ASSESSMENTS OF PROTEIN ENERGY WASTING IN PATIENTS WITH CHRONIC KIDNEY DISEASE, ATTENDING RENAL UNIT AT TIKUR ANBESA SPECIALIZED HOSPITAL.

By:

BINYAM MAMUYE

A THESIS SUBMITTED TO THE DEPARTMENT OF PHYSIOLOGY, SCHOOL OF MEDICINE, ADDIS ABABA UNIVERSITY, IN PARTIAL FULFILMENTS OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF SCIENCE IN MEDICAL PHYSIOLOGY

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ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCE
FACULTY OF MEDICINE
DEPARTMENT OF PHYSIOLOGY

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Acronyms

ANOVA  One way analysis of variance
BMI  Body mass index
CKD  Chronic kidney disease
CRP  C-reactive protein
DEI  Dietary energy intake
DPI  Dietary protein intake
ESRD  End Stage Renal Disease
eGFR  Estimated Glomerular filtration rate
GFR  Glomerular filtration rate
HD  Hemodialysis
IGF-1  Insulin-like growth factor-1
IL-6  Interleukin 6
IL-1β  Interleukin 1 beta
NFκB  Nuclear Factor kappa light-chain enhancer of activated B cells
ISRN  International Society of Renal Nutrition and Metabolism
IRS-1  Insulin-Receptor Substrate-1
KDOQI  Kidney Disease Outcomes Quality Initiative
LBM  Lean body mass
MAC  Mid-Arm Circumference
MAMC  Mid-Arm Muscle Circumference
NHANES  National Health and Nutrition Examination Surveys
PEW  Protein-energy wasting
PI3K/Akt  Phosphatidylinositol 3-kinase Akt pathway.
SGA  Subjective global nutritional assessment
TSF  Triceps Skinfold Thickness
TNF  Tumour Nephrotic Syndrome
TC  Total Cholesterol
WHO  World Health Organization
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Figure 5: Mean ±SD value for mid arm muscle circumference (MAMC) in (cm) among controls and CKD patients
Abstract

**Background:** Protein energy wasting (PEW) is highly prevalent in patients with chronic kidney disease (CKD) and is a strong predictor of morbidity and mortality. Although data concerning the prevalence of PEW in CKD are scarce in Ethiopia, it is hypothesized that there would be comparable numbers of CKD patients with PEW in the country.

**Objectives:** The aim of the study was to assess protein energy wasting in patients with chronic kidney disease attending Renal unit at Tikur Anbesa Specialized Hospital.

**Methodology:** A cross sectional study design was conducted on 125 subjects at Tikur Anbessa Specialized Hospital. Out of the total, 85 were CKD patients and 40 were controls. Based on their GFR values, CKD patients were further divided into three groups. Group-I (n=39) (GFR 30-60 ml/min/1.73m²), Group-II (n=28) (GFR 15-29 ml/min/1.73m²) and Group-III (n=19) (GFR <15 ml/min/1.73m²). Data were presented as mean ± SD. Data entry and analysis was performed using SPSS version 20 statistical software. A level of p<0.05 was considered statistically significant.

**Result:** The prevalence of protein energy wasting in CKD patients was found to be 20% (17/85). There was significant lowering of serum albumin, BMI and mid arm muscle circumference (MAMC) among all groups of CKD patients when compared with controls p<0.05. Group III patients had maximum percentage of MAMC reduction >10% >6 months, and lowest BMI values < 18.5 kg/m² (42.1%, 63.2%) respectively. Maximum percentage of cases having weight loss > 10% > 6 months (47.4%) and s-albumin below the reference of 3.8g/dl (42.1%) were also in Group-III patients. GFR was found to be strongly correlated with s-albumin, BMI, and MAMC, while negatively correlated with unintentional weight loss.

**Conclusion:** The prevalence of protein energy wasting increased with advancing stage of CKD. Biochemical and anthropometric parameters deteriorated as kidney function decreased.

**Key words:** Chronic kidney disease, Protein energy wasting, Mid Arm Muscle Circumference, Body mass index, Unintentional weight loss, serum albumin
1. Introduction

Chronic kidney disease (CKD) is a world-wide public health problem associated with adverse outcomes of cardiovascular disease and premature death. It has been estimated that the prevalence of CKD is 8-16% of world population (Jha, Garcia-Garcia and Iseki, 2013). In sub-Saharan African countries like Ethiopia, the incidence of CKD is rising because of increased risk factors such as high blood pressure, glomerulonephritis and diabetes mellitus (John, Bocheng, Scott, Nicole, Romita, Naicker, UptalPatelion people, 2014). The true prevalence of CKD in Ethiopia is unknown, largely due to a lack of national registries as well as lack of community-based studies.

Chronic kidney disease (CKD) is defined as an irreversible and progressive disease state leading to renal dysfunction and related morbidity (National Kidney Foundation, 2002). According to the kidney disease improving global outcomes (KDIGO) guidelines, chronic kidney disease is defined as abnormalities of kidney structure or function present for more than three consecutive months. This includes all people with markers of kidney damage and those with a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m² (GFR categories G3a-G5) for >three months indicate CKD. The degree of renal insufficiency is classified based on the magnitude of the estimated GFR for 1.73 m² body surface, using ‘G’ to denote the GFR category (G1–G5).

Table: 1 GFR categories in Chronic Kidney Disease

<table>
<thead>
<tr>
<th>GFR category</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&gt;90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60–89</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>G3a</td>
<td>45–59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30–44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15–29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>
Nutritional health is one of the most important considerations in patients with chronic kidney disease. Advanced kidney disease and renal replacement therapy lead to a number of metabolic and nutritional derangements, which can be termed as protein energy wasting (PEW) of chronic kidney disease (Fouque, Kalantar-Zadeh and Kopple, 2008).

Protein energy wasting is highly prevalent in patients with chronic kidney disease and is a strong predictor of morbidity and mortality (Stenvinkel and Lindoholm, 2004). The prevalence increases progressively along with the loss of residual renal functions and is high in dialysis patients.

Nutritional disorders in CKD have been reported in the literature with numerous and confusing terms such as malnutrition, sarcopenia, cachexia and the malnutrition-inflammation-atherosclerosis syndrome. These terms describe a part of the problem but do not cover the many mechanisms that influence patient health and prognosis. In 2008, the International Society of Renal Nutrition and Metabolism (ISRNM) proposed that the term protein energy wasting (PEW) be adopted as a unifying nomenclature and the starting point for a better knowledge and treatment of these problems in uremic patients.

The International Society of Renal Nutrition and Metabolism (ISRNM) panel has described PEW as a state of decreased body stores of protein and energy fuels. It describes a progressive loss of adipose tissue and lean body mass, with cachexia constituting the severe form of protein energy wasting (PEW) (Fouque et al., 2008). Usually, this deterioration of the clinical nutritional status is characterized by low visceral proteins levels (serum albumin, prealbumin), cholesterol and decreased anthropometric measurements (Mehrotra and Kopple, 2003).

The prevalence of PEW in CKD patients varies depending on assessment methods, selected cutoff points, and geographical location (Carrero, Stenvike, Lilian, Ikizler, Kalantar-Zadeh, George, William, Russ, Wanner, Wang, Wee and Franch, 2013). Depending on the method used, PEW was identified in patients on hemodialysis (HD) and peritoneal dialysis (PD) in 17%-65% using subjective global assessment score (SGA) (Mazairac, Wit, Penne, 2011), and in 46%-60% using malnutrition inflammation score (MIS) (Szeto, Kwan, Chow, Law and Li, 2010). Moreover study in Japan showed that 15% of hemodialysis patients had PEW according to the ISRNM criterion (Sonoko, Yumiko, Mayu, Sayaka, Yu, Kazuaki, Eiji, Chikao and Yasuhiro, 2012).
In the dialysis population, PEW traditionally has a wide prevalence of 18-75% (Leinig, Moraes, Ribeiro, Riella, Olandoski, Martins, 2011). Several studies have shown the prevalence of PEW in dialysis patients than among other CKD groups. In their studies using subjective global assessment (SGA) methods, (Campbell, Ash, and Bauer, 2008), found that the prevalence of PEW is 12% to 18% in stages 3 and 4 patients. It is also showed that stages 4 and 5 CKD patients are more likely accompanied by worsening protein energy status (Kovesdy, Kopple, and Kalantar-Zadeh, 2013).

As a result, PEW is more common in the later stages of CKD. In recent study using ISRNM criterion, (Srivastava, Kumar, Singh, Mishra, Mishra and Singh, 2012) found the prevalence of PEW in CKD to be about 42.7% and increases as CKD progresses.

While protein energy wasting is a well-known risk factor in chronic kidney disease, its diagnosis is still controversial. Nutritional researchers use different nutritional scoring systems to diagnose protein energy wasting. This include 7–scale subjective global assessment (SGA), malnutrition-inflammation score (MIS), and the International Society of Renal Nutrition and Metabolism (ISRNM) criteria (Kalantar-Zadeh, Kopple, Block and Humphreys, 2001). However, Amparo, Cordeiro, Carrero, Cuppari, Lindholm, Amodeo, Sousa and, Kamimura, 2012), demonstrated that the criteria proposed by the ISRNM were the best nutritional scoring system associated with cardiovascular events and mortality in non-dialysis-dependent chronic kidney disease patients.

