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THE ROLE OF INSULIN LIKE GROWTH FACTOR-1(IGF-1) IN DEVELOPING PROSTATE DISORDER IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT
This study was to investigate on the coexistence of diabetes mellitus type 2 and BPH and to correlate among these conditions could exist. Furthermore, the relationship between benign prostatic hyperplasia and serum insulin-like growth factor-1 levels in those patients, by examination the correlation of prostate size with serum IGF1, age, prostatic specific antigen levels in patient groups are to be compared to non diabetic age – matched controls. Fasting blood specimens from sixty type 2 diabetic males, 33 of them had normal prostatic specific antigen levels (<4 ng/ml) and enlarged prostate according to digital rectal examination and trans abdominal ultrasound with lower urinary tract symptoms as a result of benign prostatic hyperplasia (BPH), as group a- (with a mean age of 62.4±5.1 years) and the rest (27) of them without BPH, as group b- (had a mean age of 56 ±5.2 years), who were attending the Al-Sader Teaching Hospital in Al-Najaf/Iraq, besides nineteen apparently healthy control males. Serum insulin-like growth factor-1, insulin, prostate specific antigen (PSA) concentrations were measured by a ELISA kits. The mean serum IGF-1 levels were significantly elevated in type 2 diabetic patients with BPH compared to diabetics without BPH (145 ± 41.1 and 88 ± 41.1 ng/ml respectively), while control group had a mean serum IGF-1 levels of 75±19.1ng/ml, Whereas, PSA values (2.37±0.98) were significantly elevated in diabetics with BPH compared to the other groups (0.7 ± 0.3 and 0.9± 0.2). A significant correlation was detected between prostatic size & IGF-1 levels in diabetics with BPH (r= 0.554, p< 0.001), which was undetectable in diabetics without BPH (r=0.256 , *P*=0.197). Our findings suggest that insulin-like growth factor-1 may have an etiologic role in BPH development in type 2 diabetic patient whose duration of diabetes less than 7 years.

KEYWORDS: diabetes mellitus, benign prostatic hyperplasia, serum insulin, PSA values.

INTRODUCTION

Type 2 diabetes is a chronic progressive metabolic disease characterized by hyperglycemia resulting from too little insulin secretion, resistance to the action of insulin or both[1,2]. Initially insulin resistance led to B cell compensation, which causes hyperinsulinemia. Increase insulin secretion from the pancreas into the portal circulation may lead to increased hepatic growth hormone-mediated synthesis of IGF-1, insulin also increase IGF-1 bioavailability through the down regulation IGFBP1 and IGFBP2[3,4,5]. However, with increasing duration of disease ,the pancreas loses its ability to secrete insulin because of damage to the pancreatic B cell, and circulating levels of insulin decrease[6]. So that, low portal insulin concentration decrease growth hormone receptor expression on the hepatocyte surface and decrease sensitivity of the liver for growth hormone, ultimatly decrease IGF-1 output from the liver[7]. IGF-1 plays an important role in understanding the etiology of prostate disease, including BPH. IGF-1 exbibit autocrine, paracrine manner to promote normal growth and cellular proliferation[8,9]. Because IGF-1 is a single chain polypeptide that is structurally and functionally similar to insulin[10]. The insulin receptor (IR) isoforms and the IGF type 1 receptor (IGF-1R) share a high degree of structural homology [11]. Several studies have shown a significant relationship between diabetes or hyperinsulinemia and larger prostate size[12-14]. Clinically, BPH may be associated with lower urinary tract symptoms (LUTS) secondary to the prostate enlargement. About 60% of men aged ＞50 years have histologic evidence of BPH. This prevalence increases to 80% in patients aged ≥70 years [15,16].

The initial assessments of BPH should include the following domains:

1- Patient's history: a family history of prostatic disease and prostatic cancer and a history of administration of alpha-blockers, 5-alpha reductase inhibitors [17].
2- Transabdominal ultrasound: can be used to assess prostate volume, which is the most extensively studied of the risk factors for BPH progression. Men with a PV of ≥ 30 CC are more likely to suffer moderate- to-severe symptoms compared with men with PV < 30 CC [18].
3- Physical Examination including a digital rectal examination (DRE): allows the examiner to appreciate the gland's morphology, including any irregular, nodular, or indurated areas, where there is a suspicion for malignancy [19].
4- Serum PSA Measurement: Prostate: it is a serine protease produced by benign and malignant prostate tissue[20]. With digital rectal examination (DRE), prostate specific antigen (PSA) is a major screening tool for prostate cancer [21]. The normal range is 0 to 4 ng/ml; 30% of men with a PSA in the range of 4 to 10 ng/ml and 50% of those with a PSA >10 mg/ml will have cancer [22].

