Association of Insulin Resistance with Overactive Bladder Syndrome in Female Patients

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ABSTRACT:

BACKGROUND:

Overactive bladder Syndrome refers to a group of lower urinary tract symptoms related to the storage of urine in the bladder. Normally the bladder fills and stores urine without discomfort or leakage. The sensation of bladder fullness gradually increases until the need to void comes to conscious awareness. In those who have overactive bladder, however, the sensation to void is altered (and generally delayed) to the extent that involuntary urination may occur. current evidence suggests that it may be associated with insulin resistance .

AIM OF STUDY:

We aimed to investigate the association of insulin resistance with overactive bladder in female patients.

PATIENT AND METHODS :

We prospectively conducted the study in our urogynecological department. Female patients aged between 30 and 76 years with or without overactive bladder syndrome OABS symptoms were enrolled. Fifty patients with OABS and fifty age-matched controls without OABS were included in the study. Fasting serum insulin and fasting blood sugar were measured. Insulin resistance value was obtained via the homeostasis model assessment of insulin resistance (HOMA-IR) calculator.

RESULTS:

There was no significant difference in the age, and mode of delivery between women with or without overactive bladder (OAB), while BMI and parity number were significantly higher in OABS women. FBS, fasting insulin (11.2 vs. 7.9 **µ**U/ml) , HOMA-IR value (2.62 vs. 1.77) and insulin resistance (IR) was significantly higher in OABS women, in which 50% had IR while 12% had IR in women with or without OABS. In multivariate analysis insulin resistance (IR≥2.5) , age, increased BMI, higher parity, and CS history were independent predictors of overactive bladder.

CONCLUSION:

- insulin resistance is associated with overactive bladder syndrome, and about half of the women with overactive bladder presented with insulin resistance
- Hyperinsulinemia is strongly associated with overactive bladder
- Obesity is an independent predictor of overactive bladder
- HOMA-IR equation can be used as diagnostic methods that assist in confirmation of overactive bladder diagnosis by 20 – 25% additional increase in the index of suspicion.

KEYWORDS: Insulin resistance, Overactive bladder, Mode of delivery, Metabolic syndrome

INTRODUCTION:

The International Continence Society (ICS) defined the Overactive Bladder Syndrome (OABS) in 2002 and more recently in 2010 as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology." [1] According to the ICS, frequency is defined as when the patient "considers that he/she voids too often by day," and nocturia is when at least one micturition interrupts sleep at night. [2]

OABS affects nearly 100 million people in the Western world (33 million in the US and 66 million in the European Union) and has severe effects on quality of life and ability to work [3].

Worldwide prevalence of (OABS) is 12.8% for women [4].

Insulin resistance, defined as the impaired capacity of insulin to stimulate glucose sequestration, plays a major role in the pathogenesis of type 2 diabetes and is associated with several peripheral complications, such as cardiovascular disease and lower urinary tract symptoms (LUTS) [5,6].

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The pathophysiology relationships between insulin resistance and voiding problem have been substantially poorly understood, and metabolic syndrome (Metabolic syndrome is a cluster of visceral obesity, dyslipidemia, hypertension and glucose intolerance). has been elucidated to play a significant role in etiopathogenesis [7] .

Recent clinical studies have provided emerging evidence that metabolic syndrome and obesity may play a significant role in the development of lower urinary tract symptoms (LUTS) in OABS in females. Insulin resistance (IR) is the underlying pathogenesis and is likely to be a significant link between the components of metabolic syndrome. Sympathetic overactivity, proinflammatory status, oxidative stress and other pathological conditions are known to be associated to metabolic syndrome-IR state. In addition, these mechanisms are also supposed to be involved in the development of OABS [8,9] .

AIM OF THE STUDY:

To assess the relations between insulin resistance with the overactive bladder Syndrome in female patients.

PATIENTS AND METHODS:

study design and setting

This is a prospective study was carried out in the Department of Obstetrics and Gynecology/ Baghdad Teaching Hospital, medical city Baghdad, Iraq. This study was conducted over a period of 12 months (starting from first of January 2018 to first of January 2019)

One hundred Female patients aged between 30 and 76 years were enrolled in this study.

Fifty studied group and fifty control group.

Inclusion criteria were primi and multiparous , Age (30-76) years old and had episiotomy in first delivery.

