

## Hypothyroidism and AMH in Iraqi Patients with Chronic Kidney Disease

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### Abstract:

This study was conducted to investigate thyroid function and Anti-Müllerian hormone (AMH) in (Chronic kidney disease) CKD patients by evaluating their levels in CKD patients, 50 patients were diagnosed to have CKD stage-5, their ages ranged between 20-50 years (25 males and 25 females) who attended the Nephrology and Transplant Center in Medical City of Baghdad- Iraq, they were recruited from April 2018 to July 2018 and were enrolled into the study. The control group consisted of 20 healthy individuals, their ages ranged between 20-48 years (10 males and 10 females). The study showed non-significant ( $p > 0.05$ ) increase in AMH level in CKD patients compared to the control group. On the other hand, TSH was recorded a highly significant ( $P < 0.01$ ) increase in CKD patients in comparison with control. While T3 and T4 levels recorded highly significant ( $P < 0.01$ ) decrease in CKD patients in comparison with control.

**Key words:** CKD, Hypothyroidism, TSH, T3, AMH.

### Introduction:

Chronic kidney disease (CKD) is a worldwide health problem affecting millions of peoples (1,2). The incidence of 1-3 per 10,000 per year in the general population may seem small and the magnitude of the problem is poorly described by the number of people that will initiate renal replacement therapy (hemodialysis, peritoneal dialysis and renal transplantation) (1- 4). A reduction in renal function may affect hormonal action in number of ways, many hormones are metabolized or excreted by the kidneys, and sensitive feedback mechanisms are destabilized by CKD (5).

Thyroid hormones have distinct effects on cellular growth and differentiation, they also modulate important physiological functions in virtually every human tissue (6). About 93 % of the metabolically active hormones secreted by the thyroid gland is T4, and 7 % T3. However, almost all the T4 is eventually converted to T3 in the tissues, so that both are functionally important. T3 is about four times as potent as T4, but it is present in the blood in much smaller quantities and persists for a much shorter time than does T4 (7, 8). Abnormalities in both the thyroid gland's function and structure (increased volume of the thyroid gland

and higher prevalence of goiter) are common in CKD patients. Uremia affects the hypothalamus pituitary thyroid axis, as well as the peripheral metabolism of thyroid hormones, thus serum concentrations of thyroid hormones are commonly not normal in CKD patients (9). Anti-Müllerian hormone (AMH) is a glycoprotein with a fundamental role in male sex differentiation, in women, AMH plays a critical role in folliculogenesis, with circulating levels directly reflecting the number of developing pre-antral follicles and indirectly the number of primordial follicles in the ovaries (10). As such, AMH is now recognized as the best available biomarker of both the functional and true ovarian reserve (11). In male serum AMH is correlated with spermatogenesis. The Sertoli cells secrete AMH, and it is a specific marker of Sertoli cell function and secreted in the serum and seminal fluid, the main physiological role of AMH in the adult male seems to be the autocrine and paracrine control of testicular function (12). CKD and its consequences affect the production of AMH, resulting in change in plasma AMH levels, this may indicate impaired function of Sertoli cells (13). In women with CKD the aforementioned fertility disturbances may be caused

by the damage of the ovaries by uremia, this may reflect an intrinsic dysregulation of the granulosa cells leading to higher AMH production or alternatively AMH accumulation in ESRD requiring dialysis (14,15).

### Material and Methods:

Fifty Patient with CKD stage-5 their ages ranged between 20-50 years (25 males and 25 females) from Nephrology and Transplant Center in Medical City of Baghdad- Iraq were recruited from April 2018 to July 2018 and enrolled in this study. Twenty control their ages ranged between 20-48 years (10 males and 10 females). Patients were not included if they were pregnant, with history of hyper or hypothyroidism or who were on or underwent previous dialysis. All blood samples were collected early in the morning from all groups for measurement of TSH,T3,T4 and AMH. Thyroid hormones are estimated in serum of all subjects by using an automated quantitative COBAS e411 test (from Roche, Germany). While serum AMH was measured by ELISA using a kit supplied by Beckman Coulter- Germany.