The etiology of PEW in chronic kidney disease (CKD) is complex. Some mechanisms that might lead to PEW include inflammation, metabolic acidosis, resistance to anabolic properties of insulin and growth hormone (Carrero et al., 2013).

1.1. 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:

- Biochemical measures (serum albumin, prealbumin and total cholesterol)
- Measures of body mass (body mass index [BMI], unintentional weight loss, and total body fat)
- Measures of muscle mass (total muscle mass, mid-arm muscle circumference); and
- Measures of dietary intake (dietary protein and energy intake).
The expert panel recommended that at least three of the four diagnostic categories (and at least one test in each of the selected category) must be abnormal for the diagnosis of PEW.

**Table 2: Protein Energy Wasting: Diagnostic Criteria**

<table>
<thead>
<tr>
<th>Criteria proposed by the International Society of Renal Nutrition and Metabolism expert panel to classify the nutritional status of CKD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Serum Chemistry</strong></td>
</tr>
<tr>
<td>Serum albumin &lt; 3.8 g/100 ml (Bromocresol Green)</td>
</tr>
<tr>
<td>Serum prealbumin (transthyretine) &lt; 30 mg/ml**</td>
</tr>
<tr>
<td>Serum cholesterol &lt; 100 mg/100 ml</td>
</tr>
<tr>
<td><strong>2. Body Mass</strong></td>
</tr>
<tr>
<td>BMI &lt; 23kg/m²</td>
</tr>
<tr>
<td>Unintentional weight loss over time: 5% over 3 months or 10% over 6 months</td>
</tr>
<tr>
<td>Total body fat percentage &lt; 10%**</td>
</tr>
<tr>
<td><strong>3. Muscle Mass</strong></td>
</tr>
<tr>
<td>Muscle wasting: Reduced muscle mass 5% over three months or 10% over 6 months **</td>
</tr>
<tr>
<td>Mid-arm muscle circumference area: reduction &gt; 10% in relation to 50th percentile of National Health and Nutrition Examination Surveys II (NHANES II).</td>
</tr>
<tr>
<td><strong>4. Dietary Intake</strong></td>
</tr>
<tr>
<td>Unintentional low dietary protein intake &lt; 0.8 g/kg/day for 2 months for dialysis patients &lt; 0.6 g/kg/day, for patients with CKD stage 2-5 **</td>
</tr>
<tr>
<td>Unintentional low dietary energy intake (DEI) &lt; 25 kcal/kg/day for 2 months. **</td>
</tr>
</tbody>
</table>

BMI: body mass index; **: criteria not considered for diagnosis of PEW in this study, because they were not assessed during data collection.
1.2. **Nomenclature of PEW and Malnutrition in CKD**

Malnutrition in the context of CKD occurs when an inappropriate dietary intake of one or more macro- or micro-nutrients results due to an inadequate diet. Meanwhile, protein energy wasting is the result of metabolic abnormalities such as, systemic inflammation, insulin and insulin-like growth factor resistance, and metabolic acidosis that cannot be corrected solely by an improved diet (Mak and Cheung, 2006). Responses in malnutrition are adaptive whereas those in wasting/cachexia are maladaptive. Hunger, which is an adaptive response, characterizes malnutrition whereas anorexia is prevalent in patients with cachexia (Kalantar-Zadeh, Block, McAllister, Humphreys and Kopple, 2004). Energy expenditure decreases as a protective mechanism in malnutrition whereas it remains inappropriately high in cachexia (Sea, MM, Sanderson, Lui, Li, Woo, 2004). In malnutrition, such as in simple starvation, fat tissues are preferentially lost and lean body mass (LBM) and muscle mass is preserved until the advanced stages, whereas in cachexia, muscle is wasted and fat is relatively underutilized (Mak and Cheung, 2006). Restoring adequate food intake or altering the composition of the diet reverses malnutrition whereas protein energy wasting can be reversed by correction of acidosis, inflammation and endocrine disturbances (Mak, Cheung and Purnell, 2007).

1.3. **Nomenclature of PEW and Sarcopenia in CKD**

Wasting/cachexia is a complex metabolic syndrome characterized by a severe and involuntary loss of muscle mass with or without wasting of fat mass (Von Haehling and Anker, 2014). In contrast sarcopenia is characterized by the slow and progressive loss of muscle mass that is associated with ageing in the absence of any underlying disease or condition (Carmeli, Coleman, Reznick, 2002). It is important to note that sarcopenia and cachexia can often run in parallel, with many elderly patients.

1.4. **Etiology of Protein-Energy Wasting in chronic kidney disease Patients**

1.4.1. **Anorexia as a cause of PEW in CKD**

Anorexia, as evidenced by decreased dietary protein and energy intake, is an important cause of PEW in CKD. Studies have shown that dietary nutrient intake decreased as a result of worsening kidney function (Ikizler, Greene, Wingard, Parker and Hakim, 1995).
The prevalence of anorexia has been reported at 35–50% in end stage renal disease (ESRD) patients (Bossola, Tazza, Giungi and Luciani, 2006).

The factors influencing food intake are complex involving not only metabolic signals but also psychological and acquired aspects, including a desire for pleasure, social behavior and customs (Carrero, 2011). Anorexia in many settings is mediated by circulating appetite regulators, such as gastric mediators (cholecystokinin, peptide YY, ghrelin), adipokines (such as leptin and visfatin) or cytokines (such as TNF, IL-6, IL-1β) (Chung, Carrero and Lindholm, 2011).

Inflammatory cytokines, such as tumor necrosis factor- (TNF-α), interleukin- (IL-) 1, IL-6, and interferon- (IFN-γ) have been postulated to play a key pathogenic role in the decreased food intake and increased energy expenditure seen in most chronic conditions associated with the anorexia and cachexia syndrome (Plata-Salaman, 2001). Increased cytokines in the hypothalamus enhance serotoninergic tone through tryptophan, resulting in activation of proopiomelanocortin (POMC) neurons and subsequent anorexia (Laviano, Meguid and Rossi-Fanelli et al., 2003).

CKD patients have markedly elevated leptin levels caused by impaired renal clearance, and it is possible that this uremic hyperleptinemia contributes to anorexia (Stenvinkel, Pecoits-Filho and Lindholm, 2003). Leptin is taken up into the central nervous system by a saturable transport system and binds to the long form of the leptin receptor in the arcuate nucleus of the hypothalamus. Recently, leptin signaling in the central nervous system has been shown to be an important cause of anorexia in uremic rats via signaling through the central melanocortin system (Delano and Moldawer, 2006).

Increased total ghrelin levels in CKD are primarily due to decreased degradation of ghrelin in the kidney (Mak, Cheung and Purnell, 2007). The two major forms of circulating ghrelin are acylated and des-acyl ghrelin. Acylated ghrelin promotes food intake while des-acyl ghrelin induces negative energy balance. Most of the investigators have used the traditional radioimmunoassay method to analyze the sum of both acylated and des-acyl ghrelin. However, only plasma desacyl ghrelin levels were elevated in CKD patients compared with those patients with normal renal functions. Recent studies have suggested that elevated des-acyl ghrelin levels could be involved in the anorexia on CKD patients (Yoshimoto, Mori, Sugawara, Mukovama, Yahata and Suganami, 2002).
Although reduced intake of food or poor absorption of nutrients plays a critical role in most cases of PEW, the science of starvation suggests that additional mechanisms are needed for PEW to occur. Research showed that decreased energy intake reduces insulin secretion and stimulates the production of sugar from glycogen and increased mobilization of fatty acids. Activation of these systems contributes to a reduction in basal metabolic rate and mobilization of free fatty acids and amino acid (Shetty, 1999).

1.4.2. Inflammation as a causes of PEW

Recent evidences indicate that increased proinflammatory cytokines contribute to the development of protein energy wasting during chronic kidney disease progression (Pecoits-Filohet, Sylvestre and Stenvinkel, 2005). It has been reported that inflammation presented in 30 to 50% of end stage renal disease patients (Stenvinkel, 2001). Inflammation in CKD can be caused by increased oxidative stress, decreased renal clearance, altered tissue perfusion, uremic toxins and factors associated with dialysis procedure (Pecoits-Filohet et al., 2005). Infusion of cytokines such as tumor necrosis factor (TNF-α), interleukin (IL) 1, IL-6, interferon (IFN)-γ enhance muscle protein degradation via activation of ubiquitin-proteasome system and Nuclear transcription Factor Kappa-B (NFκB) (Cheung, Paik and Mak, 2010).

