Serum Anti-Mullerian Hormone Concentration and Function of The Pituitary-Gonadal Axis in Iraqi Patients with Chronic Kidney Disease

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Abstract

Infertility among patients with chronic kidney disease (CKD) has been extensively investigated. However, reproductive function in these patients is less well-characterized. The present study was aimed to examine the associations among chronic kidney disease (CKD) and fertility status by evaluation levels of: Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH). Estrogen (E2) and Progesterone (P4) for females and Testosterone for males along with Anti-Mullerian Hormone (AMH) in CKD patients. The study has been registered at Nephrology and Transplant Center in Medical City of Baghdad- Iraq from April 2018 to July 2018. The study included 50 patients who are diagnosed to have CKD stage-5, their ages ranged between 20-50 years (25 males and 25 females) and 20 matched apparently healthy as control, their ages ranged between 20-48 years (10 males and 10 females). This study showed a highly significant ($P<0.01$) increase in LH, FSH levels in CKD patients compared to the control group. Highly significant ($P<0.01$) decrease in E2 level in CKD females patients compared to the control group, while there was non-significant ($P>0.05$) decrease in P4 level in CKD females patients compared to the control group. In parallel, there is significant ($P<0.05$) decrease in Testosterone level in CKD males patients compared to the control group. On the other hand, the study showed non-significant ($p>0.05$) increase in AMH level in CKD patients compared to the control group.

Keywords: *CKD, AMH, LH, FSH, E2, P4, Testosterone.*

Introduction

The genesis of sexual dysfunction in patients with chronic kidney disease (CKD) is multifactorial [1]. Hormonal dysfunction in CKD is clinically accompanied by sexual dysfunction that influences the life quality of these patients, in advanced stages of CKD, these sexual dysfunctions can be more evident, several changes in hormone levels have been demonstrated, these changes can be because of decreased renal excretion and disturbance of the endocrine system because of uremic effects [2]. Disturbances in the hypothalamic-pituitary-gonadal axis, resulting in alterations in signal-feedback mechanisms and hormone production, are seen already in patients with moderate reduction in the glomerular filtration rate and often become more obvious as kidney failure progresses [2,3]. Earlier studies have shown elevated levels gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [4]. Decreased levels of free and total testosterone have also been reported in patients with CKD [5,6]. In those patients, level LH and FSH rise up [7]. In uremic patients, GnRH releasing from the hypothalamus and GnRH- LH signal are impaired. In these patients, bioactivity of LH changes and then a series of function inhibitors of LH are made [8].

Anti-Müllerian hormone (AMH) is a glycoprotein with a fundamental role in male sex differentiation [9]. As such, AMH is now recognized as the best available biomarker of both the functional and true ovarian reserve [10]. In male serum AMH is correlated with spermatogenesis, the Sertoli cells secrete AMH, and it is a specific marker of Sertoli cell function [11]. CKD and its consequences affect the production of AMH, resulting in change in AMH levels, this may indicate impaired function of Sertoli cells [12]. 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 CKD patients requiring dialysis [13,14].

Material and methods

The study has been registered at Nephrology and Transplant Center in Medical City of Baghdad- Iraq from April 2018 to July 2018. This study included two groups, patients and control group. The study included 50 patients are diagnosed to have CKD stage 5, their ages ranged between 20-50 years (25 males and 25 females) and 20 control their ages ranged between 20-48 years (10 males and 10 females). Blood samples were collected from all groups for estimation of (LH, FSH, E2, P4, Testosterone), All those biomarkers were estimated in serum of all subjects by using an automated quantitative COBAS e 411 test (from Roche, Germany). Serum AMH was measured by ELISA using a kit supplied by Beckman Coulter- Germany.

Results

In this study the level of LH (7.10 ± 0. 57) was highly significant increased (P<0.01) in comparison with control (3.62 ± 0.45). Also, the level of FSH showed high significant increase (P<0.01) in patients group (8.01 ± 0.50) when compared with control group (4.79 ± 0.55), Table (1).

Table 1: Comparison between patients and control in level of LH, and FSH.

Group	Mean ± SE	
	LH mIU/ml	FSH mIU/ml
Patients	7.10 ± 0. 57	8.01 ± 0.50
Control	3.62 ± 0.45	4.79 ± 0.55
T-Test	1.897 **	1.732 **
P-value	0.0005	0.0004
** (P<0.01): Highly Significant		

On the other hand the mean of serum E2 and P4 levels in the females of study groups are summarized in Table (2). E2 level (7.89 ± 1.17) in patients group observed highly significant decrease (P<0.01) in comparison with control group (20.80 ± 5.04), while P4 levels showed non-significant decrease (0.407 ± 0.06) in patients compered to control group (0.408 ± 0.10) .

Table 2: Compare between patients and control (Female) in E2 and P4.

Group	Mean ± SE	
	E2 Pg/ml	P4 ng/ml
Patients	7.89 ± 1.17	0.407 ± 0.06
Control	20.80 ± 5.04	0.408 ± 0.10
T-Test	7.318 **	0.249 NS
P-value	0.0008	0.997
** (P<0.01): Highly Significant ; NS: Non-Significant.		

