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PREVALENCE OF MALNUTRITION-INflAMMATION COMPLEX SYNDROME IN HEMODIALYSIS PATIENTS AND ITS CORRELATION WITH CHANGES IN SERUM THYROID HORMONES

[1]Mohamed Omar Al sayed Ali, [2]Mohammed Ali Fahmy El Zanaty, [3]Tamer Mohamed Goda

Abstract:

Background*: Low levels of thyroid hormones, total triiodothyronine (T3) and free triiodothyronine (FT3) in haemodialysis patients are a marker of malnutrition and inflammation and are predictors of mortality.* ***Aim and objectives****: The aim of this study is improving the quality of life and decreasing morbidity in hemodialysis patients by focusing on malnutrition-inflammation complex syndrome (MICS) and clarify the relationship between it and changes in serum thyroid hormones****, Subjects and methods****: this is a cross sectional study that was carried out at hemodialysis units of Zagazig university hospitals and Fakous general hospital, and the study was conducted on 91 patients with more than three months on HD, three sessions/ week, age between 18 and 69 years, and without known thyroid disease, all patients were referred for measurement of IL-6.Level,* ***Results:*** *prevalence of MIC was 56% and there is high significant relation between MIC and albumin, IL-6 and transferrin, also there is significant relation between MIC and cholesterol, while there is no significant relation between MIC and HB, TLC, glucose, TG, T3, T4 and TSH,* ***Conclusion****: MICS significantly correlated with BMI, duration of hemodialysis, SBP, DBP, serum creatinine, serum cholesterol, triglycerides, IL 6, transferrin and a negative correlation with serum albumin ,*

Keywords*: MIC, Hemodialysis, Thyroid Hormones, Prevalence.*

I. Introduction

Malnutrition is common serious problem in patients undergoing hemodialysis **(1), (2).** This condition has been called “malnutrition-inflammation Complex syndrome (MICS)” **(3),** currently is also known as “energy

[1] *Internal Medicin Department, Faculty of Medicine, Zagazig University, Egypt.*
[2] *Internal Medicin Department, Faculty of Medicine, Zagazig University, Egypt.*
[3] *Internal Medicin Department, Faculty of Medicine, Zagazig University, Egypt.*

protein wasting syndrome**" (1).** Inflammatory and non-inflammatory causes in patients with chronic kidney disease lead to loss of protein reserves and energy, factors involved are: uremia, oxidative stress, diet, blood loss by hemodyalizers, the effect of anabolic hormones and acidosis **(1).** The diagnosis of malnutrition-inflammation complex syndrome is made by a recent and valid survey called "Malnutrition Inflammation Score (MIS)", **(4)**, **(5).**

In patients with chronic kidney disease, there is an alteration of the metabolism, degradation, distribution, and excretion of thyroid hormones **(6), (7),** the most commonly observed is low total triiodothyronine (T3) concentration **(8).**

The real causes of these changes in the thyroid hormones in patients with chronic kidney disease are not entirely understood yet, but there are a number of contributing variables which may cause these thyroid disorders: metabolic acidosis, malnutrition, use of heparin in hemodialysis (HD), advanced age, infection by hepatitis C virus, a decreased activity of deiodinase, and reduction in the excretion of inorganic iodine **(9), (10).**

Previous studies on CKD patients have found a relationship between low triiodothyronine (T3)and high concentrations of inflammatory markers (interleukin 6 [IL-6]), malnourishment (decrease in serum prealbumin concentration), endothelial dysfunction, deterioration of cardiac function, poor survival and greater mortality from other causes **(11)**. Other authors have shown that low serum free triiodothyronine (FT3) is associated with an increase in mortality, explained in part by its underlying association with poor nutritional status and inflammation **(12), (13).**

II. Subjects and Methods

In order to fulfill the objectives of this study, the following techniques were followed:

A. Technical design:

1-Study design: This was Cross sectional study .

2- Study setting: The study was carried out at hemodialysis units of Zagazig university hospitals and Fakous general hospital.

3-Target population and criteria for inclusion: It had been conducted on any case had the following inclusion criteria**.**

- **Inclusion criteria**:

Both male and female patients with more than three months on HD, three sessions/ week, age between 18 and 69 years, and without known thyroid disease.

- **Exclusion criteria:**
- Patients with less than three months on HD.
- Patients younger than18 years old.
- Patients older than 69years old.