Inflammation activates the ubiquitin-proteasome system which, is the major system involved in muscle proteolysis (Du, Wang, Miereles, Bailey, Debigare and Zheng, 2004). TNF-α also enhances muscle wasting by inhibition of myocyte differentiation through NFκβ activation, causing muscle wasting (Langen, Schols, Kelders, Wouters and Janssen-Heininger, 2001). Furthermore, inflammation may affect muscle wasting by suppressing insulin signaling and increases production of glucocorticoids (Hu, Wang, Lee, Du and Mitch, 2009). In addition chronic inflammatory response appears to be crucial for the development of lipolysis and increased energy expenditure (Stenvinke, Lindholm and Lonnqvist, 2000).
1.4.3. Metabolic acidosis as a causes of PEW

Metabolic acidosis, a common abnormality in patients with progressive CKD, promotes PEW by increasing protein catabolism especially in muscle (Bailey, Wang, England, Price, Ding and Mitch, 1996). It promotes protein degradation by stimulation of the ubiquitin proteosome system, through which proteins are generally targeted for digestion to peptides and amino acids and via suppression of insulin/insulin growth factor-1 signaling which produce anti-anabolic effects (Du et al., 2004). In addition Graham, Reaich, Channon, Downie and Goodship (1997), proved that acidosis stimulates the oxidation of essential amino acids to raise protein requirements in CKD patients.

Metabolic acidosis induces increased adrenal glucocorticoid production. Glucocorticoid causes insulin/IGF-1 resistance in skeletal muscle by altering the same signaling pathways that are affected by acidosis, but they act on slightly different signaling molecules within the pathway (Zheng, Ohkawa, Li, Roberts-Wilson and Price, 2010).

1.4.4. Insulin resistance/deficiency as a cause of PEW in CKD

Patients with CKD secondary to diabetes mellitus (DM) have a higher incidence of PEW when compared to non-diabetic patients (Cano, Roth and Aparicio, 2002). The degree of insulin resistance and/or insulin deprivation seems to play the most critical role in regulation of protein synthesis and degradation in skeletal muscle. It is proved that insulin-deficiency and insulin resistance causes a decrease in muscle PI3K (phosphatidylinositol 3 kinase), leading to enhanced activation of the ubiquitin proteasome pathway and caspase-3 hyperactivity pathway (Duet et al., 2004) Activation of ubiquitin proteasome results in degradation of protein.

Furthermore, even in the absence of diabetes mellitus or severe obesity, insulin resistance is detectable in late stages of CKD patients and is strongly associated with increased muscle protein breakdown, primarily mediated by the ubiquitin–proteasome pathway (Siew, Pupim, Majchrzak, Shintani, Flakoll and Ikizler, 2007). It is reported that inflammatory cytokines, acidosis and glucocorticoids share a common mechanism of muscle wasting via impairment of insulin/IGF-1 actions by altering signaling through the phosphatidylinositol 3-kinase (PI3-kinase)/Akt pathway (Ding, Gao, Hirschberg, Vadgama and Kopple, 1996).
1.5. **Statement of the problem**

The clinical consequence of PEW may be severe and requires rapid and effective treatment since it is associated with increased overall and cardiovascular mortality. However, regrettably, many hospitals still do not incorporate measures to evaluate and monitor the nutritional state of patients. Likewise, early identification of patients with kidney disease is recommended, as measures may be instituted to slow progression and mitigation of cardiovascular risks.

The true significance of these alterations is not studied in Ethiopia as there are no long term studies done to assess protein energy wasting in chronic kidney disease. The purpose of this study is to assess protein energy wasting in patients with chronic kidney diseases.

1.6. **Rationale of the study**

PEW is highly prevalent in CKD and is linked with co-morbidities such as cardiovascular disease, and is associated with lower quality of life, increased hospitalizations and increased in risk of death.

Assessments of PEW should be performed to identify the risks and causes of deterioration of the nutritional status, and to establish a nutritional diagnosis. In addition, this will allow the establishment of nutritional goals to prevent and treat PEW.

The present study aimed to assess protein energy wasting in different stages of chronic kidney disease by using ISRNM criterion. Besides, it can also serve as baseline information to undertake further studies on similar setting in the future.
2. Objectives

2.1. General Objectives
- To assess protein energy wasting in patients with chronic kidney disease, using the International Society of Renal Nutrition and Metabolism (ISRNM) criteria.

2.2. Specific Objectives
- To study the prevalence of PEW
- To assess anthropometry and biochemical parameters levels at different glomerular filtration rate (GFR)
- To correlate biochemical and anthropometric parameters with glomerular filtration rate (GFR)
3. Methodology

3.1. Study Area and period

The study was conducted in Tikur Anbessa Specialized Hospital in Addis Ababa from March to June, 2015.

3.2. Study Design

A cross sectional study design was conducted to assess protein energy wasting in patients with chronic kidney disease, using the International Society of Renal Nutrition and Metabolism (ISRNM) criteria.

3.3. Source and Study population

The source population includes all Patients with chronic kidney diseases and healthy control group with normal renal function in Addis Ababa.

The study population: - includes

- Patient with chronic kidney diseases from Tikur Anbessa Specialized Hospital who attend Renal unit
- Healthy control group with normal renal function from friends, family members and colleagues of the patients to be selected using a set of inclusion and exclusion criteria.

3.4. Study subject

The study subjects were age 18 years and above, those who have attended in the study periods, who fulfilled the inclusion criteria and who gave their informed consent were included.

3.5. Inclusion and Exclusion criteria

3.5.1. Inclusion criteria

CKD patients: - includes all confirmed CKD patients of any cause for at least 3 months.

- Age 18 years and above

Control group: - these were the relatives/ friends accompanying the patients to the Renal unit OPD.
These volunteers had

- No previous diagnosis of CKD
- Age 18 years and above
- No other systemic complications

### 3.5.2. Exclusion Criteria

Both patients and control group were excluded if they had history of diabetes, endocrine disorders, obesity, pregnancy, malignancy, patients with acute inflammatory illness, and active hepatitis B or C, current participation in drug trial, age less than 18 years and patients on hemodialysis / peritoneal dialysis were excluded from the study.

### 3.6. Variables

#### 3.6.1. Dependent variable:
- Protein energy wasting

#### 3.6.2. Independent variable:
- Chronic kidney diseases
- Total cholesterol
- Serum Albumin
- Body mass index
- Mid Arm Muscle Circumference
- Unintentional weight loss

### 3.7. Sampling procedures and Sample size determination

Anon-probability convenience sampling methods was used and a total of 125 subjects were recruited in the study including 85 CKD patients and 40 healthy control groups matched for age and sex.

CKD patients were further divided into three groups based on stages of the disease. Group-I consisted of 39 patients with a GFR between 30 and 60 ml/min/1.73m². Group-II consisted of 28 patients with a GFR between 15 and 29 ml/min/1.73m² while, Group -III consisted of 19 patients with a GFR < 15 ml/min/1.73m².
3.8. Sample and Data Collection Techniques and Procedures

Data were collected by preparing a standardized questionnaire that contains information about the socio-demography and health status. Then, from the study participants who fulfill the inclusion criteria, under aseptic precautions, 5ml of fasting (9 to 14 hour fast) venous blood was collected from healthy control groups and patients with chronic kidney disease. The blood sample was immediately centrifuged at 3000 RPM for five minutes; the serum was separated and stored at -20°C. Serum albumin, creatinine and total cholesterol were determined from the stored serum. Patients were also asked to cooperate for the anthropometric parameters included, body weight, height, arm circumference and skin fold thickness (SKF) of triceps.

3.9. Data quality control

The English version of the questionnaire was translated into Amharic language. The data collectors (Nurses at Renal unit) were given explanation in accordance with the contents, methods and procedures of the study. Every day, the principal investigator collect and cross check the questionnaire to assure completeness of the information and centrifuge the collected blood sample and store the serum at appropriate storage place until analysis. Routine laboratory test were done in Tikur Anbesa Specialized Hospital main laboratory.

3.10. Methods of Data collection and Analysis

3.10.1. Anthropometric Measurement

3.10.1.1. Dry Weight (Wt.)

Electronic weighing scale was used to obtain the weight. The scale was placed on a hard floor surface. Patients were asked to remove their heavy outer garments. Weight measured in all patients and taken to the nearest 0.1 kg.

3.10.1.2. Height (Ht.)

Height was measured in all participants, with the patients bare footed and head upright. The height was measured with the measuring rod attached to the balanced beam scale. The floor surface next to the height rule was hard. The height was reported to the nearest 0.5 cm. (Tayyem and Mrayyanm, 2007).
3.10.1.3. **Body mass index (BMI).**

Body mass index was calculated as following formula:

\[
\text{BMI} = \frac{\text{Weight in kilograms}}{\text{Height in meters}^2}
\]

3.10.1.4. **Mid Arm Circumference (MAC).**

Mid arm circumference was measured with a flexible non stretchable measure tape. The patients were asked to stand with his/her feet together, shoulders relaxed, and arms hanging freely at the sides. The midpoint on the posterior aspect of the upper arm was established between the acromial and olecranon and marked with a pencil. The measuring tape was placed around the upper arm at midpoint and pulled snugly enough to ensure contact with the arm. The measurement was recorded to the nearest centimeter. Three measurements of MAC were obtained and the average was calculated (National Kidney Foundation, 2000).