Exclusion criteria were Patients suffering from urinary tract infection Patients with chronic Hypertension , Patients with diabetes mellitus , Patients with congenital, neurologic or severe psychiatric diseases .

data collection

A full history: about, age, menstrual state, parity, mode of delivery, episiotomy in the first delivery, past medical history (to exclude hypertension, diabetes, psychological impairments because cognitive ability is necessary for continence maintenance, Women with severe physical handicaps or restricted mobility may simply not have time to reach the toilet, especially in the setting of urinary urgency/overactive bladder , Conditions such as congestive heart failure, hypothyroidism, venous insufficiency, Finally, history of stool impaction resulting from poor bowel habits and constipation can contribute to overactive bladder symptoms This is perhaps from local irritation or direct compression against the bladder wall) , drug history to exclude diuretic use and the effects of certain medications which contribute to peripheral edema leading to urinary frequency and nocturia when a patient is supine , history of obstetrical trauma, assessment of urinary symptoms and their duration (including storage and voiding symptoms) , an assessment of the patient's quality of life and history of polycystic ovarian syndrome .

clinical examination including: general inspection , abdominal, pelvic perineal examination , bimanual examination may reveal an enlarged pelvic mass or a uterus enlarged by leiomyomas or adenomyosis These may create lower urinary tract symptoms through increased external pressure transmitted to the bladder , brief neurologic examination, Bonney test and cough reflex test to exclude stress incontinance , Pelvic Organ Prolapse Evaluation, And Measurement of weight (Kg), Height (cm) to calculate the BMI.

Both groups exposed to the following lab investigations:

Fasting blood sugar ,Fasting serum insulin .,Mid-stream urine test to exclude UTI.

,Renal function test (blood urea, serum creatinine). & ultrasound to exclude Renal pathology.

Field working procedure

Overnight fasting a blood sample had been drawn about 5 ml then centrifuged to collect the serum, through which part of it used for analysis of biochemical test listed above and part for the (2cc) were freezed at -20C temperature centrifuge the sample again after thawing before assay (avoiding repeated freeze thaw cycles) to be used for fasting serum insulin assessment by using the Kit .

Insulin blood samples was stored after the serum was separated within no more than 5 h, and then stored in a refrigerator for up to 24 h. insulin was measured by immunoassay.HOMA-IR (Mass Units) is an approximating equation for insulin resistance Formula :HOMA-IR= ((fasting insulin (mU/mL) x fasting glucose (mg/dL))/405

Ethical considerations

The purpose and the procedure was explained to all participants and were given the right to participate or not, verbal consent was taken from all participants.

Statistical analysis

Independent t test used for continuous data analysis, while Mann Whitney U test used if data did not adhere to normal distribution, chi square test used for categorical variables analysis, logistic regression used to calculate the odd ratio, while Receiver operator curve (ROC) used as calculate the area under the curve and the diagnostic utility parameters. All analysis carried out using SPSS 22.0.0 (Chicago, IL), p value considered when appropriate to be significant if less than 0.05 .

RESULTS:

There was no significant difference in the age, and mode of delivery between women with or without overactive bladder Syndrome (OABS), BMI and parity number was significantly higher in OABS women, as illustrated in table 1

Table 1: Assessment of demographic and maternal characteristics.

	OABS (-)	OABS (+)	p-value
Number	50	50	-
Age (y), mean ± SD	35.8±5.5	37.9±8.0	0.115[a]
BMI (kg/m^2), mean ± SD	24.6±4.5	30.7±6.7	<0.001[a]
Mode of delivery, n (%)			0.424[b]
Vaginal	43 (86.0%)	40 (80.0%)	
CS	7 (14.0%)	10 (20.0%)	
Parity, mean ± SD	0.3 ± 0.7	3.1 ± 2.0	<0.001[c]
[an] Independent t-test [b] Chi square test [c] Mann Whitney U test			

FBS, fasting insulin, and insulin resistance was Significantly higher in OABS women, as illustrated in table 2 .

Table 2: Laboratory and insulin resistance findings.

Variables	OABS (-)	OABS (+)	p-value
Number	50	50	-
FBS (mg/dl), mean ± SD	92.1±4.8	96.1±11.4	0.025[a]
Insulin (µU/ml), medina (IQR)	7.9 (1.2-9.5)	11.2 (5.6-19.0)	0.012[b]
HOMA-IR, median (IQR)	1.77 (0.25-2.21)	2.62 (1.18-4.19)	0.006[b]
Insulin resistance, n (%)			<0.001[c]
<2.5	44 (88.0%)	25 (50.0%)	
≥2.5	6 (12.0%)	25 (50.0%)	
[an] Independent t-test [b] Chi square test [c] Mann Whitney U test			

There was no significant difference in PCOS and menopausal status between women with or without OABS, as illustrated in table 3 .

Table 3: Assessment of PCOS and menopause.

	OABS (-)	OABS (+)	p-value
Number	50	50	-
PCOS status			0.678
No PCOS	46 (92.0%)	48 (96.0%)	
PCOS	4 (8.0%)	2 (4.0%)	
Menopause status			0.056
Reproductive age group	50 (100.0%)	45 (90.0%)	
Menopause group	0 (0.0%)	5 (10.0%)	
Fisher exact test			

In multivariate analysis insulin resistance (IR≥2.5), increased BMI, and higher parity, were independent predictors of overactive bladder, while history of CS reduce the risk of OABS, as illustrated in table .4

Table 4: Multivariate analysis of the predictors of OAB.