5- Symptom Assessment: International Prostatic Symptom Score (IPSS) is the most commonly used questionnaire by most clinician's .This questionnaire consists of 7 items that determines the severity of irritative and obstructive voiding symptoms. On the basis of this score, the symptoms can be classed as mild (IPSS score 0–7), moderate (IPSS score 8–19), or severe (IPSS score 20–35) [23].

At approximately age 50, the steady growth of the prostate slowly accelerates with an increase in α1-adrenoceptor mRNA expression has been observed in aged human prostate[24]. Because testosterone is converted to estradiol in adipose tissue, therefore obese men have a low testosterone, high estrogen hormonal environment compared with normal-weight men[25]. estrogens have been shown to up regulate the levels of RhoA/ROCK signaling which is the major factor responsible for maintaining bladder smooth muscle tone, so that hyperactivity of the RhoA/ROCK pathway leading to altered bladder smooth muscle tone .Obese men are also more likely to have hyperinsulinemia, which has been associated with increased prostate growth and potential development of symptomatic BPH [26].

MATERIALS & METHODS

Patient's selection

Between November /2013 and April/2014, at the Endocrinology and Diabetes Center and by the Urology Clinic in Al-Sader Teaching Hospital/Al-Najaf city, Iraq, male participants underwent serial prostate examinations and anthropometric measures The study included (60) patients who had been diagnosed as having type 2 diabetes and under treatment with oral anti-diabetic agents and/or insulin therapy. Thirty three type 2 diabetic patients with BPH with age of >45 years who had normal prostate specific antigen (PSA; <4 ng/ml) levels and normal digital rectal examination (DRE) of the prostate with complaints of lower urinary tract symptoms and (27) type 2 diabetic patients without BPH, and normal prostate size and no lower urinary tract symptoms. In addition to (19) apparently healthy male subjects as a control group having normal fasting serum glucose and normal prostate size. All participants were well informed about the study and gave their consent to participate prior to having blood samples taken.

We excluded those men with: 1- a history of prostate cancer before the study or those diagnosed with prostate cancer during the study; 2- serum PSA concentration more than or equal to 4.0 ng/ml and/or an abnormal digital rectal examination which is consider as important features suggestive of prostate cancer; 3- α-blockers or 5-α reductase Inhibitors medications (that decreases prostate volume) 4- previous surgery for prostate enlargement.

Specimen Collection

An overnight fasting venous blood sample was obtained from each participant, to obtain serum samples that were frozen at -20ºC until tested.

Biochemical Analysis

Fasting serum insulin was assessed by using the demeditec insulin ELISA kit which is a solid phase enzyme-linked immunosorbent assay (ELISA) [27]. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as a marker of insulin resistance[28].IGF-1concentration was measured by demeditec IGF-I 600 ELISA Kit (Demeditec Diagnostics, Germany) [29].

For statistical analysis, we used the one way analysis of variance (ANOVA) test evaluate significant differences between means of different groups. The results were expressed as mean ± standard deviation. Pearson's correlation coefficient (r) was used to test for statistically significant correlation between studied parameters. Data were analyzed using SPSS statistical software.

TABLE 1. Demographic Data of Groups Included in The Study

Variable	Type 2 diabetic with BPH patients Group1	Type 2 diabetic patients without prostatic hypertrophy Group 2	Control subjects Group 3
Number	33	27	19
Age (years)	62.4±5.1* ϫ	56.6±5.2	56.1±5.2
Duration of diabetes (years)	3.9±1.8 ϫ	8.6±2.8	-
Hb_{A1C} (% Hb)	7.4±0.7 * ϫ	8.1±1.19*	5.7±0.4
BMI(kg/m2)	27.01±1.8 ϫ	23.8±1.8	25.5±1.7
Prostate volume(cm3)	64.94±17.21* ϫ	26.24±3.5	24.2±3.4
Prostatic Acid Phosphatase (U/L)	3.03±1.0* ϫ	1.0±0.5	1.1±0.3
PSA(ng/ ml)	2.3±0.988* ϫ	0.7±0.3	0.9±0.21

*Values of continuous variables are shown as mean ±standard deviation;

* = significant difference from control, ϫ: significant difference from type 2 diabetic patients without benign prostatic hypertrophy, p<0.05.PSA=Prostate specific antigen.