3.10.1.5. **Triceps Skin-Fold Thickness (TSF)**

Triceps skin-fold thickness was measured with a body fat caliper (Harpenden Skin fold Calipers). At the midpoint where the skin was marked, a fold of skin with subcutaneous adipose tissue was grasped gently with the thumb and forefinger. With the jaws of the caliper perpendicular to the length of the fold, they were closed around the skin-fold. The skin-fold thickness was measured to the nearest 1 mm. The measurement was repeated three times and the average was calculated (National Kidney Foundation, 2000).

4.10.1.6. **Mid-Arm Muscle Circumference (MAMC)**

Mid-arm arm muscle circumference was calculated from the MAC and the TSF by the following formula: \[\text{MAMC (cm)} = \text{MAC (cm)} - [3.1415 \times \text{TSF (cm)}] \] (National Kidney Foundation, 2000)

3.10.1.6. **Unintentional weight loss**

\[
\text{Percentage of weight change} = \frac{\text{Usual weight} - \text{Present weight}}{\text{Usual weight}} \times 100
\]

Significant weight loss occurs when a patient loses 5% his/her weight over 3 months or 10% over 6 months.
3.10.2. Laboratory testing Methods

The biochemical parameters were determined by different methods; serum albumin by Bromocresol- Green end point method, serum total cholesterol by enzymatic end point method and serum creatinine by alkaline picrate method. All the above tests were done by the fully automatic analyzer (RFCL, Flexor – XL).

3.10.2.1. Serum albumin assays

Albumin binds with Bromocresol Green (BCG) at a pH value of 3.5- 4.3 to form a blue-green complex. The colour intensity of the blue-green complex is directly proportional to the albumin concentration and was determined spectrophotometrically at 632nm. Laboratory normal range is 3.8– 5.0 g/L.

\[
\text{Albumin + BCG} \quad \text{PH 4.3} \quad \text{Albumin- BCG complex (blue-green)} \quad \text{(Working manual 2014)}
\]

**Procedure:** 4.0 ml working dye solution was pipette into test tubes then 20 μl of standard, control, test sample were added separately for each measurement, mixed properly and absorbance was measured immediately within 30 seconds at 632 nm after setting the instrument to zero absorbance with the working dye solution (Working manual 2014)

3.10.2.2. Measurements of serum total cholesterol

Cholesterol is determined by enzymatic colorimetric method. Cholesterol esters are hydrolyzed to free cholesterol by cholesterol ester hydrolase. The free cholesterol produced is oxidized by cholesterol oxidase to cholest-4-en-3-one with the simultaneous production of hydrogen peroxide, which oxidatively couples with 4-aminophenazone and phenol in the presence of peroxidase to yield a chromogen. The absorbance is measured at 400 nm.

The reaction sequence is as follow:

\[
\text{Cholesteryl ester + H}_2\text{O} \xrightarrow{\text{Cholesteryl Ester Hydrolase}} \text{Cholesterol + Fatty acid}
\]

\[
\text{Cholesterol + O}_2 \xrightarrow{\text{Cholesterol oxidase}} \text{Cholest-4-en-3-one + H}_2\text{O}_2
\]

\[
2\text{H}_2\text{O}_2 + 4\text{-aminophenazone + Phenol} \xrightarrow{\text{Peroxide}} \text{Quinoneimine + 4H}_2\text{O}
\]
For this study, the specimen or sample was serum of human, and the reagents are standard and ready for use on automated analyzer. Enzymatic assay was adjusted at 400 nm in wavelength, 1 cm in optical path, 37 °C in temperature and measurement done against reagent blank.

**Procedure:** Samples, standard and reagent blank were preincubated for 5 minutes at 37 °C. Samples (10 L) or standard (10 L) and reagent blank (1000 L) were pipetted into cuvette and mixed thoroughly by inversion. The cuvettes were inserted into the cell holder and stopwatch was started to count. The absorbance of sample, standard and the reagent blank were measured at 400 nm within 60 minutes. Finally the absorbance of the sample (A sample) and the standard (A standard) against the reagent blank were calculated

\[
\text{TC concentration} (m/d) = \frac{\Delta A_{\text{sample}}}{\Delta A_{\text{standard}}} \times C_{\text{sample}}
\]

### 3.10.2.3. Measurements of Creatinine

Coloriometric estimation of serum Creatinine is done by using the alkaline picrate method via Jaffé’s Method (Peak and Whitining, 2006). Creatinine in alkaline medium forms a colored complex with picric acid. The formation rate of the complex measured colorimetrically through the increase of the absorbance in a prefixed interval of time is proportional to the concentration of Creatinine in the sample.

\[
\text{Creatinine} + \text{Picric acid (yellow)} \xrightarrow{\text{NaOH (alkaline medium)}} \text{Creatinine picrate (Orange)}
\]

**Procedure:** Working reagent, sample and standard were pre-incubated at 37 °C. The spectrophotometer was adjusted to zero absorbance with air. Working reagent (10 l) and sample (10 l) was pipette into cuvette and mixed gently. The cuvettes were put into the cell holder and stopwatch started to count. The absorbance was recorded at 400 nm and 30 milliseconds (A1) and after 90 seconds (A2) of the sample or standard addition.

\[
\text{Creatinine concentration} (m/d) = \frac{\Delta A_{\text{sample}}}{\Delta A_{\text{standard}}} \times C_{\text{sample}}
\]

### 3.10.2.4. Estimation of Glomerular Filtration Rate

GFR based on age, sex, and creatinine was calculated separately for men and women by using the following Modification of Diet in Renal Disease (MDRD) formula.

\[
\text{GFR (mL/min/1.73 m2)} = 175 \times \text{Scr}^{-1.154} \times \text{Age}^{0.203} \times 0.742 \text{ (if female)} \times 1.21
\]
3.11. Statistical Analysis

Statistical analysis was done using SPSS version 20 statistical software. In the descriptive analysis, continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as count (percentages). All studied variables had normal distribution. Differences in mean between control group and CKD groups were analyzed using independent- \( t \) test. Correlations between GFR and biochemical and anthropometric parameters were calculated using Pearson’s correlation coefficients. One way analysis of variance (ANOVA) was used to compare mean difference between controls and CKD patients at different groups of GFR. Each variable under protein energy wasting were graded 0 and 1, representing no PEW and PEW respectively. A level of \( p<0.05 \) was considered as statistically significant.

3.12. Ethical Consideration

The study was approved by the research and ethical committee of Department of Physiology and Internal Medicine, School of Medicine College of Health Sciences, Addis Ababa University. A consent form was prepared with detailed explanation of objectives, risks, and benefits of the study subject and the confidentiality of responses were given to participants. Data were collected after obtaining informed consent and agreement from the study subjects. Sample collection was performed by trained health professionals following ethical steps and procedures.
4. Results

4.1. Socio-demographic characteristics of the study participants

In this study, out of the 125 subjects, 54.4% were male and 45.6% were females. The mean and standard deviation of age was 53.4±12.4 years. The majority of subjects were between the ages of 50-59 years and these accounts to 33.6%. Most of the participants (76%) were high school and above. Out of the total, the majorities (75.2%) were married and the rest were bachelors. With regard to religion, the majority of the participants were Christians (orthodox, protestant and catholic) accounting 74% and the rest were Muslims.

The mean duration of CKD in group-III was 7.6±2.8 years, 4.5±1.9 years in Group-II and 3.2±1.6 in Group-I patient respectively.

Table 3: Socio-demographic characteristics of the studied Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frequency</th>
<th>Valid percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
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<td></td>
</tr>
<tr>
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</tr>
<tr>
<td>Female</td>
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<td>45.6</td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
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<td>3.2</td>
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<td>5.6</td>
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<tr>
<td>40-49</td>
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<tr>
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<tr>
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<td>Elementary school</td>
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<td>High School</td>
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<td>23.2</td>
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<td>Diploma</td>
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<td>24.8</td>
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<tr>
<td>Degree</td>
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<td>20.8</td>
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<tr>
<td>Above Degree</td>
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<td>7.2</td>
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<td>Marital Status</td>
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<td></td>
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<td>----------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Married</td>
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<td>75.2</td>
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<tr>
<td>Divorced</td>
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<td>6.4</td>
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<td>2.4</td>
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<table>
<thead>
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<th>Religion</th>
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</thead>
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<td>Orthodox</td>
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<td>51.2</td>
</tr>
<tr>
<td>Protestant</td>
<td>27</td>
<td>21.6</td>
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<tr>
<td>Muslim</td>
<td>31</td>
<td>24.8</td>
</tr>
<tr>
<td>Catholic</td>
<td>3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

4.2. Anthropometric and biochemical parameters among control and CKD Patients in different GFR categories

The anthropometry and biochemical parameter of CKD patients in different GFR categories and control group is shown in Table 4.