### Results:

The Mean  $\pm$  SE (standard error) of thyroid hormone in patients and control is shown in Table 1 TSH level in patients group ( $12.12 \pm 1.97$ ) showed high significant ( $P < 0.01$ ) increase in comparison with control ( $1.73 \pm 0.24$ ). On the other hand T3 level ( $0.970 \pm 0.05$ ) demonstrated highly significant ( $P < 0.01$ ) decrease in patients groups in comparison with control ( $1.43 \pm 0.11$ ) and T4 ( $6.81 \pm 0.32$ ) showed highly significant decrease ( $P < 0.01$ ) in patients group when compared with control group ( $9.21 \pm 0.25$ ).

**Table 1. Compare between Level of TSH,T3 and T4 in patients and control**

| Group    | Mean $\pm$ SE    |                  |                 |
|----------|------------------|------------------|-----------------|
|          | TSH mu/ml        | T3 ng/ml         | T4 mg/dl        |
| Patients | $12.12 \pm 1.97$ | $0.970 \pm 0.05$ | $6.81 \pm 0.32$ |
| Control  | $1.73 \pm 0.24$  | $1.43 \pm 0.11$  | $9.21 \pm 0.25$ |
| T-Test   | 6.256 **         | 0.229 **         | 1.059 **        |
| P-value  | 0.0015           | 0.0001           | 0.0001          |

\*\* ( $P < 0.01$ ): Highly Significant

In this study, as shown in Table 2 level of serum AMH found to be slightly elevated but not significant in patients with CKD in comparison to control group. AMH levels in both groups ( $9.03 \pm 1.58$ ), ( $7.76 \pm 1.75$ ) respectively showed non-significant difference ( $p > 0.05$ ).

**Table 2. Compare between patients and control in level of AMH.**

| Group    | Mean $\pm$ SE of AMH ng/ml |
|----------|----------------------------|
| Patients | $9.03 \pm 1.58$            |
| Control  | $7.76 \pm 1.75$            |
| T-Test   | 5.490 NS                   |
| P-value  | 0.645                      |

NS: Non-Significant.

Statistical analyses from Table 3 indicate a correlation coefficient between thyroid hormones and AMH hormone in this study. There was non-significant ( $p > 0.05$ ) negative correlation between TSH, T3 and T4 with AMH.

**Table 3. Correlation coefficient between TSH, T3, T4 and AMH.**

| Parameters | Correlation coefficient-r and Level of significant |          |          |
|------------|--|----------|----------|
|            | TSH  | T3       | T4       |
| AMH        | -0.02 NS   | -0.14 NS | -0.03 NS |

NS: Non-Significant.

### Discussion

The data of this study suggest that patients with CKD stage-5 have elevated but not significant AMH compared with subjects without kidney disease. Results of this study go in agreement with those that have been found with (15), who showed that CKD patients were found to have non-significant increase in AMH concentrations compared with control. The results of this study were compatible with data reported by (14), who found that serum AMH concentration was higher in haemodialysed women with CKD and had menstrual cycle abnormalities in comparison to those with regular menstrual cycles, and suggested that serum AMH clearance is reduced in CKD patients and AMH similar to other protein hormones probably accumulates in those patients (16). On the other hand, AMH is of similar size to other molecules perceived to be uremic 'toxins' (17).

This study disagrees with those that have been found with (16), who reported that male patients with CKD have close to 60% lower serum levels of AMH versus controls and this was an unexpected finding, the author explained that this finding of low AMH levels indicate a dysfunction of both Sertoli cells and Leydig cells in men with CKD. The results of this study also in disagreement with (18), who showed that plasma AMH levels were lower in CKD stages 1-4 by 30% and by 70% in CKD stage 5 compared with controls, he said that this reduction in AMH is unclear, but can be linked to altered Sertoli cell function. The cause of

decreased plasma AMH levels is unknown, but it speculate on effects of inflammation, uremic toxicity, or other causes. The results of this study support that the molecular weight of AMH (140 kDa) indicates that it is not eliminated by glomerular filtration or dialysis, if this is the case, an increase in plasma AMH levels would be expected with advancing CKD stages (15,16,17).

