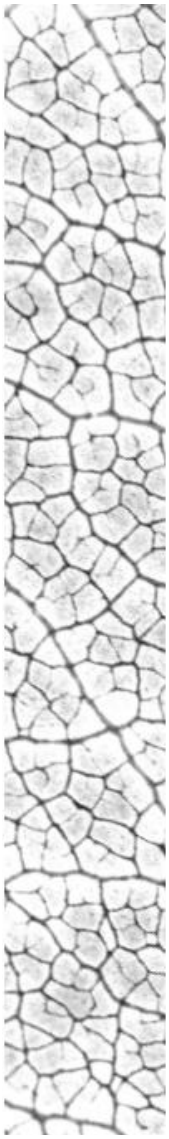

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Association between metabolic syndrome (MetS) and benign prostatic hyperplasia (BPH) in Amara city, Iraq

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Abstract

Background: Benign prostatic hyperplasia (BPH) is most common in aging men and causes actual adverse effects on health. Recently the researches have suggested that metabolic syndrome (MetS) individuals' may be exposure to development of benign prostatic hyperplasia (BPH), this study aimed to evaluated the association between BPH and MetS. **Methods:** 66 men with BPH (43 without MetS and 23 with MetS) and 30 healthy individuals (as a control group) were included in this study. Sex hormones: Testosterone (T), Estradiol II (E2), Prolactin (PRL), luteinizing hormone (LH), Follicle stimulating hormone (FSH), and lipid profile were all evaluated. **Results**: There were significant decreasing ($p<0.01$) in T and E2 level in BPH patients compared to control group, while DHT level had significant increase ($p<0.01$) in BPH patients compared to control group. No significant differences were found in T, E2, PRL, LH, FSH between BPH with MetS and without MetS except level of DHT had recorded significantly increase ($p<0.01$) in BPH with MetS compared to without MetS. In term of lipid profile, TC, TG, LDL, VLDL were no significant differences between the BPH with MetS and without MetS, while HDL level revealed significantly decrease ($p>0.05$) in BPH with MetS compared to without MetS. **Conclusions:** Our study confirmed on most the association between BPH and MetS related change in the sex hormones (DHT) and metabolic derangement in lipid profile.

Keywords: sex hormones, benign prostatic hyperplasia, metabolic syndrome

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INTRODUCTION

Benign prostatic hyperplasia (BPH), a benign proliferative featured by the growth of hyperplasic nodules diffuse in the transition zone of the prostate, the overall rise prostate volume (prostatic enlargement), and the dealing lower urinary tract symptoms (LUTS), is highly most among middle-aged and elderly men (Zhao *et al.* 2016, Foram *et al.* 2019). It's happening rise by 42% in men between 40-50 years up to 90% in those over 80 years (La Vignera *et al.* 2016) .The two factor determinants of the risk of BPH are elderly and sex hormones; however, risk factors such as obesity and less of physical activity have an vital role in the BPH etiology (Abdollah *et al*. 2011, Da Silva *et al*. 2019).

Many previous reports suggesting that an association between BPH and MetS may be plausible (Gacci *et al*. 2015, Zhao *et al*. 2016) although it is not yet fully understood. Recently, Vignozzi *et al*. (2014) proposed an interesting three-hit hypothesis on the development of BPH, which may also be helpful in understating the mutual relationship between BPH and MetS. According to this hypothesis, an overt or subclinical inflammation (first hit) could be autosustained or overlapped by metabolic alternations (second hit) and changes in sex-hormone levels (third hit). The combined effects of these may result in overexpression of toll-like receptors, transformation of prostatic cells into antigen-presenting cells, and up-regulation of growth factors (andromedins), leading to prostate enlargement, among hormonal determinants of BPH, the majority of studies have reported sex steroid imbalances between total or free testosterone, dihydrotestosterone, estrogen, and progesterone levels (Rohrmann *et al*. 2007, Antunes *et al*. 2014).

In brief, MetS characterize a complex of disorders regarding to metabolic abnormality, including hypertension ,central obesity, dyslipidemia , insulin-resistance with compensatory hyperinsulinemia, and impaired glucose metabolism that rise risk of cardiovascular disease and diabetes type 2, with the core of MetS lies in the group or collection of these metabolic risk factors (Gacci *et al.* 2015, Wang *et al*. 2016, Lanini *et al.* 2019). At the molecular and

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biochemical level, several systemic disorders associated with MetS, composing the systemic pro-inflammatory state, sex steroids variations, high insulin-like growth factor, and autonomic hyperactivity, have been implicated in the development of BPH (Zhao *et al*. 2016). Conversely, results from epidemiological studies; however, although generally in favor of association between MetS and BPH, were somewhat conflicting (De Nunzio *et al*. 2012, Vignozzi *et al.* 2016).