S-Albumin

Group-III CKD patients, with GFR value of <15 ml/min/1.73m² showed a significantly lower s-albumin level (3.8±0.3 g/dl Vs.4.6±0.3 g/dl) compared to the control (p=0.001). The fall in s-albumin concentration accounted to a significant decrease of about 18% from the control. Further, comparing Group-II CKD patients to control also resulted in a significant decrease of s-albumin ((3.9±0.3 g/dl Vs.4.6±0.31 g/dl), (p=0.001)) that accounted to a fall of 14%. Comparing CKD patients to each other s-albumin concentration was significantly (p=0.008) lower in Group-II patients than Group-I patients (3.9±0.3 g/dl Vs.4.21±0.4 g/dl respectively), accounting to a decrease of about 7%. Group-III patients (3.8±0.3 g/dl) had significantly lower s-albumin as compared with Group-I patients (4.2±0.4 g/dl), (p=0.001). There was no statistical mean difference detected between Group-II and Group-III CKD patients (3.9±0.3 g/dl Vs.3.8±0.3 g/dl respectively), (p=0.324).

The study has also compared s-albumin concentration of all CKD patients without categorizing them into groups. As compared with the control group (4.6±0.3 g/dl), patients with CKD (4.0±0.4 g/dl) had significantly lower s-albumin (p=0.01). This indicates a significant fall in s-albumin concentration of about 12% in CKD patients than control groups.
Figure 6: Mean ±SD level of s-albumin concentration (g/dl) among controls and CKD patients categorized into group I, II and III.

*p<0.05 in Control vs. Group-I, Control vs. Group-II, Control vs. Group-III

** P<0.05 in Group- I vs. Group- II, Group- I vs. Group- III
Total cholesterol

Generally, total cholesterol (TC) concentrations remained unchanged when comparing controls (166.3±48.4 mg/dl) with kidney patients (166.8±47.5 mg/dl), (p=0.400). However, chronically ill patients classified under group-III showed a relative decrease of about 12% compared to the control (147.9±57.0 Vs 166.3±48.4), (P = 0.002). Furthermore, there were no significant differences in total cholesterol levels among the three groups of CKD patients.

![Bar chart](chart.png)

**Figure 7:** Mean ±SD level of total cholesterol concentration (mg/dl) among controls and CKD patients categorized into group I, II and III.

* p<0.05 in Control vs. Group-III
**Body max index**

The BMI was significantly lower in patients with CKD (20.1±2.5 kg/m²) compared to the control (23.4±2.5 kg/m²), (p=0.01). Group-III patients (18.7±2.0 kg/m²) showed a significant lowering of BMI levels from that of the control (23.4±2.5 kg/m²) and Group-I patients (21.3±2.7 kg/m²) at a significant level of (p=0.001 and p=0.001) respectively. However, there was no statistical significant difference observed between Group-III and Group-II (18.7±2.0 kg/m² Vs 19.4±1.8 kg/m²) patients (p=0.758). The fall of BMI value in Group-III patients accounted to a significant decrease of about 20% from the control and 13% from Group-I patients. Compared to controls (23.4±2.5 kg/m²) and Group-I (21.3±2.7 kg/m²), Group-II (19.4±1.8 kg/m²) patients showed a significant lowering of BMI (p=0.001and p=0.013) respectively.

![Figure 8: Mean ±SD level of BMI (kg/m²) among controls and CKD patients categorized into group I, II and III.](image)

* p<0.05 in Control vs. Group-I, Control vs. Group-II, Control vs. Group-III

**P<0.05 in Group-I vs. Group-II, Group-I vs. Group-III**
Unintentional weight loss

CKD patients (-2.5±1.7 kg) lost their weight significantly compared to control group (-1.0±0.8 kg), (p=0.003). Patients who were in Group-III had experienced significant weight loss in the previous 6 months (-4.1±1.3 kg) compared with Group-I (-2.1±1.5 kg), and Group-II (-2.2±1.5 kg), p=0.001. The decrease in body weight between Group-I and Group-II were not significant (P=0.997).

Figure 9: Mean ±SD level of unintentional weight loss in (kg) among controls and CKD Patients categorized into group I, II and III.

* p<0.05 in Control vs. Group-I, Control vs. Group-II, Control vs. Group-III

** P<0.05 in Group-I vs. Group-III

*** P<0.05 in Group-II vs. Group-III
Mid Arm Muscle Circumference

The results of this study showed that mean values of MAMC in the three CKD groups (21.4±2.9cm) was lower than the control group (23.2±2.1cm), (p=0.014). On comparing controls with each groups of CKD patients, the difference was significant only in patients with Group-III (19.0±2.2cm) and Group-II (20.7±2.4cm), (P=0.001) and was not significant in the group-I (23.2±2.1cm),(P=0.987). The mean values of MAMC significantly decreased in Group-II and Group -III compared to Group-I CKD patients, (p=0.001). However, on comparing group-II with the group-III the mean value of MAMC showed no significant difference (P=0.076).

Figure 10: Mean ±SD level of mid arm muscle circumference (MAMC) in (cm) among controls and CKD patients categorized into group I, II and III.

* p<0.05 in Control vs. Group-II, Control vs. Group-III

** P<0.05 in Group- I vs. Group II, Group-I vs. Group- III
Table 4: Comparison of anthropometry and biochemical parameters of CKD patients in different GFR categories and control groups at Tikur Anbesa Hospital, (n=125)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group</th>
<th>GFR 30-60 ml/min/1.73m² (I)</th>
<th>GFR 15-29 ml/min/1.73m² (II)</th>
<th>GFR &lt;15 ml/min/1.73m² (III)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>95% CI</td>
<td>Mean ± SD</td>
<td>95% CI</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>4.6±0.3</td>
<td>4.5-4.7</td>
<td>4.2±0.4</td>
<td>4.1-4.3</td>
<td>3.9±0.3</td>
</tr>
<tr>
<td></td>
<td>(C) vs (I)=0.001</td>
<td>(C) vs (II)=0.001</td>
<td>(C) vs (III)=0.001</td>
<td>(I) vs (II)=0.008</td>
<td>(I) vs (III)=0.001</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td>166.3±48.3</td>
<td>146.4-171.4</td>
<td>169.6±40.1</td>
<td>156.5-182.8</td>
<td>175.9±47.9</td>
</tr>
<tr>
<td></td>
<td>(C) vs (I)=0.070</td>
<td>(C) vs (II)=0.326</td>
<td>(C) vs (III)=0.002</td>
<td>(I) vs (II)=0.944</td>
<td>(I) vs (III)=0.313</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>23.4±2.5</td>
<td>22.6-24.2</td>
<td>21.3±2.7</td>
<td>20.4-22.2</td>
<td>19.4±1.8</td>
</tr>
<tr>
<td></td>
<td>(C) vs (I)=0.001</td>
<td>(C) vs (II)=0.001</td>
<td>(C) vs (III)=0.001</td>
<td>(I) vs (II)=0.013</td>
<td>(I) vs (III)=0.001</td>
</tr>
<tr>
<td><strong>Unintentional weight loss</strong></td>
<td>1.0±0.8</td>
<td>0.7-1.4</td>
<td>2.1±1.5</td>
<td>1.6-2.6</td>
<td>2.2±1.5</td>
</tr>
<tr>
<td></td>
<td>(C) vs (I)=0.028</td>
<td>(C) vs (II)=0.026</td>
<td>(C) vs (III)=0.001</td>
<td>(I) vs (II)=0.997</td>
<td>(I) vs (III)=0.001</td>
</tr>
<tr>
<td><strong>Mid arm circumference</strong></td>
<td>23.2±2.1</td>
<td>22.7-24.3</td>
<td>23.2±2.3</td>
<td>22.5-23.9</td>
<td>20.7±2.4</td>
</tr>
<tr>
<td></td>
<td>(C) vs (I)=0.987</td>
<td>(C) vs (II)=0.001</td>
<td>(C) vs (III)=0.001</td>
<td>(I) vs (II)=0.001</td>
<td>(I) vs (III)=0.001</td>
</tr>
</tbody>
</table>
4.3. **Correlation between GFR and some anthropometric and biochemical variables**

Table 5 shows association of GFR with some biochemical and anthropometric parameters.

Pearson correlation analysis showed that there was a significant positive correlation between GFR and s-albumin \((r=0.688, P=0.001)\). Significant positive correlations were also observed between GFR and BMI \((r=0.553, P=0.001)\), and MAMC \((r=0.724, P=0.001)\). On the other hand, GFR weakly correlated with total cholesterol \((r=0.225, p=0.038)\). There was a strong negative correlation of unintentional weight loss with GFR \((r=-0.447, p=0.001)\).

**Table 5: Correlation between GFR and some anthropometric and biochemical variables**

<table>
<thead>
<tr>
<th>Measures</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Albumin</td>
<td>.668**</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>.225*</td>
</tr>
<tr>
<td>BMI</td>
<td>.553**</td>
</tr>
<tr>
<td>MAMC</td>
<td>.724**</td>
</tr>
<tr>
<td>Unintentional weight loss</td>
<td>-.447**</td>
</tr>
</tbody>
</table>

**NB.** **Express strong correlation, *express weak correlation**

4.4. **Criteria of PEW in different GFR categories according to ISRN**

As shown in Table: 2 the ISRN expert panel recommends at least one criterion in three of the four categories proposed (biochemical, body mass, muscle mass and dietary intake criteria) to be recognized for the diagnosis of PEW.