- Patients with known thyroid diseases.
- Patients taking drugs that affect serum thyroid hormones.
- Patients with chronic diseases except diabetes mellitus and hypertension.
- Patients with a positive panel for human immunodeficiency virus, hepatitis B or C virus, or with a documented infection in the previous 6 weeks.
- Patients with known neoplastic diseases

4-Sampling technique and sample size determination:

A) Sample size: 91 cases was included in the study from hemodialysis units of Zagazig university hospital and Fakous general hospital.

B) Sampling technique: The participants were choosed by systematic random sampling Serial numbers from 1-100 were randomized from Patients admitted at hemodialysis units of Zagazig university hospitals and Fakous general hospital

5-Study tools:

C) Methods: The cases had been selected from hemodialysis units of Zagazig university hospitals and Fakous general hospital

All cases had undergone:

- Identification of the patients who were meeting the inclusion criteria.
- Full history taking.
- Full clinical examination.
- **Laboratory Investigations:** Blood samples had been obtained before the initiation of the HD session and after an 8 hours fasting, blood measurements will include:
  - Complete blood count(CBC).
  - Blood glucose level.
  - Serum urea, Creatinine.
  - Serum ferritin, transferrin.
  - Cholesterol, triglycerides.
  - Albumin.
  - IL-6.
  - TSH, T3, FT3 and FT4.

All patients were referred for measurement of *IL-6.Level*

III. Results:

Table (1) Demographic variables in groups with and without MIC

	Without N = 40	With N = 50	T P
Age "years" $\tilde{X}$ ± SD Range	45.5 ± 14.4 25 – 70	57.6 ± 7.7 42 – 70	** 5.1 < 0.001
Gender Male Female	20 ⇒ 50 % 20 ⇒ 50 %	32 62.7 19 37.3	X^2 1.49 0.2
BMI $\tilde{X}$ ± SD Range	24.4 ± 3.2 18 – 30	20.7 ± 4.6 16.5 – 28	** 4.2 < 0.001
Months on "HD" $\tilde{X}$ ± SD Range	39.4 ± 9.2 24 – 50	65.1 ± 10.4 45 – 84	** 12.3 < 0.001

This table shows that there is high significant relation between MIC and age, BMI and months on hemodailysis, while there is no significant relation between MIC and gender.

Table (2) Biochemical differences between patients with and without MICS

	Without MICS **N = 40**	**With MICS** **N = 51**	**T P**
Hemoglobin $\tilde{X}$ **± SD** **Range**	**10.5 ± 2.1** **6.6 ± 14.6**	**11.5 ± 2.0** **7.5 – 15.9**	**1.9 0.06**

TLC **$\tilde{X}$ ± SD** **Range**	**7.6 ± 4.5** **2.7 – 25.5**	**7.7 ± 4.3** **2.4 – 25**	**0.04** **0.96**
Glucose **$\tilde{X}$ ± SD** **range**	**98.1 ± 23** **70 – 150**	**107.0 ± 22.2** **70 – 150**	**1.8 0.06**
Albumin **$\tilde{X}$ ± SD** **range**	**3.5 ± 0.7** **2 – 4.5**	**2.9 ± 0.7** **2 – 4.0**	****** **4.1 <** **0.001**
cholesterol **$\tilde{X}$ ± SD** **range**	**132.1± 27** **90 – 190**	**153.6 ± 32.5** **100 – 210**	***** **3.2** **0.014**
TG **$\tilde{X}$ ± SD** **range**	**143.9 ± 36** **75 – 200**	**146.8 ± 35.7** **80 – 225**	**0.3 0.69**
IL – 6 **$\tilde{X}$ ± SD** **range** **Median**	**4.0 ± 4.1** **0 – 20** **3**	**22.1 ± 26** **0 – 90** **12**	****** **4.2 <0.001**
Transferrin **$\tilde{X}$ ± SD** **range**	**228.2 ± 28** **180 -300**	**203± 27.7** **150 – 255**	****** **4.1 <0.001**
T3 **$\tilde{X}$ ± SD**	**0.96 ± 0.6**	**1.01 ± 0.4**	**0.42** **0.67**

range	**0.45 – 2.9**	**0.1 – 1.89**	
T4 **$\bar{x}$ ± SD** **range**	**1.26 ± 0.8** **0.24 – 3.76**	**1.56 ± 0.8** **0.4 – 5.12**	**1.71** **0.08**
TSH **$\bar{x}$ ± SD** **range**	**1.99 ± 1.1** **0.35 – 4.55**	**2.28 ± 1.4** **0.14 – 4.97**	**1.03 0.3**

This table shows there is high significant relation between MIC and albumin, IL-6 and transferrin, also there is significant rerelation between MIC and cholesterol, while there is no significant relation between MIC and HB, TLC, glucose, TG, T3, T4 and TSH.