The present study displayed, significant decrease (P<0.05) in Testosterone level in male patients with CKD (1.57 ± 0.25) in comparison with healthy control group (2.73 ± 0.58).as shown in Table (3).

Table 3: Compare between patients and control (Male) in level of Testosterone.

Group	Mean ± SE of Testosterone ng/ml
Patients	1.57 ± 0.25
Control	2.73 ± 0.58
T-Test	1.097 *
P-value	0.0387
* (P<0.05): Significant	

On the other hand, in this study as shown in Table (4), 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 ± 1.58), (7.76 ± 1.75) respectively showed non-significant difference (p>0.05).

Table 4: Compare between patients and control in level of AMH.

Group	Mean ± SE of AMH ng/ml
Patients	9.03 ± 1.58
Control	7.76 ± 1.75
T-Test	5.490 NS
P-value	0.645
NS: Non-Significant.	

Statistically, the finding in Table (5) indicate a correlation coefficient between AMH hormone and other parameter in this study. As showed there is a highly significant (P<0.01) positive correlation between AMH with Testosterone, non-significant (p>0.05) positive correlation between AMH and FSH, E2. On the other hands there is non-significant (p>0.05) negative correlation between AMH with LH and P4.

Table 5: Correlation coefficient between AMH and other parameters.

Parameters	Correlation coefficient (r) and Level of significant
	AMH
LH	-0.15 NS
FSH	0.09 NS
E2	0.001 NS
P4 -0.16 NS	
Testosterone	0.22**
* (P<0.05), ** (P<0.01), NS: Non-significant.	

Discussion

End stage renal disease (ESRD), has a strong influence on the hypothalamic-pituitary-gonadal axis resulting in hormonal disturbances and deterioration in gonads function. [2,15]. The results of this study on elevated levels of LH and FSH in CKD patients are consistent with previous study reported by Anatharamaa and Schmidt [16], who found that changes in pulsatile release of GnRH and LH reduce feedback inhibition of LH production (because of low levels of testosterone) contribute to high levels of LH, FSH secretion in CKD patients. With CKD there was a significant increase in LH and FSH and development of pattern of hyper gonadotropic hypogonadism, which indicates that uremic metabolite tend to increase CKD effect on testes and ovaries more than hypothalamic or pituitary function [17].

The results of this study agree with those that have been found with previous studies [7,8,15], who showed that low concentration of E2 has been seen in uremic patients, nevertheless it has insufficient concentration in the puberty, while in the second half of menstrual cycle serum P4 concentrations are decreased due to the defective follicle luteinization. In this study P4 levels are slightly decreased with no significance compared to the control group, previous reports go in agreement with the results of this study which reported that mean P4 levels in patients were not significantly different from those of control subjects [18,19].

In this study, the results of testosterone in male patients indicated significant decrease (P<0.05) in CKD patients, and this result was also approved by several previous studies as testosterone which is normally reduced in CKD patients and when LH level is arise in response to low levels of testosterone, so that the hypothalamic pituitary axis in CKD is reset in such a way that it is more sensitive to the negative feedback inhibition of testosterone [16,17,20,21]. Rathi and Ramachandren. [22], showed that low testosterone is due to decreased production, increased metabolic and dialytic clearance, alteration in testosterone binding capacity.

The data of this study suggest that patients with CKD stage-5 have elevated but not significant AMH compared with control and this results go in agreement with those that have been found with Stoumpos *el al*. [14], who showed that CKD patients were found to have non-significant increase in AMH concentrations compared with control. Also, the results of this study was compatible with data reported by Sikora-Grabkaa *et al*. [13], 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 [14]. On the other hand, AMH is of similar size to other molecules perceived to be uremic 'toxins' [1].

This study disagrees with those that have been found with Eckersten *et al*. [1], who they reported that male patients with CKD have lower serum AMH levels 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 Eckersten *et al*. [23], 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, the author 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 [1,14,24].

Results of this study showed that LH has negative correlation with serum AMH in men and women with CKD, this finding disagree with another finding [25], who found no relationship between AMH and LH. Another study also showed no significant correlation between AMH and LH [26]. Results of current study showed positive no significant correlation between AMH and FSH and this result was in agreement with other study which reported that AMH positive correlated with FSH [27]. Fiza *et al*. [28], showed a negative relationship between the levels of AMH and FSH and this results disagreement with the results of this study.

Thus, the higher levels of AMH are associated with lower level of the FSH and support this result by another study which reported that the excess of AMH is involved in diminishing FSH induced aromatize activity and this results disagreement with this study [9,29,30]. High AMH levels are probably related to the follicular arrest during the selection process of the dominant follicle, through a negative interaction between AMH and FSH [31].

In this study E2 showed non-significant positive correlation with AMH and this result was in agreement with other study which reported that AMH was negative correlated to LH and positive correlated with FSH and E2 [27].

Conclusions

This study confirms the noxious role of CKD in hormonal disruption and infertility among patients with CKD.

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Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

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