Furthermore, if MetS influences BPH through its effects on sex steroids, aimed the study was to evaluate the associations between MetS and the BPH in Iraqi patients by hormonal metabolic (lipid profile) factors.

METHODS AND MATERIALS

Study Population

The study was conducted at Al-Sadr Teaching Hospital in Amara city, Misan province from the period from November 2017 to April 2018. Total of 66 patients, 43 with BPH and 23 with both BPH and MetS (aged 40-59 years) have been participated in the study. The control group included 30 apparently healthy men aged 40-59 years.

Collection of Blood Samples

To reduce the day-to-day variation in the level of hormones, blood samples were collected during the morning period (8-10 AM) in a volume (5cc). The samples were left for 15 minutes to coagulate at room temperature and then separated by Centrifuge (3000 cycles for 5 minutes).lipid profile (total cholesterol (TC), triglycerides (TG), high–density lipoproteins (HDL), low-density lipoproteins (LDL), very low- density lipoproteins (VLDL) measured in same day, and other part of serum storage in the refrigerator (-20C^0) until measurement the level of sex hormones testosterone (T), estradiol II (E2), prolactin (PRL), luteinizing hormone (LH), and follicle stimulating hormone (FSH).

Hormones Measurements

Hormones were measured using the Mini Vidas and BioMerieux kits according to the method mentioned by Wheeler (2006).

Lipid Profile Measurements

The measurement method used is the enzymatic colorimetric method using the Biolabo kit and according to the method mentioned by Friedwald *et al.* (1972), Allain *et al.* (1974), and Lopes-Virella *et al*. (1977).

Statistical Analysis

All data were analyzed using SPSS version 19 for medium extraction, standard deviation SD, addition to (P <0.05) and (P <0.01) using independent t-test (Al-Rawi, 2000).

RESULTS

The study was carried out on BPH patients (66) and 30 men as a control, there were non-significant difference (0.981) between BPH patients aged 53.25±4.83 year and control subjects (49.58±5.31 year), also, the difference between age of BPH patients with MetS (54.95±4.39 year) and BPH without MetS (53.18±5.01 year) were non-significant (0.472) as shown in **Table 1**.

Table 1. Age of BPH patients (with MetS and without MetS) and control group

Age (year)	BPH patients (66)			Control (30)
	BPH with MetS	BPH without MetS	P value	
	54.95±4.39	53.18±5.01	0.472	49.58±5.31
	53.25±4.83			
P value	0.981			

Table 2. The levels of sex hormones (T, E2, PRL, LH, FSH, DHT) in BPH patients and control group

Hormones	BPH (n=66)	Control (n=30)	P value
T (ng/ml)	3.73±1.74	5.10±1.70	0.001**
E2 (pg/ml)	55.32±13.65	35.67±4.09	0.001**
PRL (ng/ml)	11.73±8.67	7.19±3.17	0.997
LH (m.IU/L)	4.14±2.63	3.25±1.65	0.285
FSH (m.IU/L)	5.23±3.03	4.25±1.93	0.150
DHT (ng/ml)	148.16±54.32	63.69±11.65	0.000**

The values represent Mean ± SD. **Differences is significant at the 0.01 level.

Table 3. The values of lipid profile (TC, TG, HDL, LDL, VLDL) in BPH patients and control group

Lipid profile	BPH (n=66)	Control (n=30)	P value
TC (mg/dl)	173.53±36.26	171.75±23.37	0.015*
TG (mg/dl)	209.68±89.61	180.20±45.57	0.029*
HDL (mg/dl)	31.05±4.59	39.68±25.69	0.005**
LDL (mg/dl)	97.68±28.59	91.98±37.05	0.042*
VLDL (mg/dl)	40.12±9.48	36.22±9.17	0.001**

The values represent Mean ± SD. **Differences is significant at the 0.01 level. *Differences is significant at the 0.05 level

The means of sex hormones levels (T, E2, PRL, LH, FSH, DHT) in BPH patients and control group as shown in **Table 2**, the results revealed had significantly decrease (p<0.01) in T level (3.73±1.74 ng/ml), E2 level (55.32±13.65 pg/ml) in BPH patients compared to control group (5.10±1.70 ng/ml), (35.67±4.09 pg/ml) respectively, while DHT level had significant increase (p<0.01) in BPH patients (148.16±54.32ng/ml) compared to control group (63.69±11.65 ng/ml), whereas hormones PRL, LH, FSH had non- significant differences between BPH patients and control group.

