used to determine nutritional status. Anthropometric techniques are simple and quick but affected by the hydration status and reduction in muscle mass. Its values are also affected by the variations due to inaccurate equipment, technique and observation. Assessment of body composition by DEXA and BIA can also be done to understand its impact on nutritional status. BIA is affected by the hydration status and increased fat percentage whereas DEXA is an expensive method and requires trained personnel; however it is recommended by KDOQI, [2000 (S2)] as a reference method. Biophysical assessment like measuring hand grip strength is a marker of lean muscle mass and indicates muscular strength. SGA or PGSGA can also be used in combination of other markers to

overcome the limitations of objective methods. Dietary assessment is also vital to quantify the nutrients which can be done by the tools like 24 hour recall, food records, diet history, nutrition related QOL. These methods assess intake, dietary pattern and eating related QOL.

### **CONCLUSION**

Malnutrition is poor nutritional status <sup>(1)</sup> which is highly prevalent in kidney disease. <sup>(97)</sup> To correctly identify those with malnutrition, a complete nutritional marker is needed. As per review none of the markers alone is satisfactory. Hence, combination of markers can effectively be used to identify malnutrition in chronic kidney disease patients making nutritional assessment comprehensive.

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