Variables	Wald	OR	95%CI	p-value
IR (≥2.5)	6.586	15.412	1.908-124.468	0.010 [S]
BMI	7.979	1.798	1.197-2.702	0.005 [S]
Parity	11.600	19.481	3.528-107.582	0.001 [S]
History of CS	6.953	0.011	0.001-0.318	0.008 [S]
PCOS	0.179	1.908	0.096-37.922	0.672
R^2 (Cox & Snell) = 0.636				

Since the positive LH ratio is between (3 – 4) indicate IR had 20 – 25% increase in probability to confirm OABS, while negative LH value above 0.5 indicate it had <15% increased probability to exclude OABS, indicating the presence of IR increased the probability of OABS by (20 – 25%), as illustrated in table .5 and figure .1.

Table 5: ROC analysis of the role of insulin resistance to predict OAB.

AUC	95%CI	p-value	Cut-off	SN	SP	+LH	-LH
0.659	0.558-0.751	0.005	>2.211	56%	82%	3.11	0.54
AUC: area under the curve, SN: sensitivity, SP: specificity, LH: likelihood ratio, ROC: receiver operator characteristics							

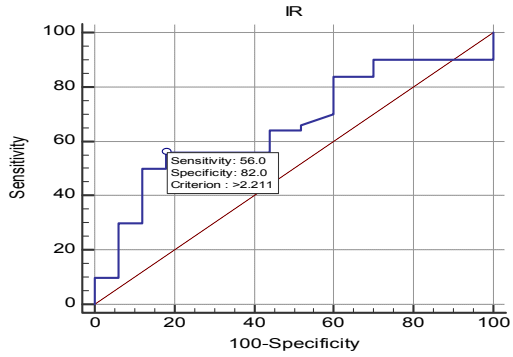

Figure 1: ROC curve analysis of the IR as predictor of OABS.

DISCUSSION:

In the present study serum insulin levels and insulin resistance relationship with overactive bladder (OABS) were studied, we found that serum fasting insulin was significantly higher in OABS women compared to control (11.2 vs. 7.9 □U/ml), the same was true for HOMA-IR (insulin resistance) with 2.62 vs. 1.77, in addition fasting blood sugar (FBS) was significantly higher in OAB women (96.1±11.4 vs. 92.1±4.8 mg/dL).

These findings agreed with Uzun et al study, this prospective study examined 122 women with OABS and 62 normal women, they found that FBS was significantly higher in OABS (107.4±6.1 vs. 94.5±7.3 mg/dL), HOMA-IR also was significantly higher in OAB (2.86 vs. 1.32), and serum fasting insulin was significantly higher in OAB (11.5±6.2 vs. 6.4±2.1 µU/mL) [9].

A possible explanation of the role of IR with OABS is through inflammatory and oxidative stress mechanism, Tyagi et al reported an elevated level of inflammatory markers in OABS (macrophage inflammatory protein, IL-5, and epidermal growth factor) were significantly higher in OABS (10) . While in another study Lee WC,et al histological examination of the bladders revealed leukocyte infiltration around the endothelium of vessels and into the interstitial tissue, hypoxia and fibrosis (11).

Masuda H et al. found that oxidative stress had been play a significant role in pathogenesis of OAB .[12]

In the present study IR, age, BMI, parity, and positive previous history of CS were independently correlated with OAB, additionally IR had 15 folds increased risk of having OAB. This indicate that not only IR is associated with OAB, it is possible to correlate with OAB in more than one mechanism (other than that relate to obesity, multiple parity, and history of CS). Since the odd ratio of previous history of CS was less than 1.0 (OR = 0.011) this indicate in the present study CS inversely correlate with OAB, i.e. women with normal vaginal delivery at increased risk for OABs.

In the present study after using ROC analysis HOMA-IR at cut – off more than 2.211 predict OAB diagnosis, since the specificity at this cut – off is higher than its sensitivity (82 vs. 56%) this indicate HOMA-IR (or insulin resistance) is confirmatory test for OAB if utilized in the conformation of OAB diagnosis, additionally the positive likelihood ratio is 3.11 this indicate that HOMA-IR can increase the likelihood of OAB diagnosis by 20%.

CONCLUSION:

Insulin resistance associated with over active bladder Syndrome and about half of the women with over active bladder presented with insulin resistance.

- Hyperinsulinemia is strongly associated with overactive bladder syndrome.
- Obesity is an independent predictor of overactive bladder Syndrome.
- HOMA-IR equation can be used as diagnostic methods that assist in confirmation of overactive bladder diagnosis by 20 – 25% additional increase in index of suspicion.

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