Table 3 shown the values of lipid profile TC, TG, HDL, LDL, VLDL) in BPH patients and control group which there were recorded significantly increase (p>0.05) in concentrations of TC (173.53±36.26 mg/dl), TG (209.68±89.61 mg/dl), LDL (97.68±28.59 mg/dl) and significant increase (p>0.01) in VLDL (40.12±9.48 mg/dl) for BPH patients compared to control group (171.75±23.37 mg/dl), (180.20±45.57 mg/dl) and (91.98±37.05 mg/dl) respectively, while HDL revealed decreased significantly (p<0.01) in BPH patients (31.05±4.59 mg/dl) compared to control group (39.68±25.69 mg/dl).

The hormonal parameters (T, E2, PRL, LH and FSH) in BPH patients with MetS had non-significant difference compared to BPH patients without MetS, while DHT

Table 4. Hormonal parameters in BPH patients with and without metabolic syndrome

Hormones	BPH with MetS (23)	BPH Without MetS(43)	P Value
T(ng/ml)	3.40±1.30	3.64±1.70	0.128
E2(pg/ml)	53.76±10.95	57.11±12.34	0.818
PRL(ng/ml)	12.79±5.65	11.08±9.48	0.398
LH(m.IU/L)	4.45±2.35	4.10±2.79	0.990
FSH(m.IU/L)	4.72±2.11	4.74±2.36	0.599
DHT (ng/ml)	140.58±62.44	91.84±34.19	0.003**

The values represent Mean ± SD. ** Differences is significant at the 0.01 level

Table 5. Lipid profile in BPH patients with and without metabolic syndrome

Lipid profile	BPH With MetS (23)	BPH Without MetS (43)	P Value
TC (mg/dl)	170.30±38.58	172.51±35.85	0.897
TG (mg/dl)	211.65±110.6	205.84±74.86	0.314
HDL (mg/dl)	32.09±7.67	40.60±28.91	**0.014***
LDL (mg/dl)	97.44±35.31	91.08±37.55	0.624
VLDL (mg/dl)	42.43±22.13	48.57±36.52	0.664

The values represent Mean ± SD. *Differences is significant at the 0.05 level

level had significantly increase ($p<0.01$) in BPH patients with MetS (140.58±62.44 ng/ml) compared to BPH patients without MetS (91.84±34.19 ng/ml), as shown in **Table 4**.

The results revealed that lipid profile (TC, TG, LDL, VLDL) levels had non-significant difference in BPH with MetS and BPH without MetS, while HDL level revealed significantly decrease ($p>0.05$) in BPH with MetS (32.09±7.67 mg/dl) compared to BPH Without MetS (40.60±28.91 mg/dl) as shown in **Table 5**.

DISCUSSION

Benign prostatic hyperplasia (BPH) is the most common urological condition among aging males, it has been suggested that certain sex-hormone including lower androgen levels and higher estrogen levels may contribute to the development of BPH (Ryl *et al*. 2015) More recently, it has been suggested that individuals with metabolic syndrome (MetS) or its individual components including central obesity, hyperinsulinemia, insulin resistance, and dyslipidemia may be prone to developing BPH and LUTS (Corona *et al*. 2014, Gacci *et al.* 2018). On the other hand, some earlier studies found no such relationship (Temm *et al*. 2009).

Testosterone plays a major role in benign prostatic hyperplasia pathophysiology (Ho and Habib 2011, Wu *et al*. 2016). The level of testosterone in the serum decreases significantly after age 40 at the same time as the prostate size increases (Liu *et al*. 2007, Zeng *et al*. 2012). In the our study, indicate decease significantly testosterone level in BPH patients compared to control group, show that T is significantly associate with BPH diseases, that due to enzymatic activity of 5α-reductase (convert T to DHT) is about 7-fold higher in cultured BPH compared to normal, and the 17-hydroxysteroid dehydrogenase activity (metabolizes T to the inactive Δ4-androstenedione) is 250-fold more in BPH stromal cells, which decreased T level (Doulabi *et al*. 2013). These results are compatible with the results of Sahi *et al*. (2013) and Tewari *et al*. (2014) who found that the mean of T was significantly lower in BPH patients than in control group. The increase in serum T and E2 levels were also associated with decrease BPH risk (Litman *et al.* 2007; Nakhaei et al. 2019). Other study reported that the high levels of T converted to DHT are significantly associated with decrease risk of BPH (Kristal *et al*., 2008). These steroids are mediated factors that explain relationship of genetic or environmental features with BPH risk.

The current study shows that there is high estradiol (E2) level and possibly due to increased aromatization of testosterone which increase in BPH patients particularly in proliferative stroma suggesting local increase of estrogen levels, estrogen effects on the prostate gland may also be indirectly mediated through alterations in other serum hormones leading to increase the E2/T ratio which is the most possible important etiological factor for BPH. The study results agreed with the study of Sarma and Wei (2012), Khaleel *et al*. (2013), Corona *et al*. (2014).