In biochemical category, s-albumin and total cholesterol were analyzed. About 21 (24.7%) patients had s-albumin below the reference value (<3.8mg/dl). Across the three categories of GFR range: <15, 15-30, 30-60 ml/min/1.73m2, patients in later stage (group-III) of CKD had maximum percentage (42.1%) of serum albumin <3.8gm/dl followed by Group-II (28.6%). Concerning total cholesterol, 12(14.1%) patients had total cholesterol below 100mg/dl. Maximum percentage of cases having total cholesterol <100mg/dl were in Group-II and III (21.4%, 21%) respectively.
In Body mass category, body mass index and unintentional weight loss were studied. BMI values were ranged from 16.2-25.6 kg/m² and 30 patients (35.3%) were presented with BMI <18.5 kg/m². 63.2% of Group-III, 32.1 % of Group II and 23.7% of patients had BMI below the reference level. Regarding Unintentional weight loss, about 29 (34.1%) of patients loss up to 10% of their body weight in the past 6 months. We also observed that nearly half of Group-III and 42.9% of Group-II patient losses their weight in the past 6 months.

In muscle mass category, according to the PEW criteria based on MAMC loss> 10% of the standard, 28(32.9%) of patients were classified as muscle wasted. Of these, patients in Group-III lost maximum muscle mass (57.9%) in comparison to Group-II (46.4%) and Group-I (10.5%).

Table 6: Percentage of Chronic Kidney Disease (CKD) patients, at different GFR categories stratified according to the presence of Protein-Energy wasting (PEW) markers, defined by the International Society of Renal Nutrition and Metabolism (ISRNM)(n=85).

<table>
<thead>
<tr>
<th>PEW Variables</th>
<th>Group-I</th>
<th>Group-II</th>
<th>Group-III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>BIOCHEMICAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.8 gm/dl</td>
<td>5</td>
<td>13.2</td>
<td>8</td>
<td>28.6</td>
</tr>
<tr>
<td>&gt;3.8 gm/dl</td>
<td>33</td>
<td>86.8</td>
<td>20</td>
<td>71.4</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 mg/dl</td>
<td>2</td>
<td>5.3</td>
<td>6</td>
<td>21.4</td>
</tr>
<tr>
<td>&gt;100 mg/dl</td>
<td>36</td>
<td>94.7</td>
<td>22</td>
<td>78.6</td>
</tr>
<tr>
<td>BODY MASS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10% in &gt;6 months</td>
<td>8</td>
<td>21.0</td>
<td>12</td>
<td>42.9</td>
</tr>
<tr>
<td>&lt;10% in &gt;6 months</td>
<td>30</td>
<td>79.0</td>
<td>16</td>
<td>57.1</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5 kg/m²</td>
<td>9</td>
<td>23.7</td>
<td>9</td>
<td>32.1</td>
</tr>
<tr>
<td>&gt;18.5 kg/m²</td>
<td>29</td>
<td>76.3</td>
<td>19</td>
<td>67.9</td>
</tr>
<tr>
<td>MUSCLE MASS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAMC reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10%</td>
<td>4</td>
<td>10.5</td>
<td>13</td>
<td>46.4</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>34</td>
<td>89.5</td>
<td>15</td>
<td>53.6</td>
</tr>
</tbody>
</table>
4.5. Prevalence of PEW at different categories of GFR

As shown in Table 7 the prevalence of protein energy wasting in CKD patients according to ISRNM criteria was found 20% (17/85). The percentage was substantially higher in group-III (42.10%) compared to group-II (21.43%) and 7.9% in Group-I.

Table 7: Prevalence of PEW according to the GFR categories

<table>
<thead>
<tr>
<th>CKD categories</th>
<th>PEW categories</th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-I</td>
<td>0</td>
<td>35</td>
<td>92.1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3</td>
<td>7.9</td>
</tr>
<tr>
<td>Group-II</td>
<td>0</td>
<td>22</td>
<td>78.6</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>6</td>
<td>21.4</td>
</tr>
<tr>
<td>Group-III</td>
<td>0</td>
<td>11</td>
<td>57.9</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>8</td>
<td>42.1</td>
</tr>
<tr>
<td><strong>Total percentage of No PEW</strong></td>
<td>0</td>
<td>68</td>
<td>80</td>
</tr>
<tr>
<td><strong>Total percentage of PEW</strong></td>
<td>1</td>
<td>17</td>
<td>20</td>
</tr>
</tbody>
</table>

0= cases satisfying none or less than one criteria in three of the four categories, defined by International Society of Renal Nutrition and Metabolism (ISRNM)

1=cases satisfying at least one criteria in three of the four categories defined by ISRNM.
5. **Discussion**

5.1. **Anthropometric and biochemical parameters in different GFR categories**

According to the kidney disease improving global outcomes (KDIGO) guidelines, starting from a glomerular filtration rate (GFR) 60ml/min/1.73m$^2$, the patient should be regularly submitted to assessments of nutritional status. The ideal way to monitor the nutritional status of these patients includes various biochemical and anthropometric parameters. In the current study, we compared the CKD patients at different GFR categories and control groups to see if significant change occurred. We also saw association between kidney function and parameters of nutritional assessments.

**S-albumin**

The results of this study showed that mean s-albumin levels decreased in CKD patients as compared with control group. In our patients, s-albumin concentration decreased significantly as GFR level decreased, showing that reduced s-albumin was related to the deteriorating kidney function. As expected, patients with advanced stages of CKD showed low serum albumin concentration compared to patients with early renal insufficiency. S-albumin concentration may be decreased as a consequence of a decrease in the rate of albumin synthesis or as a result of increased albumin catabolic rate. Don and Kaysen, (2004), confirmed that inflammation and malnutrition may reduce albumin concentration by decreasing its rate of synthesis and increased catabolic rate. Metabolic acidosis has also been shown in a variety of animal models to induce hypoalbuminemia by means of up regulating the adenosine triphosphate (ATP)-dependent ubiquitin proteosome pathway and increasing proteolysis (Mitch and Goldberg, 1996). Our results agreed with Kopple, Greene and Chumlea, (2000), who demonstrated a strong cross-sectional association between hypoalbuminaemia and lower glomerular filtration rate (GFR) among patients with moderate to advanced kidney dysfunction. In our study, we have also found a significant positive correlation between GFR and s-albumin.
Total Cholesterol

In our result we found that mean values of total cholesterol increased in Group-I and Group-II patient compared to control group, however the value was not significant. Patients in Group-III showed significant decreased total cholesterol compared to control group. This might be due to dietary restriction and increased inflammation as kidney function deteriorating to the ESRD (Kuhlmann, Kribben, Wittwer and Walter, 2007). Our result is agreed with Rao et al., 2010, that showed no statistical difference in mean value of total cholesterol in any of CKD groups. In contrast to our study, Sabeela, Nudrat, Fasiha, Tahseen and Khalilullah, (2014) reported that total cholesterol increased significantly in ESRD compared to the control group and early to moderate stages of CKD.

Body mass index

In this study, it was showed that the mean value of BMI was significantly lower in patients with CKD compared to controls. On comparing CKD groups, a significant reduction of BMI occurred after GFR fell below 15ml/min/1.73m². The reduced BMI values in CKD patients might be due to changes in fat mass, muscle mass or extracellular fluid (Bigaard, Frederiksen and Tjonneland, 2004). Our result is consistent with a study by Pollock, Ibels, Zhu, Warrant, Caterson, Waugh and Mahony, (1997), who showed a significant reduction of BMI as GFR falls below 50 ml/min/1.73 m². Positive correlation was also detected between GFR and BMI, indicating that the progressive loss of kidney function is accompanied by a decline of body mass index. Our result is in line with Guerra, Angeloco, Furtado, Coelho and Chiarello, (2015), who found a strong association between BMI and GFR.

Unintentional weight loss

Regarding unintentional weight loss, the present study revealed that patients with CKD loss a significant amount of their baseline weight in comparison to the control group. Weight loss increased as GFR decline, with higher impact in Group-III. This result is agreed with the finding of Shobha, Chertow, Kirsten, Johansen, Yan, and Manjula, (2013), which confirmed that patients in ESRD experienced maximum weight loss. The causes of weight loss may be due to depletion of fat free mass and fat mass caused by increased metabolic rate and decreased caloric intake, systemic inflammation (Jagoe and Engelen, 2003). There was also a highly significant negative correlation between unintentional weight losses and GFR, suggesting that weight loss increased as GFR decline.
**Mid Arm Muscle Circumference (MAMC)**

In the present study, we found a significant decrease in MAMC mean values in CKD patients as compared to the control group. Mean value of MAMC reduced as the severity of disease increased; the reduction in Group-III where GFR < 15 ml/min/1.73m² was very severe.

