

Elevation of Gonadotropin Hormones as Early Predictor Marker for Subfertility among Sudanese Patient with Chronic Kidney Disease Stage-5

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Abstract:

Background: Chronic kidney disease (CKD) is defined as the decrease of glomerular filtration rate (GFR) that leads to a progressive deterioration of fluid-electrolyte balance and metabolic or endocrinological functions. Furthermore, the relation of CKD with infertility and sexual dysfunction is well-known to affect medical health status as well as physiological status. Additionally, in men with CKD, gonadal dysfunction with elevation of serum gonadotropin concentration is a frequent finding, affecting 26% – 66 % of men with different stages of CKD. The objective of this study is to investigate the serum gonadotropins LH and FSH in patients with CKD. **Methods:** This case-control study was conducted at military hospital, police hospital and Kidney transplantation association within six months from November 2017 to April 2018. More importantly, the study was carried out on a total of 80 samples including 40 CKD patients as case and 40 healthy individuals as control group. Finally, serum FSH and LH levels were estimated using ELISA technique and data was analyzed using SPSS software program version 21. **Results:** This study has found significant elevation in FSH and LH levels with *p*-value (0.000, 0.001) respectively in CKD patients compared to control group. Moreover, the study found that FSH level is positively correlated with BMI and duration of disease, while LH level is positively correlated with the duration of disease only. **Conclusion:** Our study concluded that patients with CKD have elevated gonadotropins (FSH&LH) levels.

Key words: CKD, Obesity, Duration of Disease, FSH & LH.

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Introduction:

Chronic kidney disease (CKD) is defined as the decrease of glomerular filtration rate (GFR) that leads to a progressive deterioration of fluid-electrolyte balance and metabolic or endocrinological functions (KDIGO, 2013). The major risk factors of CKD include diabetes, hypertension, obesity, older age and smoking (Sarnak *et al.*, 2003; Gelber *et al.*, 2005). Furthermore, the relation of CKD with infertility and sexual dysfunction is well-known to affect medical health status as well as physiological status (Süleymanlar, 2011). Moreover, Hormone abnormalities and endocrine dysfunction are common in patients with CKD. Further, changes in gonadotropins levels are caused by altered function of the hypothalamic-pituitary axis and

uremic syndrome (Periklis *et al.*, 2014).

However, in men with CKD, gonadal dysfunction with elevation of serum gonadotropin concentration is a frequent finding, affecting 26% – 66 % of men with different stages of CKD (Iglesias, 2012). More importantly, changes of gonadotropins synthesis and metabolism develop early after the onset of renal insufficiency (Alice *et al.*, 2002). Multiple factors are responsible for the elevation in FSH and LH in CKD resulting in a reduced clearance of gonadotropin-releasing hormone (GnRH), LH and FSH leading to elevated serum levels of these hormones (Molina, 2013; Songul, *et al.*, 2016; Nannan, *et al.*, 2015). Moreover, the baseline levels of LH are high, due to impaired negative feedback from low testosterone and because of

to the reduced renal clearance as well. In addition to these secretory changes, the normal signaling of luteinizing hormone is inhibited in CKD (Matthew, 2017; Iglesias, 2012).

The plasma FSH concentration tends to be highest in those uremic patients with the most severe damage to seminiferous tubules and presumably the lowest levels of inhibin B (Mahboob and Shirin, 2008; Piotr *et al.*, 2015). In addition, Hormonal abnormalities might improve but rarely normalize with institution of maintenance dialysis (Rosas *et al.*, 2003; Diemont *et al.*, 2000). To elaborate, beside CKD, several other factors play a major part in the disturbance of Gonadotropins hormones such as obesity and the duration of kidney disease.

Obesity, defined as BMI greater than 30 Kg/m², has been

abundantly increasing among people in last decades. More importantly, it is an established factor of risk for numerous pathologic conditions including infertility (Mihalca *et al.*, 2014). Obesity is associated with adult male fertility as it affects the GnRH-FSH/LH pulses and impairs the function of Leydig and Sertoli cells (Sallmen *et al.*, 2006). Several studies showed strong relationship between obesity and gonadotropins hormones and different results were obtained. In fact, with the increase of BMI, the production of inhibin B decreases (Winters *et al.*, 2006; Miro *et al.*, 2016) the lack of negative feedback leads to an increased level of production in FSH (Xin-Mei *et al.*, 2015).

In CKD patients, especially those with end stage renal disease, when kidney function is severely impaired, the renal clearance will

probably be impaired as well. In fact, GFR decreases and, as a result, toxins build up in the body. More importantly, high levels of uremic metabolism in blood affect hypothalamic-pituitary function leading to elevated gonadotropin hormones levels (Kerstin *et al.*, 2017; Hylander and Lehtihet, 2015). These abnormalities are already seen in patients with moderate reduction in the glomerular filtration rate and often become more obvious as kidney failure progresses. Otherwise, disturbances in the hypothalamic-pituitary-gonadal axis can be detected before the need for dialysis but continues to worsen once dialytic therapy is initiated (Palmer, 2003).