RESULTS

As shown in tablet -2 the mean serum glucose, insulin, HOMA-IR and IGF-1 of diabetics with BPH, were 166.18±26.56(mg/dl), 21.3±7.1(µIU/ml), 8.6±3.3, and 145.7±41.1 (ng/ ml), respectively, those were significantly different from diabetics without BPH as well as the control.

By calculating Pearson's correlation coefficient (to examine the relationships between prostate size in diabetic groups 1 and 2 according to age, IGF-1 and PSA

separately, (Table- 3).There was a significant positive correlation between age and prostate size in group 1. However, there was non significant correlation between these two items in the group 2. Similarly, a significant correlation between serum IGF-1 levels and prostate size was detected in group 1, but not in group 2. While the correlation between these two items was non significant statistically in group 2. Whereas prostate size and PSA were positively correlated in group 1 only.

TABLE 2. Measured Parameters Among Studied Groups

Variable	Type 2 diabetic with BPH patients Group 1	Type 2 diabetic patients without prostatic hypertrophy Group 2	Control subjects Group
Number	33	27	19
FSG(mg/dl)	166.18±26.56* Ϫ	211.4±63.8*	106.21±17.44
Insulin(µIU/ml)	21.3±7.1* Ϫ	6.7±3.4*	12.9±3.6
HOMA-IR	8.6±3.3* Ϫ	3.5±1.9	3.5±1.4
IGF-1 serum level(ng/ ml)	145.7±41.1* Ϫ	88.7±41.2*	75.8±19.1

*Values of continuous variables are shown as mean ±standard deviation;
* = significant difference from their control, Ϫ: significant difference from Type 2 diabetic patients without prostatic hypertrophy, p<0.05.HOMA-IR= Homeostatic model assessment of insulin resistance

TABLE 3. Correlation Between Prostate Size In Diabetic Groups 1 and 2 with Age,IGF-1 and PSA :

	Group1		*Group2*	
	r value	*p* value	*r* value	*p* value
Age	0.412*	0.017	0.222	0.267
IGF1	0.554**	0.001	0.256	0.197
PSA	0.507**	0.003	-0.024	0.904
Duration of DM	0.086	0.63	0.035	0.81

*Correlation is significant at the 0.01 level **Correlation is significant at the 0.01 level

DISCUSSION

Fasting serum insulin levels in group1 expressed a significant higher levels than diabetic patients group 2 (as illustrated in table -2) ,this result could be related to their older age and to longer duration of diabetes mellitus which causes a progressive deterioration in β-cell function and mass over the time [30,31]. Whereas, at the early stage of disease it was found that a physiological adaptive expansion of ß-cell mass can occur via a net increase in the generation of new ß-cells, or an increase in ß-cell size as a compensating mechanism resulting in elevating plasma insulin levels to maintain normoglycemia[32]. Such variation in insulin level is reflected by variations in FPG & HOMA-IR values among these groups. When β- cells exposed to sustained stress as a consequence of exhaustion caused by unsustainable demands and this naturally results in progressive loss of b-cell function and mass with a steady decline in insulin secretion from pancreatic b cells and reduction in circulating insulin, leading to poorly regulated blood glucose levels[33]. While during type-2 diabetes, in order to counteract resistance of the insulin receptor in responsive tissues, there will be an attempting to alleviate hyperglycemia by increasing insulin secretion [34].Hyperinsulinemia stimulates the liver to produce more insulin-like growth factor (IGF), another mitogen and an anti-apoptotic agent which binds insulin receptor /IGF receptor and stimulates prostate growth[36]. Prostatic cells express IGF-1 receptors and are very sensitive to stimulation by IGF[37]. So, our results found an association between prostate volume and IGF1 levels in type 2 diabetic patient whose duration of DM was less than 7 years. It must be emphasized that BPH is present in the majority of older males, thus our study show significant correlation between age and prostate size in group 1 but not in group 2. Because the present study was performed on a relatively small sample size, thus statistical significance was not a guarantee that chance did not contribute to the generation of results. In conclusion, the results of the present study raise the possibility that IGF-1 has a role in the etiology of BPH development in patients with type 2 DM. As a result, the risk of BPH initially to be increased among men recently diagnosed with diabetes, but risk may later be reduced as insulin levels decreased. This interpretation is strengthened by the significant difference observed between serum insulin-like growth factor-1 levels in type 2 diabetic patients with benign prostatic hyperplasia and type 2 diabetic patients without prostatic hyperplasia. However, the above potentially constitutes the key for the contribution of the insulin effect and the abnormalities of glucose homeostasis in the development of BPH.

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