The current study demonstrated that TSH increased significantly and both T3, T4 decreased significantly between patients and control. The impact of thyroid dysfunction on CKD is linked to the role of the kidneys in metabolism, degradation and excretion of several substances including thyroid hormones. It is therefore expected that any impairment in kidney function could lead to altered thyroid physiology (19). There are many studies in the world that have dealt with thyroid hormone levels in CKD patients, one of these studies which has come in supporting these results has been stated by (20), who showed that TSH were increased while serum total T3, T4 were decreased in CKD patients. Other studies which were conducted by (21, 22), revealed low T3 and T4 level with high TSH level suggesting maintenance of pituitary thyroid axis. This study results are similar to the study done by (23), who found that there was an increasing trend for the population of low T3 according to the increase of CKD stage. In a study in Saudi Arabia, there was a significant decrease in the levels of serum total T3, and total T4 in CKD patients when compared with the control (24). This study is in partial disagreement with the results of (25), who showed that there are low T3, T4 and normal or mild elevation of TSH in CKD patients. However, the results of this study in a partial disagreement with a another study on CKD patients who found that both T3 and T4 were significantly reduced whereas TSH remains to be unchanged in patient group compared to controls (26, 27).

The results of this study disagree with a another study conducted in Libya done by (28), who showed that CKD patients of Pre-Haemodialysis have higher blood thyroid hormones than post Haemodialysis patients. The explanation of the high levels is because thyroid hormones profile undergoes changes due to dialysis independent of that due to CKD, dialysis also changes the previous serum thyroid hormone status in patients with renal failure (29).

From the various studies, it has been suggested that this thyroid profile derangements are a part of body adaptation mechanism to conserve energy (25). The correlation between thyroid hormone and AMH level in the (Table 3) showed negative non significant correlation and this result

was in agreement with (30), who reported that elevated TSH levels may have deleterious effects on ovarian function. Anti-Müllerian hormone (AMH), a known biomarker of ovarian function, may be affected by impaired thyroid hormone. However, the relationship between AMH and thyroid hormone has not been elucidated. Thyroid hormones plays an important role in follicular development, in addition, TSH directly suppressed follicle development in a concentration dependent manner (31, 32).

### Conclusions:

In summary, this study confirms that thyroid dysfunction is very common in CKD patients and reveals the significant association between CKD development and thyroid dysfunction. The study also finds slightly increases in AMH as disorder in CKD, which has a noxious role of CKD in hormonal disruption and sexual function.

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### Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- The author has signed an animal welfare statement.
- Ethical Clearance: The project was approved by the local ethical committee in Mustansiriyah University.

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## قصور الغدة الدرقية و هرمون المضاد لمولر لدى المرضى العراقيين المصابين بأمراض فشل الكلى المزمنة

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### الخلاصة:

اجريت الدراسة الحالية للتحري في وظائف الغدة الدرقية و هرمون المضاد لمولر من خلال تقييم مستوياتهم في مرضى الفشل الكلى المزمنة. تمت الدراسة على 50 مريض تم تشخيص اصابتهم بمرض الفشل الكلى المزمن المرحلة الخامسة اعمارهم بين 20 الى 50 عام (25 ذكور و 25 اناث) و 20 شخص كمجموعة سيطرة تراوحت اعمارهم بين 20-48 عام (10 ذكور و 10 اناث) ، الذين حظروا الى مركز أمراض الكلى وزراعة الأعضاء في مدينة الطب ببغداد في العراق من أبريل 2018 إلى يوليو 2018. اظهرت الدراسة الحالية وجود زيادة غير معنوية في مستويات هرمون الانتي ميوليرين في المرضى مقارنة مع مجموعة السيطرة. بينما لوحظ زيادة معنوية عالية في مستويات الهرمون المحفز للغدة الدرقية مقارنة مع مجموعة السيطرة. بينما وجد انخفاض معنوي عالي في مستويات هرمون ثالث يود الثيرونين وهرمون الثيرونكسين في مرضى الفشل الكلى المزمن مقارنة مع مجموعة السيطرة.

**الكلمات المفتاحية:** الفشل الكلى المزمن، قصور الغدة الدرقية، الهرمون المحفز للغدة الدرقية، هرمون ثالث يود الثيرونين، هرمون الثيرونكسين، الانتي ميوليرين.