Table (3) correlation between T3,T4 and laboratory parameters

	T3 R P	T4 R P	TSH R P
MIC Age	0.005 NS 0.19 >0.05 NS	0.18 0.17	0.11 0.29*
HB	-0.03 NS	- 0.1	- 0.02
TLC	0.23 NS	0.03	0.2
PIT	- 0.1 NS	0.01	0.08
Glucose	0.07 NS	0.26 *	0.01
Albumin	- 0.02 NS	- 0.26*	- 0.34*
T.Cholesterol	0.14	50	0.41**
Triglycerides	0.34 **	0.0 NS	0.23*
Urea	0.05	0.26*	0.11

Creatinine	0.17	0.11	0.05
Transferrin	0.12	0.16	0.18
IL6	0.1	0.07	0.13

This table shows that there is significant positive correlation between T3 and TG, also there is significant positive correlation between T4 and glucose, urea and negative correlation with serum albumin. TSH positively correlated with age, T. cholesterol and triglycerides but negatively correlated with serum albumin.

IV. Discussion

Malnutrition is a frequent and serious problem in patients undergoing dialysis with estimated prevalence about 18–75%.(Reference)

It is referred as "malnutrition-inflammation complex syndrome (MICS) **(Chávez Valencia et al.,2018)** or "energy protein wasting syndrome"

(Beddhu et al.,2017).

MICS is a condition in which there is a loss of protein reserves and energy resulting from inflammatory and non-inflammatory causes in patients with chronic kidney disease (CKD) **(Mitchell,2015).**

The etiology is multifactorial including diet, oxidative stress, acidemia, blood loss by hemodyalizers and through feces, uremic medium and the effect of anabolic hormones **(Chávez Valencia et al., 2018).** The possible causes of MICS include comorbid illnesses, oxidative and carbonyl stress, nutrient loss through dialysis, anorexia and a low nutrient intake, uraemic toxins, a decreased clearance of the inflammatory cytokines, a volume overload, and dialysis-related factors.

MICS is believed to be main cause of erythropoietin hyporesponsiveness, low free triiodothyronine(FT3), a high rate of cardiovascular atherosclerotic disease, a decreased quality of life, and increased mortality and hospitalization among the dialysis patients. **(Vlatković et al.,2017)**

Low FT3 syndrome is defined as low FT3 with normal thyroid stimulating hormone (TSH) and normal or slightly reduced free thyroxine (FT4) level. This has been correlated with parameters of malnutrition and inflammation **(Vlatković et al.,2017).**

In CKD, there is an alteration of the metabolism, distribution, degradation and excretion of thyroid hormones9,10 the most commonly observed is a decrease in total triiodothyronine (T3) concentration **(Kastanias et al.,2017).**

The etiology of thyroid disorders in CKD is multifactorial and it is not entirely understood. There are a number of contributing variables: a decreased activity of deiodinase, reduction in the excretion of inorganic iodine, presence of uremic toxins, metabolic acidosis, malnutrition, use of heparin in hemodialysis (HD),

advanced age, infection by hepatitis C virus and drugs (amiodarone, steroids, beta-blockers, lithium, rifampin, sunitinib, sorafenib, imatinib, among others) **(Singh et al.,2018).**

Some studies in CKD patients have found correlations between low concentrations of T3 with high concentrations of inflammatory markers (highly sensitive C reactive protein [hsCRP], interleukin 6 [IL-6]), malnourishment (decrease in serum prealbumin concentration), endothelial dysfunction, deterioration of cardiac function, poor survival and greater mortality from all causes. Other authors have shown that low serum concentrations of FT3 are associated with an increase in mortality, explained in part by its underlying association with poor nutritional status and inflammation **(Singh et al., 2018).**

The current study aimed to improve the quality of life and to decrease morbidity in hemodialysis patients by focusing on malnutrition-inflammation complex syndrome (MICS) and clarify the relationship between it and changes in serum thyroid hormones.

This study included 91 hemodialysis patients with mean age of the studied group was 52.3 ± 12.7 with range of (25 – 70)years, 57.1 % were males and 42.9 % were females, prevalence of MIC was 56%. **Table (1).**

In comparable with many studies, **Chávez Valencia et al.,2018** conducted a cross-sectional study, from January 4 to July 30, 2016 at the Regional General Hospital of the Mexican Social Security Institute (IMSS) over 128 patients, 50.8% women, with frequency of MICS was 53.9%.