Wasting of muscle mass may be due to an impaired balance between protein synthesis and protein breakdown. Besides nutritional abnormalities and physical inactivity, presence of a systemic inflammation and metabolic acidosis may contribute to a negative protein balance in chronic kidney diseases (Workeneh and Mitch, 2010). In line with our results, Alice, Irene, Daniela, Antonella, Stefano, Ezio and Giacomo, (2011) showed that muscle wasting increased with the progression of kidney disease.

Our finding also showed that kidney function was positively correlated with MAMC, indicating muscle wasting increased as kidney function deteriorated. This may reflect a marked reduction in muscle bulk and somatic protein stores as GFR decline.

**5.2. Criteria of PEW in different GFR categories according to ISRNM**

According to the International Society of Renal Nutrition and Metabolism (ISRNM) expert panel, PEW is diagnosed if there are low serum levels of s-albumin and total cholesterol, decreased body mass and decreased muscle mass (Fouque et al., 2008).

**S-albumin**

Serum albumin concentration less than 3.8 g/dl is the most important biochemical indicator of PEW in patients with CKD. The present study revealed that one fourth of patients had s-albumin level less than 3.8mg/dl. Patients in later stage group-III of CKD had maximum percentage (42.1%) of serum albumin <3.8gm/dl. Reduced protein intake, inflammation, metabolic acidosis may leads to decreased albumin synthesis and increased degradation (Kaysen, Rathore, Shearer and Depner, 1995). In line with our result, Chan, Kelly, Batterham&Tapsell, (2014) proved that patient in later stages of CKD or lower GFR level had highest percentage of s-albumin below referencerange.
Total Cholesterol

Low serum cholesterol levels represent one of the more controversial diagnostic criteria of PEW, due to the belief that such low levels are beneficial toward preventing cardiovascular events and cardiovascular mortality in the general population (Kalantar-Zadeh, Block, Humphreys and Kopple et al., 2003). Contrary to the general population, a high cholesterol level in the CKD and dialysis population is associated with improved survival. However, positive association between high cholesterol levels and increased survival of patients observed only when malnutrition and inflammation were controlled (Liu, Coresh, Eustace, Longenecker, Jaar, and Fink, 2004). Kovesdy, Anderson, and Kalantar-Zadeh (2007) reported that a lower plasma total cholesterol level was associated with a significantly higher risk of death from cardiovascular disease in late stages of CKD. Low cholesterol in CKD can be caused by presence of malnutrition and inflammation (Liu et al., 2004).

Results of the present study noted that nearly 15% of CKD patients showed total cholesterol <100 mg/dl. More than 85% of patient showed total cholesterol levels >100 mg/dl. However, hypercholesterolemia was not observed in the majority of CKD patients. Our result is in agreement with an Indian studies by Rao, Bitla, Reddy, Sivakumar, and Srinivasa (2010), who did not find hypercholesterolemia in any of the CKD groups.

5.2.1.1.1. Body mass index

Body mass index is the most commonly applied measure representing the weight-for-height relationship. A BMI level <23 kg/m2 can be used as a means to define PEW (Fouque et al., 2008).

Although ISRNM suggests a specific cut off point for BMI (23 kg/m2) in CKD, the average BMI of the general Ethiopian populations is less than the recommended. Because the criterion of BMI <23 kg/m2 was described based on an American population, ISRNM has recognized that the threshold for BMI criteria (<23 kg/m2) may need further adjustment; especially in some populations, such as those from Southeast Asia, and other ethnic population (Stevens and Nowicki, 2003). Thus, the cutoff point established by ISRNM does not seem to be a reliable marker of PEW in our populations, further studies are required.
In our setup we used the World Health Organization normal BMI for the general population, 18.5–25 kg/m² and 18.5 kg/m² as a cutoff point to diagnose PEW.

The present study showed that more than one third of the patients had BMI less than the recommended BMI (18.5 kg/m²) for CKD patients, and the reduction increased as GFR decline. From these about two third of patients with GFR below 15 ml/min/1.73m² have BMI less than 18.5 kg/m². Our result is in agreement with Chan, (2014), who showed the probability of BMI lower than the reference value increased as GFR decline.

The paradoxical association of high body mass index (BMI) with better survival and of low BMI with worse survival in advanced stages of CKD patients has been described as “reverse epidemiology”. Observational studies by Molnar, Streja, Kovesdy, Bunnapradist, Sampaio, Jing, Krishnan, Nissenson, Danovitch and Kalantar-Zadeh,(2011) and Kalantar-Zadeh, Kopple, Kilpatrick, McAllister, Shinaberger and Gjertson,(2005) have suggested that a decline in BMI over time may be associated with increased mortality. On the other hand, a study by Fleischmann, Teal, Dudley, May, Bower and Salahudeen, (1999), reported a significantly higher survival rate in overweight and obese CKD patients than in those with a normal weight and underweight counterparts. One proposed mechanism for better survival in obese patients might be due to the presence of increased adipose tissue and are therefore, less likely to suffer from energy deficits (Abdulla and Salahudeen2003).

**Unintentional Weight loss**

Unintentional weight loss is considered a diagnostic criterion of PEW: it is recommended that a loss of 10% dry weight over 6 months should be considered diagnostic of PEW independent of the baseline weight (Fouqueet al, 2008).

In the current study, 29 patients (34.1%) had suffered a weight loss of up to 10% in the last six months. The percentage of weight loss increased when GFR decline below 30ml/min/1.73m². This finding of ours agreed to Shobhaet al., 2013, who showed weight loss increase as kidney functions deteriorate. This may be due to loss of both adipose tissues and skeletal muscle mass as GFR decline.
Mid Arm Muscle Circumference

Reduced muscle mass appears to be the most valid criterion for the presence of PEW in CKD (Fouque et al., 2008).

Based on ISRNM criteria muscle wasting is determined by reduction of MAMC > 10% in relation to 50th percentile of the reference population. The measures in a CKD patient population are compared to a “normal” reference population (the U.S. NHANES National Health and Nutrition Examination Survey-II) data (Margaret, McDowell, Cheryl, Cynthia, and Katherine, 2003-2006). Patients with values lower than the reference population may be at risk of protein energy wasting and therefore, have a lower muscle mass.

However, the criterion concept of PEW may not reflect the true nutritional status for our population given that it was described on the United States population. It is therefore unclear how these measures compare in an Ethiopian population as no reference tables for these assessments have been published.

Studies by Osmani, (1997) and, Smith and Haddad, (1999) indicated that East Asia and Pacific have, on average, similar anthropometric indicators to Sub Saharan Africa. Since there are no current data tables of these nutritional assessments for the general population of Ethiopia in both healthy people and CKD patients, we adopt the Asian Standard to compare our data (Teo, Toh, Chan, Xu, Li and Lee et al., 2014).

In our study we found that, one third of CKD patients showed reduced MAMC in relation to the normal reference. Maximum percentage of cases (57.89%) having MAMC reduction seen in Group-III patients, GFR below 15ml/mn/1.73m2. This finding is very close to that of Neha Srivastava et al., (2012), study conducted in India, where 42.1% of CKD patients showed MAMC reduction >10 % of their reference. They also reported that maximum reduction of MAMC found in the ESRD patients. Muscle wasting may be due to marked reduction in muscle bulk and somatic protein stores associated with uremia complication such as metabolic acidosis and inflammation (Wang and Mitch, 2014).
5.3. **Prevalence of PEW at different categories of GFR**

In the current study, the prevalence of protein energy wasting in CKD patients according to ISRNM criteria was found 20%. Maximum percentages of cases under PEW status were in Group-III CKD patients, suggesting that PEW is more prevalent as kidneys functions are deteriorated. Kovesdy, Kopple, and Kalantar-Zadeh, 2013, reported that when CKD reaches stages 4 and 5, a decline in protein and energy intakes is often accompanied by worsening protein energy status; as a result, PEW is more common in the later stages of CKD.

Our prevalence is lower than that of Srivastava *et al.*, (2012) study, who found the prevalence of PEW in CKD patient was 42.7%. These differences might be because of the difference in study period. We assessed our patients for a single time in our cross-sectional studies, while they follow up their patient for about 12±2 months. This could be also due to difference in dietary habits of patients.
6. Conclusion

The prevalence of protein energy wasting increased with advancing stage of CKD. As kidney function decrease biochemical and anthropometric parameters were also found to be deteriorated.

7. Strength and Limitation of the study

Strength of the study

- The fact that this study has tried to assess PEW in CKD could be mentioned as the strength of the study, because it is not much studied and explored in Ethiopia.

Limitation of the study

- Since the study is cross sectional study, it has some limitation in establishing the cause and effect relationship.
- Presence of very limited similar studies for comparison purpose could be considered as a constraint factors for the study.
- Purposive (non-probability)sampling method was employed, which is commonly used method for such studies though it restricts further analysis of data and generalization of the result to the source of population.
- Other criteria’s of ISRNM such as percentage of body fat, prealbumin, dietary intake were not assessed.
- Some of patient’s weight were not recorded in their chart.