The non-significant increase in LH, FSH level in BPH patient was possibly a response to increase pituitary gland activity and gonadal activity or altered steroid metabolism. In addition, DHT has a minimal role in the negative feedback control of androgen secretion resulted in affecting other hormones as FSH.

Also non-significant increase in prolactin (PRL) may be due to that the prostate may not depend on pituitary PRL, however, it is can be produced by its secretory epithelium (Nevalainen *et al*. 1997), and adipose tissues itself functions as endocrine organ and leads to raise levels of PRL (McGrown *et al*. 2014). Elevated levels of PRL have significant stimulatory actions on prostate ductal development and causes hyperplastic growth in the adult gland (Hernandez *et al*., 2006; Herrara-Covarrubias *et al*., 2015). Prolactin (PRL) increases at least 30% above the normal level in the elderly and the high level of prolactin has catalytic effects on the enlargement of the prostate gland channels and leads to benign prostatic hyperplasia in the elderly (Herrera-Covarrubias *et al*. 2015).

High level of DHT in the BPH patients may be due to 5-α reductase activity and continue to produce and collect of DHT in the prostate that may promote the cells growth. The present results were compatible with results of Kristal et al. (2008), and Tewari *et al*. (2011) who reported that the increased androgen levels in BPH due to to 5-α reductase activity. Roberts *et al.* (2004) reported rise DHT activity in BPH relative to normal prostate gland, resulting as a permissive, rather than a transformative, mediator in the BPH development. Also, Al-Saadi (2013), Patel and Parson (2014) observed that men who do not synthesis DHT do not develop BPH, and the men who had the highest midlife levels of DHT had

nearly 3 times the risk of BPH compared to those of lowest levels.

The current study indicates high level of dihydrotestosterone in MetS patients that play vital role in BPH development. Fat, steroids and peptides play a crucial role in the development of benign prostatic hyperplasia (Rył *et al*., 2015). The effect of peptides and lipids on the growth of the prostate gland will be less effective than steroids, the information about the role of fat in prostate growth is few and needs more studies to illustrate. While study have indicated lipid binding with insulin resistance and secondary hyperinsulinemia (Vikram and Jena 2012)

Cholesterol is the source of the synthesis of steroid hormones and its transformation into pregnenolone is a subsequent step to the synthesis of steroid hormones (Ejike and Ezeanyika 2010).

The present results indicate significant increasing in TC and LDL-C concentration in the BPH patients may be resulted from some metabolic problems especially in lipid metabolism, caused lowering the T level which prevents hydrosterone formation that affects the lipid metabolism.

Our results agreed with the results of Corona *et al.* (2014) who noted that TC level was twice in prostate of BPH patients than in normal prostate, also Rahman *et al*. (2007) observed that prostate weight was significantly increased in hyperlipidemic rats than in controls.

Furthermore, Tewari *et al*. (2011), Mohammed *et al*. (2012), and Flelih *et al*. (2014) mentioned that the increase concentrations of TC, LDL-C, TG, and the decrease concentration of HDL-C increase the BPH risk, and cholesterol-lowering medication may be decreased this risk.

Many histopathologic and Epidemiological studies provide clinical index of a association between the correspondence of metabolic disorders within the metabolic syndrome and the benign prostatic hyperplasia pathogenesis (BPH) (Parsons et al. 2006, Parsons 2007).

The increase in estrogen levels and low sex hormone-binding globulin (SHBG) may be causes change and hyperplasia of prostate, such as the decrease in androgen this often associated with Mets and abdominal obesity, where men who suffer from LUTS and BPH and disorders Metabolism has low androgen levels and high estrogen, as estrogen enhances the effect of androgen and leads to an increase in prostate enlargement (Rył *et al*. 2015).

The present study observe the low level of high-density lipoprotein (HDL) cholesterol in Mets patients compared to BPH patients without Mets, also there is non -significant increase in TG and LDL cholesterol levels in MetS patients .The relationship between BPH and dyslipidemia has been documented in several studies. Hammarsten *et al.* (1998) examined the data of 158 men and reported that individuals with a low level of HDL cholesterol had a larger prostate volume and a higher annual BPH growth rate, individuals with diabetes who had the highest LDL cholesterol had a 4-fold higher risk of reporting BPH than did those with the lowest LDL cholesterol (Abdollah *et al*. 2011, Razumovskaya et all 2019).

CONCLUSION

In conclusion, this association may be a consequence of MetS related change in the sex hormones (DHT) and metabolic derangement, therefore the observation suggests that as obesity, dyslipidemia, insulin resistance may interact with other components of MetS to increase BPH risk.

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