Aggarwal et al.,2018 carried out their study at Kidney and Dialysis (K & D) clinic at Pt. B.D. Sharma PGIMS, Rohtak, India, on a total of 100 patients, 64 were male and 36 were female. Majority of patients (74%) were above 45 years of age and were equally distributed in all groups, prevalence of MIC was60%.

Ebrahimzadehkor et al., 2014 reported in their study that 25% of patients on hemodialysis were normal nourished, 54.3% of patients were mild malnourished, 20.8% were moderately malnourished, and no one of them was severe malnourished.

Fan et al., 2016 conducted their study at Shanghai ninth people's hospital, on a total of 279 CKD subjects, 149 (53.4%) men and 130 (46.6%) women, with a mean age of 67.8±14.1 years, with 50.5 percent over 70 years of age.

Zehra, 2009 conducted a cross sectional study at Department of Nephrology Jinnah Postgraduate Medical Center, Karachi from April 2009 to November 2009. Total of 62 patients were included through non probability purposive sampling. All patients diagnosed with End stage kidney disease on maintenance hemodialysis were included of them 34(55%) were female and 28(45%) were male, Frequency of MICS in patients with ESRF by using Malnutrition Inflammation score (MIS) is noted in 60(97%) patients.

In a study by **Gracia-Iguacel et al., 2013** prevalence of malnutrition was reported up to 80%.

In the present study, there was strong positive correlation of MIC with age and duration of hemodialysis, but negatively associated with BMI which came in agreement with the findings of **Aggarwal et al.,2018** where they found a positive correlation of MIC with the age but negatively correlated with BMI .

Ebrahimzadehkor et al., 2014 found MIS score correlated directly with age, it means that the older patients are the less nutrition score.And positive association with duration of hemodialysis and they

referred this to progressive and the gradual decline of health status in hemodialysis patients despite continuous dialysis.

On the other hand, **Zehra, 2009** found that moderate malnutrition complex syndrome (MICS) was higher in age groups of 31-40 years (14%) as compare to 12% in 41-50 years, 10% in 51-60 years and 4% in over 60 years.

In the present study, there was an association of higher blood pressure with MIC.

Also **Chávez Valencia et al., 2018** found in MIS survey, 53.9% of the patients had MICS of which 55 had hypertension.

In the present study, there was an association between higher serum creatinine and MIC but this could not be verified with urea.

This going with the results presented by **Aggarwal et al., 2018** where they found Patients with malnutrition had higher level of blood urea and serum creatinine indicating that advanced renal failure leads to higher prevalence of malnutrition in comparison to early stage renal failure.

While **Chávez Valencia et al., 2018** and **GARG 2001** found that MIC associated with low serum creatinine, and referred this to that serum creatinine, the universally used measure to assess GFR, is higher in individuals with a larger muscle mass. If serum creatinine is used as the sole measure to identify low GFR, then well-nourished individuals with larger muscle mass will be categorized as having a lower GFR than is truly the case. Similarly, poorly nourished individuals with lower muscle mass will be categorized as having a misleadingly higher GFR.

In the present study, MIC was strongly associated with low serum albumin, low transferrin levels, higher serum cholesterol and higher levels of IL6. While the association with hemoglobin, TLC, serum glucose, triglycerides, T3, T4 and TSH could not be proved.

Chávez Valencia et al.,2018 found that MIC was associated with low hemoglobin, albumin, cholesterol, triglycerides and total T3 and high IL6 and CRP, they refered this to that MICS is negatively associated with T3, because T3 is the active form of thyroid hormone and the serum concentrations of T3 in acute or chronic critical illnesses reflect a mechanism of adaptation to the severity of the disease, also the group of patients with MICS had reduced hemoglobin (Hb) levels which can be attributed to the inflammation as illustrated by elevation of CRP, IL-6, ferritin.

Aggarwal et al., 2018 found that urea, creatinine, phosphorus, hs-CRP and lipoprotein(a) were increased in MIC groups, while the levels of hemoglobin, serum protein, albumin and TIBC were incrementally reduced across increasing MIS groups, they referred this to Patients with malnutrition had higher level of blood urea and serum creatinine indicating that advanced renal failure leads to higher prevalence of malnutrition in comparison to early stage renal failure. Renal insufficiency is a catabolic and inflammatory state and it is evidenced by the fact that independent of relevant demographic, social, and medical condition, renal

insufficiency was strongly associated with malnutrition. In addition, serum albumin level is an indicator of visceral protein stores and low level of albumin is suggestive of malnutrition or inflammation. It is a strong predictor of mortality in hemodialysis patients.