8. Recommendations

- All patients with CKD should be assessed periodically (monthly or quarterly) for the presence of PEW.
- Health professionals who work in Renal Units need to implement this nutritional assessment protocol that consists of anthropometric and biochemical parameters to detect PEW in CKD.
- Reference values for Mid Arm Muscle Circumference and BMI should be established.
- Patient’s weight should be recorded on every attendance.
9. Reference


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Annex I: Questionnaire (English version)
Questionnaire on assessments of protein energy wasting in patient with chronic kidney disease
Thank you for your willingness to participate; your cooperation is very important to the success of the study. This is a questionnaire you are asked to fill out. Please answer the questions as frankly and accurately as possible. All information obtained in the study will be kept confidential.

Participant code no.____________

PART 1:- Socio demographic characteristics

1.1. Age _____
1.2. Sex
   A. Male
   B. Female
1.3. Marital status
   A. Married
   B. Single
   C. Divorced
   D. Widowed
1.4. Religion
   A. Orthodox
   B. Protestant
   C. Muslim
   D. Catholic
   E. Others………..
1.5. Educational level
   A. Illiterate
   B. Elementary School
   C. High School
   D. Diploma
   E. Degree
   F. Above Degree
PART 2: Participant medical History

2.1. Have you ever been told you have chronic kidney disease?
   A. Yes
   B. No

2.2. If ‘yes’ for the above question number how long has it been since you were first diagnosed?
   A. Less than a year
   B. 1-3 years
   C. 5-10 years
   D. Greater than 10 years

2.3. If ‘Yes’ for question number ‘2.1.’ are you now being treated with hemodialysis/peritoneal dialysis?
   A. Yes
   B. No

2.4. If female, are you pregnant?
   A. Yes
   B. No

2.5. Have you experienced weight change in the past 6 months?
   A. Yes
   B. No

2.6. If your answer is ‘Yes’ for the above question, how much in Kg? __________

2.7. Have you ever been diagnosed with the following?

   A. Endocrine disorders
      Yes ________  No ________

   B. Obesity
      Yes ________  No ________

   C. Diabetes
      Yes ________  No ________

   D. High blood cholesterol
      Yes ________  No ________

   E. Liver disease
      Yes ________  No ________

   F. Others __________
Annex II: የአማርኛየተዘጋጀመጠይቅ

 ventsesef/Wedamenum-Anälf/ቁጥርአንበሳ የስፋላይዝድሆስፒታልበህክምናላይየኩላሊትድክመትያለባቸዉታማሚዎችዉስ የብለሽንየፕሮቲንእናየሃይልመጠን ሲማወቅየተዘጋጀመጠይቅ የመመሪያ፤ ይህንወቅለመሙላትፍቃደኛበመሆንዎከል ይቻለዎመጠንበግል ስእና በትክክልእንዲሞሉትበአክብሮትእጠይቃለሁ፡፡ማንኛውምእርስዎንየተመለከተመረጃሚስጥራዊነቱየተጠበቀነው፡፡

ክፍል 1: የሚወስድርወርስር

1.1  እርስዎትብብርለምርምሩስኬትአስፈላጊእንደመሆኑ

1.2 ሰታ
   A. ወቃ ነብ
   B. ነብ

1.3 በሚስጥት
   A. ወቃ ነብ
   B. ወቃ ነብ

1.4 ይህ ያለው ያሉ በሚስጥት
   A. እርስዎትብብር
   B. እርስዎትብብር
   C. እርስዎትብብር
   D. እርስዎትብብር

1.5 ይህ ያለው ያሉ በሚስጥት
   A. ወቃ ነብ
   B. ወቃ ነብ
   C. ወቃ ነብ
   D. ወቃ ነብ
   E. ወቃ ነብ
   F. ወቃ ነብ


2.1. ከተለመተካከል። የጉወቃል። የሚለውን ያለው ይሁን ይታካሚውወrés እንወ<stdlib መጠን?
   A. እም
   B. ሳም

2.2. የተለመተካከል። የሚለውን ያለው ይህ ይታካሚውወrés እንወ<stdlib መጠን?
   A. ከተለመተካከል ይታካሚውወrés እንወ<stdlib መጠን
   B. ከተለመተካከል የሚለውን ያለው ይህ ይታካሚውወrés እንወ硗ወስ መጠን
   C. ከተለመተካከል የሚለውን ያለው ይህ ይታካሚውወrés እንወ硗ወስ መጠን
   D. ከተለመተካከል የሚለውን ያለው ይህ ይታካሚውወrés እንወ硗ወስ መጠን

2.3. ከተለመተካከል። 2.1 የሚለውን ያለው ይህ ይታካሚውወrés እንወ硗ወስ መጠን?
   A. ሳም
   B. የለብኝም

2.4. የሚለውን ያለው ይህ ይታካሚውወrés እንወ硗ወስ መጠን?
   A. እም
   B. ሳም

2.5. ከተለመተካከል። 6 የሚለውን ያለው ይህ ይታካሚውወrés እንወ硗ወስ መጠን?
   A. እም
   B. ሳም

2.6. ከተለመተካከል። 2.5 የሚለውን ያለው ይህ ይታካሚውወrés እንወ硗ወስ መጠን?

2.7. ከተለመተካከል። 2.5 የሚለውን ያለው ይህ ይታካሚውወrés እንወ硗ወስ መጠን?
   A. እም
   B. ሳም
   C. የለብኝም
   D. የለብኝም
   E. የለብኝም
   F. ሳም

Annex III: Information sheet and consent form for study participants
My name is Binyam Mamuye; MSc student at Addis Ababa University, College of Health Sciences, Department of Physiology. I am here to carry out a research on assessment of protein energy wasting in patient with chronic kidney disease attending Renal units at Tikur Anbessa Specialized Hospital. This study has been approved by the ethical and review committee of the Department of Physiology and Department of internal medicine , Faculty of Medicine, Addis Ababa University.

Dear client, you are kindly requested to participate in this study. Here is some important information which helps you decide to participate or not to participate in the study.

1. **Objective of the study:** the objective of this study is to assess Protein Energy Wasting in patients with chronic kidney disease, using the International Society of Renal Nutrition and Metabolism (ISRNM) criteria at Tikur Anbessa Specialized Hospital.

2. **Procedures to be carried on:** you will be requested to give 5 ml (one tea spoon) and cooperate for some anthropometric measurements. Blood will be collected from one of your arm vein by experienced laboratory technician.

3. **Risk and discomfort:** you may have minor discomfort and pain during blood drawing and there may also be mild redness, or swelling on the site where the shot was given. But this will be minimized, as the procedure will be carried out by experienced health professionals in the health facility with a standard aseptic condition.

4. **Expected benefit:** this study will assess the presence of protein energy in patients with chronic kidney disease and if there is, it helps in finding a solution for the problem and you will benefit from the results obtained.

5. **Confidentiality:** samples and information given by you will serve only for this study not for any other purpose and will be kept confidential.

6. **Termination of the study:** participation in the study is voluntary, and refusal to participate involves no penalty or loss of benefits to which you are otherwise entitled. You have every right to accept or refuse participation in this study at any time.

If you need to have further information or if you have related question on this study, you can contact us using the following address:-

Investigator: - Binyam Mamuye Mobile: - 0912069699

**Consent form**

**Code no----------------------**
Information about the study has been explained to me by the investigator. I understood that the objective of this study is to assess protein energy wasting in patients with chronic kidney disease at Tikur Anbessa Specialized Hospital. I also understand 5ml of blood which I will give will not hurt my health. It has been explained to me that I have the right to stop participation at any time in between and there is nothing I will lose if I refuse to participate. I agree to participate in the study and I hereby approve my agreement with my signature.

Participant’s signature-------------------------------Date-------------------------------

Investigators signature-------------------------------Date-------------------------------

Annex-IV: ከተናዎችየሚሰጥየፈቃደኝነትማረጋገጫቅፅ (አማርኛየተዘጋጀ) ይግባኝ:
የጥናትርዕስ፡ የኩላሊትድክመትያለባቸዉታማሚዎችዉስጥየሚገኝንየፕሮቲንእናየሃይልመጠንንማወቅ
ዋናተመራማሪ፡ የብንያምማሙዬ የህጥናትበአዲስአበባዩኒቨርስቲአስተባባሪነት፤ በተለያዩየኩላሊትድክመትደረጃላይየሚገኙትንታማሚዎችየፕሮቲንእና የሃይልመጠናቸውንበማወቅ ከው፡፡ ይእኔበዚህጥናትውስጥእንድሳተፍፍቃደኝነቴንተጠይቂያለው፡፡ በጥናቱወቅትምከእኔ 5 ላሊ (አንድየሻይማንኪያ) የደምናሙናእንዲወሰድአንዲሁምየቁመትናየክብደትመጠኔንእንድለካበሙሉፍቃደኝነት በፊርማዬአረጋግጣ ላ፡፡

______________________   ______________  
የሚስጥርቁጥ ደ በቀንፊርማ 

__________   ________  
የጥናቱባለቤትስ ደ በቀንፊርማ