Methods:

This is case-control study carried out in a total of 80 subjects

including 40 patients admitted to three nephrology units for clinical assessment as case, and 40 healthy individuals as control matching in age. The inclusion & exclusion criteria cover patients who were older than twenty years old, Stage-5, and excludes smokers, patients suffering from pituitary tumor, patients with high dose or long-term steroid abuse and those who were older than sixty-five years old. The study was performed in accordance with the Declaration of Omdurman Islamic University regarding ethical principles for medical research involving human subject and also permission was obtained from health authorities in military hospital, police hospital and Kidney transplantation association. All participants have been informed and consent is obtained prior to their inclusion

in the study. Blood specimens were collected before dialysis. Levels of FSH and LH were estimated using direct ELISA kits.

Statistical analysis:

Data was analyzed using SPSS program version 21. Results were expressed as mean±SD. Independent t-test and Personal correlation test were used; *P-value* less than 0.05 regarded statistically significant.

Results:

The present study included 40 individuals with CKD who their ages are ranging between 20 - 62

years. Our results in table 1 reveal significant increase in gonadotropins (FSH, LH) in case group compared to control group, also show that is increase in gonadotropins with increase duration of disease, FSH also increase with increase BMI, figure 1 and 2. Further, FSH levels were positively correlated with BMI and duration of disease (figure 3A, $r = 0.651$, $p = 0.000$) (figure 3C, $r = 0.340$, $p = 0.034$). In addition, positive correlation is seen between LH and duration of disease (figure 3B, $r = 0.612$, $p = 0.000$).

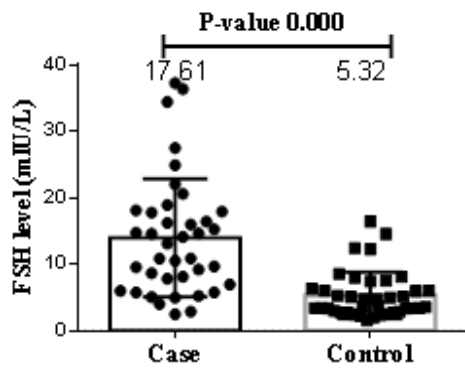


Figure1: FSH Level (P-value 0.000)

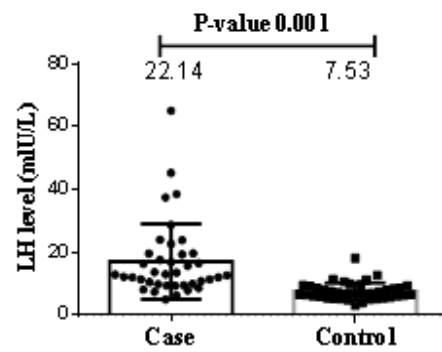
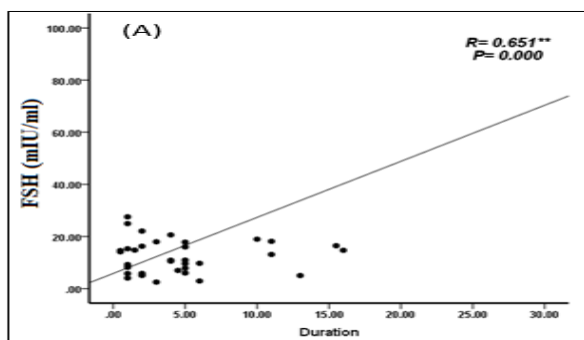
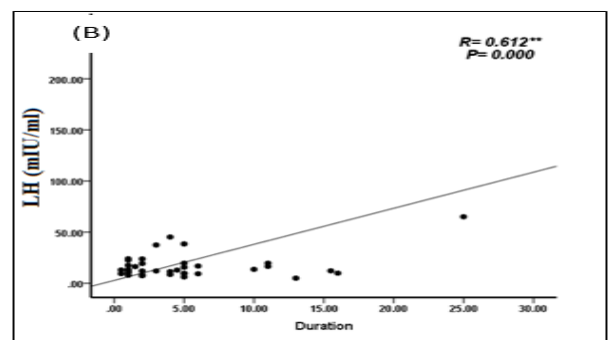