High levels of blood urea, creatinine, uric acid and phosphate were associated with poor nutritional status. Moreover, iron deficiency anemiais associated with low serum ferritin levels. Serum ferritin, which is used as a marker of iron status, is also an inflammatory marker.

On the other hand **Ebrahimzadehkor et al., 2014** stated that blood cholesterol and triglyceride levels were not significantly correlated with incidence of malnutrition. In addition, CRP index (depending on the amount of agglutination) had no significant effect in the incidence of malnutrition. The lack of relationship may be due to a qualitative estimate of CRP levels. Moreover, they referred this to that on the basis of MIS, about 3/4 of the studied patients had normal or mildly malnourished, others had moderate malnutrition and none severe malnutrition that imply relatively acceptable nutritional status for patients.

In the present study, there was normal levels of T3, T4 and TSH, and failed to find a correlation between T3, T4, TSH and MIC, this could be referred to number of patients in the study and duration of hemodialysis and the good health of our patients.

While **Chávez Valencia et al., 2018** note that, patients with MICS had higher serum concentrations of TSH and FT4 and lower serum concentrations of T3. In addition, it was observed a positive association between MICS and serum concentrations T4L and a negative association of MICS and serum concentrations T3 andT3L.And did not find an association of TSH with MICS, and attributed this to the fact that, in acute phase of critical illness TSH may be normal and in the chronic phase it may be unchanged or be reduced as a sign of recovery**(Economidou et al., 2011).**

Also **Yavuz et al.,2014** demonstrated that MICS is negatively associated with T3 and T3L, because T3 is the active form of thyroid hormone and the serum concentrations of T3 in acute or chronic critical illnesses reflect a mechanism of adaptation to the severity of the disease.

In the present study, TSH found to be positively correlated with age, cholesterol, triglycerides and negatively correlated with serum albumin.

This agreed with **Chávez Valencia et al., 2018** that found a positive correlation between TSH and age in addition to CRP, IL-6, ferritin.

On the other hand **(Carrero et al., 2007)**found no significant correlation of TSH with albumin, cholesterol and hemoglobin.

T3 in the present study was found to be correlated positively with triglycerides while failed to be correlated with MIC, creatinine,transferrin and IL6.

Chávez Valencia et al., 2018 found T3 and MIS correlated significantly, also T3Lwas positively correlated with age and albumin but they could not found an association between T3L and CRP or IL-6.

While**(Fan et al., 2016)** found that T3 level was positively correlated to protein-energy malnutrition (PEM) indicators (low levels of serum albumin, pre-albumin, transferrin), and negatively correlated with inflammation

related indicators (CRP, IL-6, Fg).

(Carrero et al., 2007) found a positive correlation between T3 and serum albumen and hemoglobin and a negative correlation with IL6 and hs CRP.

In the crrent study, no correlation of T4 with MIC was detected but we found a positive correlation between T4 and glucose and urea while negative correlation was found with serum albumin.

(Economidou et al., 2011) stated that T4 concentrations during chronic phase of critical diseases, the concentration of T4L may remain in the normal range, unless the disease is severe and prolonged in which case there is a decrease in TSH as well as in T4 and T4L, being predictor of poor prognosis.

Chávez Valencia et al., 2018 found The T4L level was increased in the MICS group and alsowas positively correlated with inflammation (IL-6, ferritin and albumin).This is contrary to the report by **(Carrero et al.,2007)** whereFT4 was negatively corelated with IL6 and cholesterol but positively corelated with serum albumin and hemoglobin,suggesting that high T4L couldbe reflect nutritional status and inflammation, which wasevidenced by the associations of T4L with other acute phase reactants (PCR, IL-6, ferritin and albumin).

V. CONCLUSION

MICS syndrome are frequent in dialysis, the longer the duration the more the MICS , there was significant correlation between MICS and BMI, duration of hemodialysis, SBP, DBP, serum creatinine, serum cholesterol, triglycerides, IL 6, transferrin and a negative correlation with serum albumin.

While the study failed to prove a correlation between MICS and T3, T4, TSH. Nevertheless, TSH was correlated positively with age, serum cholesterol and triglycerides and negatively with serum albumin. And T3 was positively correlated with triglycerides and T4 was positively correlated with glucose and urea and negatively with serum albumin.

Yet the limitation to the present study was the transversal collection of data, it is not possible to establish causality or sequence of events, Number of the patients included in the study should be more, randomization of age groups and long-term follow up was obstacles in this study.

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