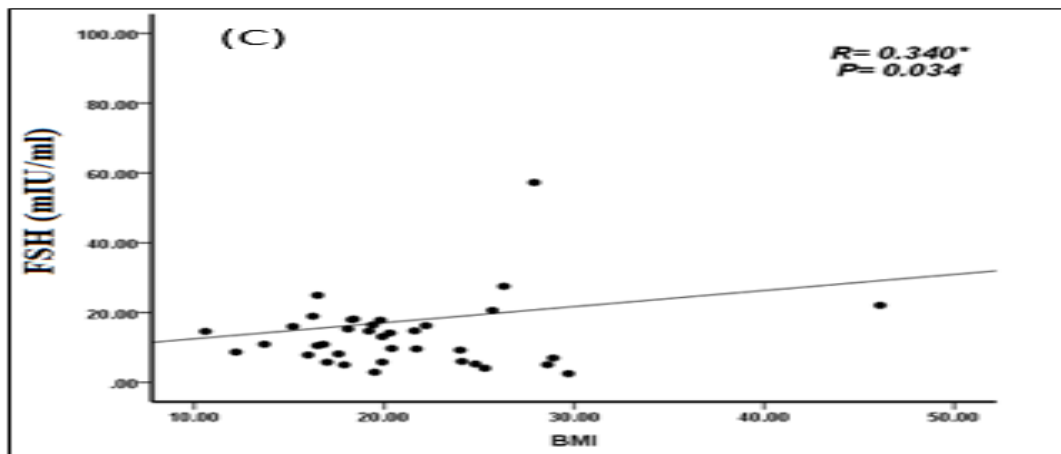
Figure2: LH Level (P-value 0.002)



Duration of disease



Duration of Disease



BMI

Figure 3: A: Duration is correlated significantly in a positive manner with FSH values ($r = 0.651$, $p = 0.000$). B: Duration is correlated significantly in a positive manner with LH values ($r = 0.612$, $p = 0.000$). C: BMI is correlated significantly in a positive manner with FSH values ($r = 0.340$, $p = 0.034$).

Table (1): show mean levels of FSH and LH in case and control groups with duration of disease and BMI.

Parameters	Case (Mean ± SD)	Control (Mean ± SD)	P-value
FSH (mlU/ml)	17.61±10.62	5.32±3.43	0.000
LH (mlU/ml)	22.14±12.94	7.53±2.70	0.001
Variables			P-value
Duration of disease	<5 Years (Mean± SD)	≥ 5 Years (Mean ± SD)	
FSH (mlU/ml)	14.35 ± 11.39	22.80 ± 19.89	0.023
LH (mlU/ml)	15.72 ± 9.34	32.42 ± 16.37	0.013
BMI	Normal weight (Mean± SD)	Overweight (Mean ± SD)	P-value
FSH (mlU/L)	14.92 ± 13.98	29.85 ± 24.05	0.005

Discussion:

Chronic kidney disease (CKD) is defined as the decrease of glomerular filtration rate (GFR) leading to a progressive deterioration of fluid-electrolyte balance and metabolic or endocrinological functions (KDIGO, 2013). Additionally, in men with CKD, gonadal dysfunction with elevation of serum gonadotropin concentration is a frequent finding, affecting 26% – 66 % of men with different stages of CKD (Britta and Mikael, 2015).

The results of present study in table1, figure1 and 2, show that the FSH and LH are significantly increased in CKD patients compared to control group with *P*-values (0.000, 0.001) respectively, In agreement with the previous study (Songul, *et al.*, 2016) this presumably due to prolonged half-life, reduced renal clearance for both, and lack of normal feedback inhibition of LH by testosterone, the secretion of which from Leydig cells is diminished. FSH concentration tend to be highest in uremic patient with the most severe damage to the seminiferous tubules and presumably the lowest level of inhibin (Molina, 2013). On other hand, table1 shows that there were significant increases in gonadotropin hormones (FSH and LH) in CKD patients with increase duration of disease *p*-values (0.023, 0.013) for both hormones respectively. The renal clearance may be impaired as GFR decrease and hence the observation of elevation in gonadotropin hormones, and uremic metabolism at advance stages of CKD affect hypothalamic-

pituitary function lead to hormonal abnormalities (Kerstin *et al.*, 2017; Hylander and Lehtihet, 2015). Additionally there statistically significant increase in the level of FSH with increase BMI (*p-value* 0.034) in previous study found that there were decrease in production of inhibin B with increase obesity (Winters *et al.*, 2006) which act as negative feedback mechanism for FSH secretion. Further, in the present study in figure (3/A-B) we found FSH and LH levels have positive correlation with duration of CKD ($r = 0.651$, $p= 0.000$, $r = 0.612$, $p= 0.000$) respectively which is similar to the results found by (Britta and Mikael, 2015). On the other hand, FSH in figure (1-C) has positive correlation with BMI ($r = 0.014$, $p= 0.932$) and this matches with study of (Xin-Mei *et al.*, 2015).

Conclusion:

Gonadal dysfunction is very common in male with CKD. The pathophysiology of gonadal dysfunction in CKD is multifactorial. Hence, hypergonadotropic hypogonadism is a frequent finding in CKD patients. This study showed that gonadotropins levels are significantly increased in male patients with CKD compared to control group. Significant positive correlation between FSH levels appears with BMI and duration of disease. In further, significant positive correlation appear between LH and duration of disease.

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